Regulation of signal transduction pathways in colorectal cancer: implications for therapeutic resistance

Yeelon Yeoh, Teck Yew Low, Nadiah Abu and Pey Yee Lee

UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

ABSTRACT

Resistance to anti-cancer treatments is a critical and widespread health issue that has brought serious impacts on lives, the economy and public policies. Mounting research has suggested that a selected spectrum of patients with advanced colorectal cancer (CRC) tend to respond poorly to both chemotherapeutic and targeted therapeutic regimens. Drug resistance in tumours can occur in an intrinsic or acquired manner, rendering cancer cells insensitive to the treatment of anti-cancer therapies. Multiple factors have been associated with drug resistance. The most well-established factors are the emergence of cancer stem cell-like properties and overexpression of ABC transporters that mediate drug efflux. Besides, there is emerging evidence that signalling pathways that modulate cell survival and drug metabolism play major roles in the maintenance of multidrug resistance in CRC. This article reviews drug resistance in CRC as a result of alterations in the MAPK, PI3K/PKB, Wnt/β-catenin and Notch pathways.

INTRODUCTION

Colorectal cancer (CRC) is ranked as the most prevalent malignancy globally, after cancers of the lungs and the breast. In 2020 alone, two million new cases of CRC have been estimated worldwide, whereby 940,000 CRC cases potentially result in mortalities (International Agency for Research on Cancer, 2020). Risk factors of CRC are primarily genetic predisposition and environmental influences. As such, the development of CRC epitomizes gene-environment interaction, and multiple aetiologies that have been ascribed to CRC include genetic disorders (familial adenomatous polyposis and Lynch syndrome), family history of sporadic CRC, as well as unhealthy lifestyle (tobacco smoking, physical inactivity and heavy alcohol consumption) (Stigliano et al., 2014; Macrae, 2016; Yurgelun et al., 2017).

The genetic model of CRC carcinogenesis theorizes CRC as an accumulation of a set of driver mutations occurring in genes essential for the growth and differentiation of intestinal epithelium (Fearon & Vogelstein, 1990). Such mutations dysregulate cell signalling events in the intestinal epithelium, leading to CRC progression. Activation of oncogenes (e.g., KRAS
or BRAF) and deletions of tumour suppressor genes (e.g., APC and p53) are known to disrupt cell development which results in uncontrolled cell division and cancer metastasis (Baker et al., 1989; Sansom et al., 2004; Aoki et al., 2007; Raskov et al., 2020).

Individuals diagnosed with CRC are subsequently treated according to the severity of CRC. The treatment options are summarised in Table 1. Surgery is employed to resect early-stage cancer to prevent the metastasis of CRC and its accompanying complications (Rentsch et al., 2016; Dekker et al., 2019). Meanwhile, radiotherapy is often applied as a supplemental treatment before CRC surgery and is targeted towards locally advanced CRC in order to reduce the size of tumour prior to surgery. This renders the surgical procedure less radical and may reduce local relapse (Häfner & Debus, 2016; Ma et al., 2017). On the other hand, systemic treatments of CRC are prescribed when patients suffer from metastatic CRC (mCRC). Systemic treatments can be divided into combination chemotherapy and targeted therapy. In combination chemotherapy, cancer drugs are combined in synergistically to produce more effective cytotoxic effects on the cancer cells (Carethers, 2008; Wolpin & Mayer, 2008). FOLFOX is a standard adjuvant chemotherapy for treating advanced CRC that is made up of folinic acid (leucovorin), oxaliplatin (L-OHP) and 5-fluorouracil (5-FU) (De Gramont et al., 2000). While FOLFOX has been proven effective for treating stage III and IV CRC, FOLFOX might not be suitable for treating high-risk stage II CRC harbouring BRAF V660E mutation with or without microsatellite stable (MSS) status due to a higher chance of tumour relapse after treatment (Seppälä et al., 2015). Clinical trial data also suggests that a 6-month FOLFOX regimen results in significant neurotoxicity for high-risk stage II CRC patients, suggesting the need to reduce the duration of adjuvant chemotherapy for better treatment outcomes (Iveson et al., 2021).

XELOX (also known as CAPOX) is an alternative first-line or second-line treatment for high-risk stage II CRC which comprises capecitabine and oxaliplatin. It has been reported that a 3-month XELOX regimen exhibits a similar curative effect to a 6-month FOLFOX regimen. However, treatment benefits vary according to the patients’ medical condition and side effects of the treatment (Guo et al., 2016; Petrelli et al., 2020; Iveson et al., 2021). Targeted therapy on the other hand involves the use of small-molecule drugs or antibodies to specifically target genes or proteins that drive cancer survival and cancer metastasis (Xie, Chen & Fang, 2020a). In most cases, combination chemotherapy and targeted therapy are employed to treat mCRC after surgical removal of tumours (Kuo et al., 2005; Townsley et al., 2006; Berlin et al., 2007).

**Drug resistance in CRC**

Despite advances in the diagnostics and treatments, the global age-standardised mortality rates of CRC remain high (8.9 per 100,000 population in both sexes) (Siegel et al., 2017; Rawla, Sunkara & Barsouk, 2019). This is mainly due to the development of resistance to the standard chemotherapeutic regimens (5-FU and L-OHP) or combinational treatments (FOLFOX and XELOX) (Swanton, 2012; Weeks et al., 2012; Pai et al., 2017). In such cases, targeted therapeutic agents such as growth factor receptor inhibitors and protein kinase inhibitors are combined with the standard treatments to improve drug efficacy and patients’ response rates (Cunningham et al., 2004; Heinemann et al., 2004; Yeoh et al., 2021).
Table 1  List of treatments available for CRC patients.

| Treatment method                        | Characteristic                                                                 | Reference                                      |
|-----------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------|
| Complete mesocolic excision (CME)       | Surgery that involves removal of the affected colon and its lateral lymphatic supply by cutting the mesentry. | Dimitriou & Griniatsos (2015)                 |
| Single incision laparoscopic surgery (SILS) | Surgery involving the use of one umbilical port.                             | Greaves & Nicholson (2011)                    |
| Natural orifice transluminal endoscopic surgery (NOTES) | Surgery that involves entering the peritoneal cavity via the gastrointestinal tract using a natural orifice. | Kalloo (2007)                                |
| Robotics laparoscopic surgery           | Minimally invasive bowel resections performed by robotic system.             | Giulianotti et al. (2003)                    |
| Short-course radiotherapy               | Procedure regarding patients being exposed to radiation for 1 week with a clinical dosage of 25 Gray in 5 fractions followed by surgery 1 week later. | Pålhmn (1997)                                |
| Long-course chemoradiotherapy           | Procedure that covers radiation exposure for 5 weeks with a clinical dosage of 45–50 Gray in 25–28 fractions together with 5 concurrent fluoropyrimidine-based regimens as radiation sensitiser. This is followed by surgery 4–8 weeks later. | Bosset et al. (2006)                         |
| FOLFOX                                  | Chemotherapeutic regimen involving the use of folic acid, 5-fluorouracil (5-FU) and oxaliplatin to promote DNA cross-linking, hence inhibiting DNA synthesis and eventually induces cell death. | Gramont et al. (2000), Parker & Cheng (1990), Goldberg et al. (2004), Raymond et al. (1998) |
| FOLFIRI                                 | Chemotherapeutic regimen involving the use of folic acid, 5-FU and irinotecan to interfere with DNA uncoiling during DNA replication which ultimately induces cell death. | Klein et al. (2002), Douillard et al. (2000), Salz et al. (2000) |
| Growth factor receptor inhibitors (e.g., Bevacizumab, Cetuximab) | Therapeutic agents designed to target specific pathways supporting cancer proliferation and formation of new blood vessels that allow the spread of mCRC. | Sherwood, Parris & Folkman (1971), Venook (2005) |
| Tyrosine kinase inhibitors (e.g., Gefitinib, Erlotinib, Sorafenib) | Therapeutic agents designed to target tyrosine kinases that mediate downstream signalling events of mCRC. | Huang et al. (2004), Townsley et al. (2006), Wilhelm et al. (2006) |

2014). Nevertheless, CRC patients have also been reported to develop resistance against these targeted therapeutic agents (Chen et al., 2018a; Negri et al., 2019; Vitiello et al., 2019; Rimassa et al., 2019). Hence, cancer drug resistance represents a significant obstacle to the successful treatment of CRC patients.

Drug resistance occurs when a tumour has become insensitive to the prescribed drugs, leading to the emergence of drug-tolerant cancer persister cells which support the growth of cancer cells under treatment pressure (Ramirez et al., 2016; Russo et al., 2019). While intrinsic or primary drug resistance occurs before drug treatment, acquired or secondary drug resistance manifests itself as a gradual reduction in drug efficacy against CRC (Lippert, Ruoff & Volm, 2008). Among the factors culminating in drug resistance, overexpression of ATP-binding cassette (ABC) transporters has been identified as the main driver. ABC transporters function to mediate the efflux of drugs from the tumours, leading to reduced drug concentration and drug efficacy (Giacomini et al., 2010; Hu et al., 2016). On top of that, the development of drug resistance has been attributed to genetic and epigenetic alterations, such as the (i) overexpression and gain-of-function of oncogenes (e.g., epidermal growth factor receptor (EGFR), Kirsten rat sarcoma virus (KRAS)) (Lièvre et al., 2014).
et al., 2006; Misale et al., 2014; Wang et al., 2019; Wang, Zhang & Chen, 2019), (ii) loss-of-function of tumour suppressor genes (e.g., p53, phosphatase and tensin homolog (PTEN)) (Boyer et al., 2004; Frattini et al., 2007; Sartore-Bianchi et al., 2009), (iii) under-expression of cell signalling regulator (e.g., thymidine phosphorylase) (Meropol et al., 2006), and (iv) the change in the binding site of drug target (e.g., topoisomerase I) (Gongora et al., 2011). In addition, the evolution of CRC subclones further complicates CRC treatment due to the limited ability of the cancer therapeutics to counteract the diverse drug resistance mechanisms present in the heterogeneous cancer subpopulations (Molinari et al., 2018; Wang et al., 2019; Wang, Zhang & Chen, 2019).

It has increasingly been acknowledged that various molecular mechanisms contribute to cancer drug resistance, among which the dysregulation of signalling pathways has been shown to play critical roles (Nisar et al., 2020). As such, the study of cell signalling pathways can provide valuable insights into the cancer biology of drug-resistant CRC and improve the treatment strategies (Wan et al., 2020). Previous studies have attributed four major signalling pathways (MAPK, PI3K/PKB, Wnt/β-catenin and Notch) to the development of resistance against CRC treatment (Li et al., 2011; Corcoran et al., 2012; Xu et al., 2017; He et al., 2018). There are significant efforts focusing on delineating tumour evolution and the underlying molecular mechanisms of drug resistance linked to these signalling pathways. Numerous studies have revealed that genetic mutations and/or epigenetic alterations of these pathways contribute to drug resistance (Normanno et al., 2015; Jeantet et al., 2016; Yamada et al., 2020). Apart from that, recent evidence also indicates that resistance of the tumour cells involves highly complex and tightly controlled crosstalk between different signal transduction pathways (Duong et al., 2018). Additionally, emerging findings suggest that signalling related to tumour microenvironment (TME), metabolic reprogramming and gut microbiome are also associated with the development of drug resistance (Lotti et al., 2013; Endo et al., 2020). A summary of the molecular alterations and clinical implications associated with the treatment of CRC is provided in Table 2.

In this review article, we attempt to summarize the gap in knowledge in understanding the link between modulation of the signalling mechanisms due to diverse exogenous and endogenous factors with drug resistance in CRC. We aim to provide current updates related to the dysregulation of the four selected signal transduction pathways and their roles in conferring drug resistance in CRC. In addition, future perspectives pertinent to the involvement of other signalling pathways and resistance mechanisms due to TME, metabolic reprogramming and gut microbiome are also discussed.

**SURVEY METHODOLOGY**

To ensure a thorough and unbiased coverage of the literature, we searched the PubMed database for published articles written in English from 1990 until present. The search strings include “colorectal cancer AND (crosstalk OR communication) AND (signalling OR pathway) AND therapy resistance”, “colorectal cancer AND (monotherapy OR combinational therapy) AND drug resistance AND MAPK pathway”, “colorectal cancer AND (monotherapy OR combinational therapy) AND drug resistance AND PI3K
| Therapeutic agent | Targeted signalling pathway | CRC mutational status | Molecular alteration | Clinical implication | Reference |
|-------------------|-----------------------------|----------------------|----------------------|---------------------|-----------|
| Anti-EGFR antibodies (cetuximab and panitumumab) alone or in combination with chemotherapy | MAPK pathway | Wild-type KRAS | KRAS, NRAS, BRAF and PI3KCA mutations | • Poor prognosis for overall survival  
• Low response rate to anti-EGFR therapy | De Roock et al. (2010), Diaz et al. (2012) |
| Anti-EGFR antibodies (cetuximab, panitumumab, SYM004, MM151, trastuzumab, pertuzumab and duligotuzumab) alone or in combination with chemotherapy | MAPK pathway | Wild-type KRAS, NRAS, BRAF and PI3KCA | • HER2 gene amplification and activating mutations  
• Sustained signalling of PI3K/PKB and MAPK pathways | • Poor therapeutic response  
• Oncogenic transformation of colon epithelial cells | Kavuri et al. (2015), Belli et al. (2019) |
| RAF inhibitor (vemurafenib) | MAPK pathway | BRAF(V600E) | Feedback activation of EGFR | Treatment failure | Prahallad et al. (2012) |
| Combined RAF inhibitors (vemurafenib and cetuximab or vemurafenib and selumetinib) | MAPK pathway | BRAF(V600E) | Reactivation of MAPK pathway | Tumour relapses | Ahronian et al. (2015) |
| RAF inhibitors (GDC-0879 and vemurafenib) | MAPK pathway | BRAF(V600E) | RAF dimerization and MEK/ERK phosphorylation | Enhanced tumour growth | Hatzivassiliou et al. (2010) |
| Vemurafenib | MAPK pathway | KRAS(G13D) | Activation of ERK leads to the activation of Hippo and Rho pathways | Cancer metastasis | Kubiniok et al. (2017) |
| Chemotherapeutic drug (oxaliplatin) | MAPK pathway | Not applicable | miRNA-625-3p-mediated downregulation of MAP2K6 | Cancer progression due to reduced apoptosis. | Rasmussen et al. (2016) |
| Combinational chemotherapeutic drugs (FOLFOX and FOLFIRI) | PI3K/PKB pathway | Not applicable | PIK3CA mutations (E545K, E542K and E545D on exon 9; H1047R and H1047L on exon 20) | LGR5+ CRC stem cells survival and proliferation | Wang et al. (2018) |

(continued on next page)
| Therapeutic agent | Targeted signalling pathway | CRC mutational status | Molecular alteration | Clinical implication | Reference |
|-------------------|-----------------------------|-----------------------|----------------------|---------------------|------------|
| Cetuximab         | PI3K/PKB pathway           | Wild type KRAS and BRAF | PIK3CA mutations on exon 19 (K944N, V955I, F930S, V955G and K966E) | Decrease in progression-free survival | Xu et al. (2017) |
| Cetuximab and panitumumab | • MAPK pathway • PI3K/PKB pathway | Wild type KRAS | BRAF, NRAS, PTEN and PIK3CA mutations | • Poor prognosis for overall survival • Cancer metastasis | Sartore-Bianchi et al. (2009), Laurent-Puig et al. (2009), De Roock et al. (2010) |
| NVP-BEZ235 (dual PI3K/MTOR inhibitor) | • MAPK pathway • PI3K/PKB pathway | Not applicable | KRAS and PIK3CA mutations leads to additive activation of PI3K/PKB pathway | Suppression of BIM-induced apoptosis, which leads to cancer survival | Kim et al. (2013) |
| Chemotherapeutic drug (paclitaxel) | PI3K/PKB pathway | Not applicable | miR-29a-mediated PTEN inhibition | Reduction in drug sensitivity suppress apoptosis which supports cancer growth | Yuan et al. (2018) |
| Chemotherapeutic drug (doxorubicin) | PI3K/PKB pathway | Not applicable | miR-29a-mediated P-gp inhibition and upregulation of PTEN | Enhanced drug sensitivity which thwart cancer growth | Shi et al. (2020) |
| Chemotherapeutic drug (5-FU) | PI3K/PKB pathway | Not applicable | miR-543-mediated PTEN inhibition | Reduced drug sensitivity which supports cancer growth | Liu, Zhou & Dong (2019) |
| Chemotherapeutic drug ( vincristine) | Wnt/β-catenin pathway | Not applicable | Overexpression of Dvl1-3 leads to β-catenin/TCF-induced transcription of ABC transporters (P-gp, MRP2 and BCRP) and anti-apoptotic proteins (Survivin and Bcl-2) | CRC is protected from Vincristine-induced apoptosis which drives cancer growth | Zhang et al. (2017b) |

(continued on next page)
| Therapeutic agent | Targeted signalling pathway | CRC mutational status | Molecular alteration | Clinical implication | Reference |
|-------------------|-----------------------------|----------------------|---------------------|----------------------|-----------|
| 5-FU and oxaliplatin | Wnt/β-catenin pathway | Not applicable | Overexpression of LINC00152 inhibits CK10-dependent β-catenin phosphorylation | •Cancer metastasis •Expression of EMT markers | Yue et al. (2016), Yue et al. (2018), Bian et al. (2017) |
| 5-FU | Wnt/β-catenin pathway | Not applicable | miR-30-5p-mediated inhibition of USP22 and Wnt target genes (Axin2 and c-Myc) | Suppression of cancer stemness and chemoresistance | Ning et al. (2014), Jiang et al. (2019) |
| 5-FU and oxaliplatin | Wnt/β-catenin pathway | Not applicable | LncRNA CRNDE-mediated repression of miR-181a-5p promotes β-catenin/TCF transcriptional activity | CRC cell proliferation and chemoresistance | Han et al. (2017) |
| Small-molecule multi kinase inhibitor (regorafenib) | Notch pathway | Not applicable | Upregulation of Notch-1 and the target genes (HES1 and HEY1) | CRC cell proliferation due to reduced sensitivity to Regorafenib | Mirone et al. (2016) |
| Anti-VEGF antibody (bevacizumab) | Notch pathway | Not applicable | Upregulation of NICD | Cancer stemness | Negri & Ardizzoni (2015), Negri et al. (2019) |
| 5-FU | Notch pathway | Not applicable | HES1-mediated overexpression of ABC transporters (ABCC1, ABCC2 and P-gp1) with depressed E-cadherins and elevated N-cadherins | Tumour relapses | Gao et al. (2014), Sun et al. (2017) |
| Chemotherapeutic drug (methotrexate) | •Notch pathway •Wnt/β-catenin pathway | Not applicable | Dvl-3-related Wnt and Notch crosstalk. | Cancer stemness | Zhao et al. (2020) |
| 5-FU and Irinotecan | •Notch pathway •KRAS/Erk/ADAM pathway | KRAS(G12D, G12A, G13D, Q61L) | Aberrant Jagged1 processing leads to sustained Jag1-ICDs-mediated intrinsic reverse signalling. | Cancer progression and chemoresistance | Van Schaeybroeck et al. (2011), Pelullo et al. (2019) |
| 5-FU | Notch pathway | Not applicable | miR-139-5p-mediated inhibition of Notch-1 and downstream multidrug-resistant genes (MRP-1 and BCL-2) | Increased sensitivity to 5-FU | Liu et al. (2016) |
| 5-FU | Notch pathway | Not applicable | miR-195-5p-mediated inhibition of Notch-2 and RBPJ | Inhibition of cancer stemness and 5-FU resistance | Jin et al. (2018) |
| 5-FU | Notch pathway | Not applicable | miR-34a-mediated ABCG2 inhibition | Enhanced chemosensitivity to 5-FU | Xie, Chen & Fang (2020a), Xie et al. (2020b) |
Regulation of signalling pathways associated with drug resistance in CRC

**Mitogen-activated protein kinase (MAPK) pathway**

The MAPK pathway is mediated by mitogen-activated protein kinases (MAPKs), which comprise a family of serine/threonine-specific protein kinases that regulate a variety of cellular processes and play crucial roles in the pathogenesis of many diseases such as cancer, infection, inflammatory and autoimmune diseases (Kim & Choi, 2010). The MAPK family is divided into several subgroups. Conventional MAPKs are (i) extracellular signal-regulated kinase 1 and 2 (ERK1/2), (ii) c-Jun N-terminal kinases (JNKs), (iii) p38 (also known as MAPK14) and (iv) ERK5, all are summarised in Fig. 1 (Morrison, 2012). Atypical MAPKs comprise ERK3/4, ERK7/8 and Nemo-like kinase (NLK) (Cargnello & Roux, 2011). In the canonical ERK/MAPK signalling pathway, extracellular signals (e.g., growth factors, stress, mitogens) bind to the receptors, most of which are receptor tyrosine kinases (RTKs) at the surface of the cell membrane, leading to auto-phosphorylation of growth factors receptors and recruitment of adaptor proteins (e.g., growth factor receptor-bound protein 2 (GRB2) and son of sevenless 1 (SOS1)) (Morrison, 2012). This in turn results in the switching of the inactivated form of Ras-family GTPase (Ras in GDP bound form, Ras-GDP) to the active form of Ras-family GTPase (Ras in GTP bound form, Ras-GTP). The external signal is then transmitted via Ras-GTP to other downstream phosphorylation targets within the cytoplasm where the signalling cascade converges at the activation of a series of MAPKs, starting from MAPK kinase kinase (MAPKKK, e.g., Raf1) followed by MAPK kinase (MAPKK, e.g., MEK1/2) and MAP kinase (MAPK, e.g., ERK1/2). Finally, the MAP kinase translocates to the nucleus to phosphorylate transcription factors (e.g., c-Jun, STAT1, c-Myc) that regulate transcription of genes for different cellular processes (Wei & Liu, 2002; Fang & Richardson, 2005; Morrison, 2012) (Fig. 1).

In multidrug-resistant CRC, MAPK pathway is often reprogrammed, usually by the overexpression of RTKs, Ras and Raf; or gain-of-function mutations of Ras and Raf, which sustain the activity of MAPK signalling pathway upon treatment with MAPK and RTK inhibitors, 5-FU and oxaliplatin (Wan et al., 2004; Kavuri et al., 2015; Martinelli et al., 2017; Ressa et al., 2018). EGFR has been a favourable target for the treatment of mCRC since the last decade, mainly because they are highly expressed in most human tumours, including CRC (Yarden & Pines, 2012). In particular, monoclonal antibody targeting EGFR, such as cetuximab and panitumumab are widely used to treat mCRC patients due to their initial benefit of improving patients’ survival (Jonker et al., 2007; Vermorken et al., 2008; Pirker et al., 2009). However, some studies have shown that anti-EGFR based
therapy may not be effective in treating mCRC, indicating that a subset of CRC is resistant to the anti-EGFR treatment (Bokemeyer et al., 2009; Van Cutsem et al., 2009). Common molecular mechanisms associated with the resistance are KRAS, NRAS, BRAF and PI3KCA mutations (De Roock et al., 2010; Diaz et al., 2012). In CRC which is quadruple wild-type for KRAS, NRAS, BRAF and PI3KCA genes, HER2 gene amplification and activating mutations at the phosphorylation sites of the catalytic domain have been shown to bypass EGFR blockade by activating a compensatory signalling mechanism for cell survival (Kavuri et al., 2015; Belli et al., 2019). It has been reported that HER2 could form heterodimers with either EGFR or ERBB3 with consequent activation of ERK and Akt signalling respectively, in which the latter has been shown to promote anti-EGFR resistance (Zhang et al., 2014a; Zhang et al., 2014b). Besides, it has been found that aberrant ERBB2 activation could result in the stimulation of ERK 1/2 signalling that mediates cetuximab resistance (Yonesaka et al., 2011).

B-Raf is a MAPKKK that mediates cell growth and differentiation via the ERK/MAPK subfamily of MAPK pathway, in response to growth factors and mitogens (Morrison, 2012). B-Raf mutations, more often BRAF V600E, occur in approximately 8% of CRC and are associated with poor prognosis (Davies et al., 2002; Richman et al., 2009). BRAF V600E
mutation leads to conformational changes at the catalytic domain which renders B-Raf constitutively active, independent of Ras-GTP activation and dimerization with Raf-1 (also known as C-Raf) (Durrant & Morrison, 2018). This results in prolonged phosphorylation and activation of MEK1/2 and ERK1/2 kinases which, in turn, activates downstream substrates that mediate cell growth and survival (Fang & Richardson, 2005). It has been reported that targeting BRAF V600E using mono-therapeutic agents, such as vemurafenib (a B-Raf inhibitor, also known as PLX4032) which binds to the ATP-binding site of BRAF V600E to inhibit its activity, shows limited therapeutic response in CRC (Prahallad et al., 2012). This is because targeting BRAF V600E results in feedback activation of EGFR characterised by enhanced phosphorylation of RAS and CRAF upstream of MAPK pathway and downstream activation of RAF, MEK and ERK (Corcoran et al., 2012). In order to circumvent resistance to B-Raf inhibition, B-Raf inhibitor is used in combination with EGFR inhibitor or MEK inhibitor or both which were initially shown to offer therapeutic benefit of at least 12% response rate to the drugs and improve the suppression of ERK/MAPK pathway (Bendell et al., 2014; Corcoran et al., 2014; Tabernero et al., 2014). Despite the initial success in suppressing B-Raf resistance using the multi-target approach, there is compelling evidence that BRAF V600E mutant CRC patients could also develop resistance to the new treatment (Oddo et al., 2016). Ahronian et al. (2015) has shown that the reactivation of the MAPK pathway confers cross-resistance to the combined RAF/EGFR or RAF/MEK inhibition in BRAF-mutant CRC and further demonstrated that the use of ERK inhibitor could overcome the resistance by suppressing the MAPK signalling.

On the other hand, it has been reported that treatment using ATP-competitive inhibitors produces opposing mechanisms of action that is dependent on the cellular context and genotype of the tumour. It was found that RAF inhibitors effectively block MAPK pathway in BRAF V600E cells but activate the MAPK pathway in wild-type BRAF tumours by inducing RAF dimerization and MEK/ERK phosphorylation leading to enhanced tumour growth, suggesting that other strategies to block RAF activation are needed to improve the treatment efficacy (Hatzivassiliou et al., 2010). Furthermore, RAS mutant tumours are also known to exhibit poor response to RAF inhibitors. A time-course phosphoproteomic analysis of vemurafenib-treated RAS mutant CRC cell lines has found potential cross-talk between ERK signalling with Hippo and Rho pathways and revealed novel functional targets downstream of ERK (Kubiniok et al., 2017).

Apart from post-translational regulation of proteins as a regulatory checkpoint for cellular signalling, microRNAs (miRNAs) also exhibit a functional role in the regulation of MAPK pathway in CRC drug resistance (Rasmussen et al., 2016; Angius et al., 2019). A previous miRNA profiling study has uncovered the link between high expression of miRNA-625-3p and poor clinical response towards oxaliplatin-based therapy (Arango et al., 2004; Rasmussen et al., 2013). Mechanistically, it has been demonstrated that miRNA-625-3p mediates oxaliplatin resistance by targeting MAPK kinase MAP2K6 and abrogates MAPK14 signalling, leading to increased cell cycle progression and reduced apoptosis (Rasmussen et al., 2016).

As one of the most frequently altered signalling pathways and its important roles in CRC drug resistance, MAPK pathway represents a promising target for cancer therapy.
Significant progress has been made on the development of therapeutics targeting MAPK kinases with considerable clinical success (Bendell et al., 2014). Notably, the combination of BRAF and MEK inhibitors has been shown to improve response rates and may offer potential therapeutic benefit in BRAF-mutated CRC (Corcoran et al., 2014). Nevertheless, it is clear that we are still far from any complete understanding of the MAPK pathway. Moreover, the emergence of new resistance mechanisms prompts more further research to provide a deeper understanding on the complex regulation and interconnectivity of the underlying biological processes to overcome resistance and increase therapeutic efficacy.

**Phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, also known as AKT) pathway**

The PI3K/PKB pathway regulates cell metabolism, cell growth and cell survival. In normal condition, PI3K/PKB pathway is activated by four major sensors upstream of the pathway, namely (i) receptor tyrosine kinases (RTKs) which bind to growth factors (Hemmings, 1997), (ii) cytokine receptors (Chang et al., 2003), (iii) G protein-coupled receptors (GPCRs) that are activated by various biological molecules (Murga et al., 1998), and (iv) integrins which detect cell–cell or cell–matrix communication (Su et al., 2007). Upon ligand binding, these receptors, together with their cofactors, will activate PI3K family proteins. There are three classes of PI3K family proteins, among which only class I PI3Ks and the signalling networks they regulate are covered in this review (Fig. 2). Information about Class II and Class III PI3Ks and their roles in cellular signalling are covered in other reviews or journal articles (Falasca & Maffucci, 2012; Okkenhaug, 2013; Backer, 2016; Hawkins & Stephens, 2016). Within the class I PI3K subfamily itself, there are four catalytic isoforms (p110α, p110β, p110γ and p110δ encoded by PIK3CA, PIK3CB, PIK3CG, and PIK3CD respectively) which catalyse the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) to phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) or PIP3. p110α and p110β are expressed ubiquitously while p110γ and p110δ are expressed in immune cells. Each catalytic isoform forms a dimer with a regulatory subunit that controls the activity and subcellular localisation of the PI3K complex (Fig. 2). In response to specific external stimuli, PIP3, which acts as a secondary messenger, will recruit cytoplasmic proteins with PIP3 binding domains (typical examples of which are phosphoinositide-dependent kinase-1 (PDK1) and PKB) to specific cell membrane locations. Shortly after the transmission of the signal to downstream effectors, PIP3 is then metabolised by phosphatase and tensin homolog (PTEN), which is a tumour suppressor that negatively regulates the PI3K signal by removing 3’-phosphate from PIP3 (Danielsen et al., 2015; Fruman et al., 2017). Activation of PKB is a two-step process, whereby PDK1 phosphorylates PKB on threonine-308 to partially activate PKB (Alessi et al., 1997), followed by phosphorylation of PKB by mTORC2 on serine-473 to fully activate PKB (Sarbassov et al., 2005). The activated PKB will subsequently regulate the phosphorylation of the target substrates (the most well-known examples are glycogen synthase kinase 3 beta (GSK3β), BCL2-antagonist of death (BAD), mouse double minute homolog 2 (MDM2), forkhead box O (FOXO) and mechanistic target of rapamycin complex (mTORC1)) which mediate important cellular functions, such as glucose uptake, protein synthesis, cell survival and cell cycle progression (Manning Yeoh et al. (2021), *PeerJ*, DOI 10.7717/peerj.12338)
The activity of PKB is also negatively regulated by protein phosphatase 2A (PP2A), PH domain leucine-rich repeat protein phosphatase 1/2 (PHLPP1/2) and carboxyl-terminal modulator protein (CTMP) (Hemmings & Restuccia, 2012) (Fig. 2). In multidrug-resistant CRC, PI3K signalling is prolonged by PIK3CA mutations, null mutation of PTEN, and RAS mutations upon treatment with standard chemotherapeutic drugs and targeted therapeutic agents (Laurent-Puig et al., 2009; De Roock et al., 2010; Kim et al., 2013; Hamada, Nowak & Ogino, 2017).

PIK3CA is regarded as one of the most frequently mutated genes in CRC, which accounts for approximately 10–30% of all CRC cases (Samuels et al., 2004; Velho et al., 2005; Hamada, Nowak & Ogino, 2017). It is reported that non-random somatic mutations occurring in the coding region, mainly exon 9 (helical domain) and exon 20 (catalytic domain), have heightened basal PI3K and PKB activities which then promote cancer progression (Kang, Bader & Vogt, 2005; Ikenoue et al., 2005). Furthermore, it has been shown that PIK3CA mutations (E545K, E542K and E545D on exon 9; H1047R and H1047L on exon 20) could mediate resistance to standard chemotherapy (FOLFOX and FOLFORI) by inducing phosphorylation of PKB and expression CRC stem cell markers (LGR5) via sustained PI3K signalling, thereby promoting cancer cell survival and proliferation (Wang & Cantley, 2007).
Interestingly, PIK3CA mutations have also been found to mediate acquired cetuximab resistance in mCRC complementary to the previously reported RAS mutations. A recent circulating tumour DNA sequencing analysis from mCRC patients has revealed five novel mutations on exon 19 of PIK3CA (K944N, V955I, F930S, V955G and K966E) that may potentially drive resistance to cetuximab via EGFR-mediated activation of the PI3K/PKB signalling pathway, suggesting that combined regimens of PI3K/mTOR inhibitors (PP242 and NVP-BEZ235) with anti-EGFR therapy may be beneficial to overcome the resistance (Xu et al., 2017).

Apart from PIK3CA mutations, there is increasing evidence of the emergence of mutations involving components of MAPK and PI3K/PKB signalling pathways when treated with targeted therapeutic agents (De Roock et al., 2010; Vitiello et al., 2019). Although anti-EGFR based therapy is commonly prescribed for KRAS wild-type CRC patients, clinical evidence has indicated that the KRAS mutation status alone is insufficient to predict therapeutic response to the therapy (Allegra et al., 2009). Retrospective cohort studies of CRC cases have identified several key players in the EGFR signalling pathway (which is a signalling network shared by both MAPK and PI3K/PKB pathways) that hinder the effectiveness of anti-EGFR monoclonal antibodies in KRAS wild-type CRC patients (Sartore-Bianchi et al., 2009; Laurent-Puig et al., 2009; De Roock et al., 2010). It has been previously reported that BRAF, NRAS, PTEN and PIK3CA mutations are associated with the efficacy and clinical outcome of EGFR-targeted therapy but their exact roles in driving the resistance are still unclear (Laurent-Puig et al., 2009; De Roock et al., 2010). Surprisingly, KRAS mutations also negatively affect the outcome of treatment against PIK3CA mutant CRC. Kim et al. (2013) have shown that KRAS and PIK3CA mutations attenuate sensitivity to treatment with a dual inhibitor of PI3K and mTOR by suppressing BIM-induced apoptosis via activation of PI3K/MTOR pathway, leading to cell survival.

More recently, miRNAs have also been reported to control CRC pathogenesis via the modulation of PI3K/PKB pathway (Soleimani et al., 2019). Based on previous studies, it has been shown that miR-29a could induce or suppress tumour progression in drug-resistant cancer cells (Zhong et al., 2013; Liu et al., 2018). Yuan et al. (2018) showed that higher level of miR-29a is expressed in CRC cell lines resistant to paclitaxel which resulted in downregulation of PTEN and upregulation of phosphorylated AKT. This suggests that miR-29a has a regulatory function to PI3K/PKB pathway via inhibition of PTEN which reduces drug sensitivity and supports cancer growth. In contrast, miR-29a could potentially reduce P-gp-mediated chemoresistance via modulation of PTEN and P-gp expression in doxorubicin-resistant CRC cell lines. This means that miR-29a exerts tumour suppressive function by inhibiting membrane transporter activity through PI3K/PKB pathway (Shi et al., 2020). These seemingly contradictory roles of miR-29a have also been observed in other malignancies. In the context of regulation of drug resistance, miR-29a has been reported to increase sensitisation to gemcitabine in pancreatic cancer cells (Kwon et al., 2016) as well as sensitization to tamoxifen in breast cancer cells (Muluhngwi et al., 2017). On the other hand, miR-29a was shown to play a role in mediating adriamycin resistance in breast cancer cells via inhibiting the PTEN/AKT/GSK3β pathway (Shen et al., 2016). It is unclear whether the opposing results are due to heterogeneity in the cancer cells.
or that miR-29a could exhibit multifaceted functions in a context dependent manner. Nevertheless, these paradoxical findings demand the need for further work to clarify and elucidate the function of miR-29a more comprehensively. Similar to miR-29a, miR-543 has recently been identified as the mediator of chemoresistance in CRC cells, also by suppressing the expression of PTEN which activates PI3K/PKB pathway (Liu, Zhou & Dong, 2019). Interestingly, miR-4689 which has been identified as a negative regulator of KRAS and AKT is downregulated in KRAS mutant CRC cells and confers resistance to molecular-targeted therapy, suggesting that miR-4689 could be a promising therapeutic agent to control multidrug resistance in CRC via modulation of PI3K/PKB pathway and MAPK pathway (Hiraki et al., 2015).

Taken together, current evidence clearly shows that mutations of the MAPK/PI3K/PKB signalling pathway components are frequently observed in cancer drug resistance. However, the signalling mechanisms associated with these mutations are still not well elucidated which necessitate further investigation. Importantly, distinct molecular events that regulate drug resistance such as in KRAS wild-type and mutant CRC suggests the importance of identifying relevant drug targets in CRC with different mutational status. Moreover, future research should also focus on dissecting the link of miRNAs with cancer drug resistance and their underlying molecular mechanisms.

**Wnt/β-catenin pathway**

The Wnt/β-catenin pathway is an evolutionarily conserved system that regulates cell development, cell differentiation, cell proliferation and cell migration. The Wnt/β-catenin pathway can be grouped into β-catenin-dependent Wnt pathway (canonical Wnt pathway) and β-catenin-independent Wnt pathway (non-canonical Wnt pathway) which are further divided into the planar cell polarity Wnt pathway and the Wnt/Ca²⁺ pathway (Komiya & Habas, 2008). The canonical Wnt/β-catenin pathway is made up of the membrane proteins, degradation complex and β-catenin protein. In the absence of Wnt ligands, the degradation complex which comprises of adenomatous polyposis coli (APC), Axin, GSK3 and CK1α is formed through phosphorylation of Axin and APC by GSK3 and casein kinase 1α (CK1α). As a result, β-catenin is ubiquitinated by E3-ligase protein βTrCP (β-transducin repeats-containing proteins) through phosphorylation and targeted for proteasomal degradation (Van Kappel & Maurice, 2017) (Fig. 3). In the presence of Wnt ligands, lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptor and Frizzled (Fzd) receptor are activated which leads to phosphorylation of LRP5/6 co-receptors and binding of adaptor protein disheveled (Dvl) to the phosphorylated LRP5/6. This is followed by the recruitment of the remaining degradation complex components to the Fzd-LRP5/6 complex to inactivate the degradation complex (Janda et al., 2012) (Fig. 3). The molecular mechanism for Wnt-mediated degradation complex inactivation is still heavily disputed due to conflicting findings on the inhibition of GSK3 in the presence of Wnt signal. Several models have been proposed: (1) blockade of GSK3 catalytic site by binding to the phosphorylation motif of LRP5/6 (Wu et al., 2009). (2) Wnt-mediated dissociation of APC from GSK3 (Valvezan et al., 2012). (3) sequestration of GSK3 in endosomal vesicles through endocytosis of Fzd-LRP5/6 complex (Taelman et al., 2010). Disruption of the degradation
complex integrity in the presence of Wnt signal promotes stabilisation of β-catenin, leading to accumulation of newly synthesised β-catenin in the cytoplasm and their subsequent translocation to the nucleus. Interestingly, it is also known that, in the presence of Wnt signal, the degradation complex could remain intact to target β-catenin for degradation via phosphorylation, but ubiquitination of β-catenin is impaired which inhibits its degradation by the degradation complex (Gerlach et al., 2014). Within the nucleus, β-catenin binds to T-cell factor/lymphoid enhancing factor (TCF/LEF) which are the transcription factors that activate Wnt-responsive genes required for cell growth and survival (e.g., c-Myc, Cyclin D1). In addition, β-catenin interacts with TCF/LEF to recruit transcriptional co-activators (p300/CBP and BCL9) to the transcription factors to activate gene expression (Kretzschmar & Clevers, 2017; Taciak et al., 2018) (Fig. 3). In multidrug-resistant CRC, Wnt/β-catenin pathway is reprogrammed by overexpression of Dvl protein and non-coding RNAs that interfere with the activities of downstream signalling mediators (Yue et al., 2016; Han et al., 2017; Bian et al., 2017; Zhang et al., 2017b; Jiang et al., 2019).

Dysregulation in the key Wnt/β-catenin pathway components such as upstream regulator (Dvl protein), β-catenin degradation complex and its downstream targets

Figure 3  Deregulation of the canonical Wnt/β-catenin signalling pathway during CRC treatment. Left-hand-side of the figure describes signalling events in the absence of the Wnt signal (OFF). Right-hand-side of the figure describes signalling events in the presence of the Wnt signal (ON). Region highlighted blue represents Wnt target genes that regulate the biological processes of CRC cells treated with drug therapy.
(β-catenin and TCF/LEF) instigate tumour progression in many types of cancer (Van Kappel & Maurice, 2017). Moreover, recent studies indicate that aberrant Wnt/β-catenin signalling could trigger anti-cancer drug resistance (Zhang et al., 2017a). Zhang et al. (2017b) reported that DVL1-3 proteins are overexpressed in CRC resistant to vincristine (a chemotherapeutic drug that interferes with microtubule synthesis leading to cell cycle arrest) which results in overexpression of ABC transporters (P-glycoprotein (P-gp), MRP2 and BCRP) and anti-apoptotic proteins (Survivin and Bcl-2). Contrary to previous findings which suggest that DVL promotes β-catenin accumulation and subsequent translocation to the nucleus, it was found that DVL1-3 translocate to the nucleus and bind to β-catenin to form a transcriptional complex, independent of β-catenin accumulation and nuclear translocation (Gao & Chen, 2010; Shang, Hua & Hu, 2017). Moreover, the study also showed that silencing DVL1-3 could re-sensitise CRC cells to vincristine, 5-FU and oxaliplatin, suggesting that DVL could be a potential therapeutic target in multidrug-resistant CRC.

It has been increasingly recognised that long non-coding RNA (lncRNA, a non-coding regulatory RNA with greater than 200 nucleotides in length) regulates Wnt/β-catenin pathway in multidrug-resistant CRC (Ma et al., 2016; Lu et al., 2017). Recent studies have shown that lncRNA cytoskeleton regulator RNA (CYTOR, also known as LINC00152) is overexpressed in CRC which confers resistance to oxaliplatin-induced apoptosis (Yue et al., 2016). In addition, elevated expression of LINC00152 is also observed in CRC that gives rise to 5-FU resistance and cancer metastasis (Bian et al., 2017). However, the regulatory mechanism of LINC00152 in the Wnt/β-catenin pathway of mCRC is still unknown (Yue et al., 2016). In a recent study, Yue et al. (2018) demonstrated that LINC00152 competitively binds to β-catenin to prevent CK1α from phosphorylating β-catenin. As a result, β-catenin accumulates and translocates to the nucleus to activate the expression of epithelial-mesenchymal transition (EMT) markers (N-cadherin and Vimentin) which are hallmarks of metastatic cancer. Reciprocally, β-catenin/TCF4 transcriptional complex promotes the expression of LINC00152 to sustain Wnt/β-catenin signalling in mCRC.

Likewise, miRNA is also known to influence cancer growth and the sensitivity of cancer cells towards anti-cancer drugs (Jansson & Lund, 2012; Piletić & Kunej, 2016). Jiang et al. (2019) have demonstrated that overexpression of miR-30-5p negatively regulates the expression of Wnt/β-catenin pathway target genes (Axin2 and c-Myc) and inhibits chemoresistance in CRC cells by targeting ubiquitin-specific peptidase 22 (USP22). Mechanistically, it has been reported that USP22 induces β-catenin nuclear localisation and upregulates FoxM1 expression to promote G1/S cell cycle transition and cell proliferation (Ning et al., 2014). In another study conducted by Chen et al. (2019), miR-103/107 has been shown to repress the activity of Axin2 leading to sustained activation of Wnt/β-catenin signalling that potentiates cancer stemness and chemotherapeutic resistance. Nevertheless, despite that non-coding RNAs such as lncRNA and miRNA are known to promote resistance to therapeutic agents in CRC, the interaction network between LncRNA and miRNA is not well defined (Gao et al., 2019). Han et al. (2017) has reported that lncRNA Colorectal Neoplasia Differentially Expressed (CRNDE) binds to miR-181a-5p to repress its expression, resulting in increased levels of its downstream targets β-catenin and
transcription factor TCF4 in the Wnt/β-catenin signaling pathway. It was also demonstrated that CRNDE knockdown and miR-181a-5p overexpression inhibit Wnt/β-catenin signaling and could reduce chemoresistance and attenuate cell proliferation in CRC cells, suggesting that it could be a novel cancer therapeutic strategy.

Over the years, substantial efforts have been directed to studying the molecular mechanisms and functional effects of Wnt signalling pathway. Accumulating studies confirm the critical role Wnt signalling in drug resistance and convey important insights into its underlying mechanisms that confer resistance to different therapies. Notably, such knowledge could be potentially harnessed to facilitate the development of specific inhibitors or drug combinations to improve anticancer efficacy. Nevertheless, owing to the complexity of Wnt signalling, there are still numerous details remain be uncovered with regard to its connections to therapy resistance that warrant further investigation.

**Notch pathway**

Similar to other signalling pathways (Wnt/β-catenin, Hedgehog (Hh), and transforming growth factor-beta (TGF-β)/bone morphogenic protein (BMP)), the Notch pathway is highly conserved across species and is known to control cell development, apoptosis, cell differentiation and proliferation (Artavanis-Tsakonas, Rand & Lake, 1999). Notch receptors (Notch 1–4) are synthesised as precursors from mRNAs (known as pre-Notch receptor) which then undergo fucosylation (a type of glycosylation) in the endoplasmic reticulum. In the Golgi apparatus, Notch receptors are further modified by enzymes (one typical example is Fringe) and cleaved at site 1 (S1) by furin-like convertase to induce heterodimerisation of Notch receptors (Siebel & Lendahl, 2017) (Fig. 4). At the cell surface, Notch receptors bind to Notch ligands (e.g., Jagged1, Jagged2, Delta-like ligand 1 (Dll1), Delta-like ligand 3 (Dll3) and Delta-like ligand 4 (Dll4)) of neighbouring cells. This initiates subsequent cleavages of Notch receptors by ADAM10/17 metalloproteases and presenilin–γ-secretase enzyme complex at the outer side (site 2 (S2)) and inner side (site 3 (S3)) of the cell membrane (Bray, 2006) (Fig. 4). The end product of the proteolytic cleavages of Notch receptors known as Notch intracellular cleaved domain (NICD, an active form of the molecules which acts as transcriptional activators), travels to the nucleus to displace co-repressors (e.g., recombining binding protein J-kappa (RBPIκ) or CSL) and interacts with transcriptional co-activators (e.g., mastermind-like (MAML), histone acetyltransferase (HAT), p300), in order to activate the transcription of Notch target genes (e.g., Hes and Hey family proteins, cyclin D3, c-Myc). Notch signalling is terminated when the intracellular domain of Notch (ICN or NICD) is targeted for proteasomal degradation through a ubiquitin pathway (Vinson et al., 2016; Siebel & Lendahl, 2017) (Fig. 4). In multidrug-resistant CRC, cross-regulation of signalling pathways, post-transcriptional regulation and overexpression of genes in the Notch signalling pathway are among the common mechanisms underlying the development of resistance towards targeted or chemotherapeutic regimens (Rodilla et al., 2009; Majidinia et al., 2018; Negri et al., 2019).

There is growing evidence that upregulation of Notch receptors, Notch ligands and Notch target genes could lead to the maintenance of CRC stem cell populations and the acquisition of metastatic phenotype which are strongly related to poor survival of CRC.
patients and drug resistance (Mohamed et al., 2019; Weber et al., 2019; Shaik et al., 2020). It has been previously reported that Notch-1 signalling pathway induces EMT in non-small cell lung cancer resistant cells with acquired resistance to EGFR tyrosine kinase inhibitor, suggesting that Notch signalling may contribute to cancer drug resistance (Xie et al., 2013). In another study, Mirone et al. (2016) has reported that CRC cells that are resistant to regorafenib (a small-molecule multi kinase inhibitor) showed significant upregulation of Notch-1 and the target genes (HES1 and HEY1). The study demonstrated that knockdown of Notch-1 could partially restore the sensitivity to regorafenib and inhibit cell growth, indicating that Notch-1 may play a role in tumour resistance. In mCRC patients treated with bevacizumab-based therapy, high NICD expression was found to be associated with poorer response whereas no correlation was observed between Dll-4 expression and clinical response (Negri & Ardizzoni, 2015). In a follow-up study, Negri et al. (2019) has shown that high expression levels of NICD and CD44 are linked to cancer stemness in patients with advanced CRC treated with bevacizumab. Notably, the study demonstrated that NICDs (the functional components of Notch signalling pathway) instead of Dll-4 induce resistance to anti-angiogenic therapy in CRC via activation of Notch-induced regulation of colon cancer stem cells. Nevertheless, the functional roles of NICDs and CD44s in the CRC microenvironment during anti-angiogenic treatment are still unclear (Negri et al., 2019). HES1, which is a downstream target of Notch pathway and one of the important markers of CRC stem cells, is known to contribute to tumour relapses in CRC patients after
5-FU based chemotherapy, but the role of HES1 in chemoresistant CRC has not yet been elucidated (Gao et al., 2014). A recent study by Sun et al. (2017) has shown that HES1 modulates gene expression related to drug metabolism and EMT, notable overexpression of ABC transporters (ABCC1, ABCC2 and P-gp1) with depressed E-cadherins and elevated N-cadherins in CRC cell lines treated with 5-FU, supporting the crucial role of HES1 in promoting chemoresistance.

miRNAs are known to regulate Notch signalling pathway which results in various tumour pathology, such as metastasis, tumour relapses, cancer stemness and low survival rate (Majidinia et al., 2018; Khan et al., 2019). Recently, accumulating evidence also suggests that cross-regulation between miRNAs and Notch signalling pathway plays a critical role in cancer drug resistance. miR-139-5p is a tumour suppressor that has been found to be frequently downregulated in CRC (Shen et al., 2014). It has been reported that miR-139-5p targets Notch-1 and regulates its signal transduction to exert tumour suppressive effect in CRC (Zhang et al., 2014b). Furthermore, miR-139-5p/Notch-1 signalling has also been correlated with drug resistance in CRC. Liu et al. (2016) has shown that miR-139-5p sensitises CRC cells to 5-FU by inhibiting Notch-1 and its downstream multidrug-resistant genes (MRP-1 and BCL-2). Similarly, miR-195-5p is known to suppress cancer growth by inhibiting cell cycle progression, cell proliferation and cell migration (Luo et al., 2014). A recent study by Jin et al. (2018) has revealed that miR-195-5p could inhibit CRC cell stemness and 5-FU resistance by targeting the Notch signalling proteins Notch-2 and RBPJ, suggesting that miR-195-5p could be a potential therapeutic target in chemoresistance. On the other hand, a recent study by Xie et al. (2020b) reported that miR-34a could negatively regulate multidrug resistance protein ABCG2 via DLL1-mediated Notch signalling pathway and demonstrated that overexpression of miR-34a could overcome 5-FU resistance in CRC cells.

Overall, these findings suggest the critical role of Notch signalling pathway in cancer drug resistance. Notably, recent evidence indicates that Notch contribute to the maintenance of CRC stem cells and resistance to therapeutic agents, hence targeting Notch pathway may hold a promising prospect for cancer therapy. Thus, further studies are needed to elucidate the underlying mechanisms and the crosstalk between Notch and other signalling pathways to facilitate the design of better therapeutic approach.

Crosstalk of signalling pathways

Besides deregulated signalling events mediated by single pathway during CRC treatment, the pathological link between the crosstalk of signalling pathways and the acquisition of drug resistance in CRC has also been documented in numerous studies (Fig. 5) (Hiraki et al., 2015; Ahmed et al., 2015; Zou et al., 2017; Mesange et al., 2018). It has been shown that MAPK-mediated pathway interacts with other signalling pathways to induce drug resistance in CRC (Watanabe et al., 2011). Tyrosine kinase inhibitors such as gefitinib (EGFR inhibitor) desensitises CRC cells to the antitumour effect of the drugs by promoting the heterodimerisation of EGFR and IGF1Rβ, leading to cross-regulation of the IGFR1β and MAPK signalling pathways (Yang et al., 2011). The EGFR signalling pathway has also been reported to cooperate with the MAPK signalling pathways mediated by RTKs (MET, Axl, Yeoh et al. (2021), PeerJ, DOI 10.7717/peerj.12338

19/55
and IGF1R) to promote resistance against EGFR inhibitors such as cetuximab (Hu et al., 2016). In addition to MAPK-based signalling involving RTKs, KRAS-mediated activation of the MAPK signalling pathway in CRC has also been demonstrated to confer resistance to MEK inhibition by instigating STAT1 phosphorylation and the activation of IFN/STAT signalling (Sakahara et al., 2019). Additionally, research findings also suggest that BRAF V600E regulates the crosstalk of the KRAS-mediated MAPK signalling pathway with other signalling pathways in multidrug-resistant CRC (He et al., 2018; Duong et al., 2018). BRAF V600E promotes the expression of endosomal protein CEMIP via a β-catenin-dependant pathway that sustains ERK1/2 activation after MEK1 inhibition. The crosstalk between the Wnt/β-catenin and MAPK signalling pathways that involves CEMIP enhances the expression of c-Myc to promote cell survival (Duong et al., 2018). Inhibition of mTORC1 in BRAF V600E CRC has also been shown to disrupt the S6K1-IRS-2/PI3K negative feedback loop, leading to ERK-dependant Mcl-1 stabilisation which blocks apoptosis (He et al., 2018).

On the hand, several reports have shown that there is crosstalk between Notch and other signalling pathways that are involved in the development of chemoresistance. It has been demonstrated that Notch-1 signalling pathway could activate Wnt/β-catenin pathway by
NICD-1-mediated translocation of β-catenin to the nucleus upon binding of Notch-1 to its ligands (Ishiguro et al., 2017). On the other hand, it has been reported that the activation of Notch signalling pathway in CRC cell lines is mediated by β-catenin through up-regulation of Jagged1 (Rodilla et al., 2009). Furthermore, it has been shown that β-catenin promotes the expression of Jagged2 in CRC and contributes to tumour resistance to chemotherapy through modulation of p21 (Vaish, Kim & Shim, 2017). Besides, it has been reported that Notch and Wnt pathways were both upregulated and associated with the development of chemoresistance in CRC cells by upregulating HES1 expression (Kukcinaviciute et al., 2018). Interestingly, a recent study has revealed that Dvl scaffold protein acts as a key regulator of the Wnt and Notch crosstalk (Zhao et al., 2020). Findings from the study highlighted that Dvl-3 might have a functional role in the acquisition of Methotrexate (MTX, an inhibitor of the dihydrofolate reductase (DHFR) enzyme) resistance and stem cell-like properties in CRC cell lines, although the mechanistic details of the resistance still remain unknown. Also, it has been found that Notch pathway could mediate chemoresistance via crosstalk with KRAS pathway. It has been previously reported that KRAS mutations regulate growth factor shedding following chemotherapy treatment via the MEK/Erk/ADAM17 signalling axis and contribute to drug resistance in CRC tumours (Van Schaeybroeck et al., 2011). In a recent study conducted by Pelullo et al. (2019), it has been demonstrated that Jagged-1-ICDs (Jag1-ICDs) are produced by aberrant Jagged1 processing via KRAS/Erk/ADAM pathway in CRC tumours with mutant KRAS. The study highlighted a novel role of Jag1-ICD beyond the canonical Notch signalling in mediating the oncogenic KRAS pathway, which promotes malignant behaviour and confers chemoresistance to CRC cells.

Besides the crosstalk between the Wnt/β-catenin and Notch signalling pathways, research evidence also suggests that TGFβ1 induces the expression of FOXQ1 to promote the nuclear translocation of β-catenin. FOXQ1-mediated crosstalk of the Wnt/β-catenin and TGFβ1 signalling pathways results in resistance to chemotherapy drug-induced apoptosis, EMT and tumour invasion (Peng et al., 2015). In view of the importance of the crosstalk of signalling pathways in CRC drug resistance, future research therefore should aim to identify key regulators that mediate the such interaction to provide a holistic view of the resistance mechanism.

**CHALLENGES AND FUTURE PERSPECTIVES**

A variety of signalling pathways have also been demonstrated to induce drug resistance in CRC, other than the four signal transduction pathways discussed above (Lazzari et al., 2019; Kadioglu et al., 2021). For example, the activation of Hedgehog (Hh)-GLI pathway has been found to mediate the acquisition of chemoresistance via GLI-induced upregulation of ABC transporters in CRC (Po et al., 2020). It has also been reported that bone morphogenetic protein-2 (BMP-2) signalling activates STAT3 and promotes EMT and colon cancer stemness in CRC, which contribute to drug resistance (Kim et al., 2015). Likewise, studies have also suggested that Smad3/4 and IFN play important role in regulating multidrug-resistant CRC via STAT signalling (Moon et al., 2015; Sakahara et al., 2019). Some studies also feature other signalling events such as Hedgehog signalling in CRC.
during chemotherapy or molecular-targeted therapy, implying the underlying complexity of signalling mechanisms in multidrug-resistant CRC (Tang et al., 2018; Park et al., 2019).

On top of non-coding RNAs-based regulation of therapeutic resistance in CRC, epigenetic changes that involve DNA methylation and histone modifications have also increasingly been reported (Shen et al., 2018; Mahalakshmi, Husayn Ahmed & Mahadevan, 2018; Porcellini et al., 2018; Rezapour et al., 2019). For instances, hypermethylation of genes such as MEIS2, SLFN11 and B4GALT1 are associated with cancer progression and resistance to chemotherapy (cisplatin or oxaliplatin-based therapy) and anti-EGFR therapy (Baharudin et al., 2017; He et al., 2017; Picardo et al., 2019; Wang et al., 2019). Mechanistically, DNA methylation regulates the expression of miRNAs which influence the activity of signalling proteins in CRC with MSI-H to initiate anti-cancer drug resistance and cancer development (Shi et al., 2018). In addition, the regulatory function of histone methylation in multidrug-resistant CRC is also documented in studies that report the relationship between H3K27me3 level and oxaliplatin-induced apoptosis (Wang et al., 2020b), as well as the cancer-driving nature of histone methyltransferase SETDB1 in CRC resistant to cetuximab (Hou et al., 2020).

Besides cell-autonomous mechanisms of drug resistance, the association between tumour microenvironment (TME)-driven CRC pathogenesis and therapeutic failure has also been detailed in various studies (Hu et al., 2020; Ren et al., 2018; Hu et al., 2019; Jackstadt et al., 2019). Cancer-associated fibroblasts (CAFs), which constitute a main cellular component of the TME, have been identified as a key mediator of drug resistance in CRC by transferring exosomes to CRC cells (Kahlert & Kalluri, 2013; Herrera et al., 2018). Research evidence suggests that the transportation of exosomal miR-92a-3p from CAFs to CRC activates the Wnt/β-catenin pathway and inhibits mitochondrial apoptosis by targeting FBXW7 and MOAP1, contributing to cancer progression and chemotherapy resistance (Hou et al., 2019). The crosstalk between CAFs and CRC also involves the transfer of exosomal lncRNA H19 from CAFs to CRC cells (Ren et al., 2018). H19 activates the Wnt/β-catenin pathway by acting as a RNA sponge for miR-141, which inhibits the stemness of CRC cells (Ren et al., 2018). Correspondingly, exosomes derived from CRC cells also contain factors essential for reprogramming normal colonic fibroblast into CAFs which may in turn lead to chemoresistance in CRC (Rai et al., 2019). Potential strategies for CAFs-induced drug resistance in CRC include (i) suppressing the transformation of CAFs using small-molecule MSI-N1014 (Yadav et al., 2020), (ii) blocking tumoral IL1β-mediated signalling in normal colonic fibroblasts to thwart inflammatory CAF activation (Díaz-Maroto et al., 2021), and (iii) selective targeting of CAFs by engineered nanoparticles loaded with pro-apoptotic drug (Sitia et al., 2021). However, the failure to identify CRC subclones that mediate functional reprogramming of CAFs remains a big therapeutic hurdle for treating drug resistance in CRC that needs to be addressed. Furthermore, the components within the TME have also been reported to interact via multiple signal transduction pathways to confer drug resistance in CRC (Margolin et al., 2011). Paracrine signalling initiated by IL-17 derived from T\(_{H}17\) cells involves the crosstalk of the ERK pathway and NF-κB pathway to induce G-CSF expression, leading to the recruitment of immature myeloid cells to the TME and tumour resistance to anti-angiogenic therapy (Chung et al., 2013). Noncanonical
TGFβ pathway interacts with PI3K/PKB pathway to sustain fibroblast activation during molecular-targeted treatment that inhibits IL-1β/TGF β signalling (Díaz-Maroto et al., 2019).

In recent decades, in addition to the conventional chemotherapy and targeted therapy, immunotherapy such as immune checkpoint blockade (ICB) has emerged as a promising strategy for cancer therapeutic. ICB works by inhibiting immune checkpoints to facilitate the activation of cytotoxic T cells and enhance anti-tumour immune response (Dosset et al., 2018; Woolston et al., 2019). The acquisition of resistance against ICB therapy, including those targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1), is well documented in numerous studies but the underlying mechanisms are still not well characterized (Gurjao et al., 2019; Liao et al., 2019). Molecular events associated with resistance against anti-PD-1 therapy include (i) suppressing IFN-γ-Stat1-Irf1 signalling in CRC and reducing cytotoxic tumour-infiltrating CD8+ T cells by m6A methyltransferases-mediated downregulation of STAT1 (Wang et al., 2020a), (ii) the reduction of tumour suppressive myeloid cells via intracellular signalling initiated by myeloid receptor TREM2 (Molgora et al., 2020) and (iii) activating oncogenic myeloid-derived suppressor cells and regulatory T cells by enhanced transcription of the gene that encodes lactate transporter which induces lactate secretion (Li et al., 2020a; Li et al., 2020b). Emerging studies have also highlighted that several oncogenic signalling pathways that are involved in regulating immune response that renders resistance to ICB. Activation of the Wnt/β-catenin signalling pathway has been reported to be associated with a lack of T-cell infiltration within the tumour microenvironment in cancer patients (Spranger, Bao & Gajewski, 2015). This immunological defect was found to be mediated by decreased production of chemokine CCL4 that suppresses the recruitment of CD103+ dendritic cells, resulting in resistance to the immunotherapy. The interferon (IFN) signalling is another signalling pathway that has been implicated in resistance to ICB therapy. Patients that did not respond to anti-CTLA-4 antibody ipilimumab therapy was reported to harbour mutations in the interferon gamma (IFN-γ) pathway genes leading to the ability of the tumour cells to escape from T cells, which was identified as a primary resistance to anti-CTLA-4 therapy (Gao et al., 2016). Nevertheless, the roles of other signalling pathways that are involved in modulating the sensitivity and resistance to ICB are still largely unknown and require further studies. The current strategy to tackle anti-PD1 resistance involves reprogramming immunosuppressive myeloid cells to promote the expansion of tumour suppressive M1 macrophages (Lu et al., 2021).

In addition to CAFs and immune cells as the regulators of drug resistance in CRC, the emerging role of gut microbiota in the regulation of innate immune signalling and autophagy, which leads to chemoresistance in CRC, has also been reported. This suggests that crosstalk between different components of the TME has functional relevance in CRC development and clinical outcome, which prompts further investigation (Yu et al., 2017).

Tumour heterogeneity which is the cornerstone for the maintenance of cancer cell populations has been strongly correlated with therapy resistance (Schumacher et al., 2019). Mounting evidence has demonstrated the existence of various forms of tumour heterogeneity with the most frequently observed type being the genetic heterogeneity (Di...
et al., 2019; Loeb et al., 2019). Intra-tumour or inter-tumour genetic status was shown to influence the prognostic outcome and drug response and are determinants of resistance to anti-cancer therapy (Russo et al., 2016; De Angelis et al., 2016; Galofré et al., 2020; Bruun et al., 2020). Other types of tumour heterogeneity include cell type heterogeneity which is found between CRC subpopulations in the TME, as reported by Yoon et al. (2019) which showed that T-cell densities is highly variable in DNA mismatch repair-deficient tumour as compared to DNA mismatch repair-proficient tumour.

Tumour heterogeneity can be further classified into metabolic heterogeneity due to metabolic reprogramming in cells that contributes to disease development (Katoh, 2017). Metabolic reprogramming or alterations in the cellular metabolism is an important cancer hallmark to meet the increased energy and nutrient demand of malignant cells to promote tumour development. Notably, emerging evidence suggests that metabolic reprogramming could also contribute to resistance to antitumor drugs (Teng et al., 2017; Yu et al., 2021). The underlying mechanisms of metabolic adaptation during the development of drug resistance are still unclear, but available data implies that activation of oncogenic pathways are involved in the regulation of metabolic reprogramming implicated in resistance. Vellinga and colleagues (Vellinga et al., 2015) demonstrated that tumour metabolism was shifted from glycolysis towards oxidative phosphorylation in colon cancer cells that were exposed to chemotherapy to support tumour survival during treatment. It was discovered that the enhanced oxidative metabolism was mediated by histone deacetylase sirtuin-1 (SIRT1) and its substrate, the transcriptional coactivator PGC1α [239]. The study further showed that knockdown of SIRT1 or PGC1α sensitized the tumour cells to the drug treatment, suggesting that the SIRT1/PGC1α is a novel pathway of drug resistance that may be targeted for therapy. More recently, Barisciano et al. (2020) reported the role for miR-27a as a key regulator of metabolic reprogramming and enhancing drug resistance in CRC cells. The study revealed that miR-27a modulates several tumour-associated pathways that link metabolic rewiring with chemoresistance in CRC. It was found that miR-27a negatively regulates AMPK and positively regulates mTOR pathway to force anaerobic glycolytic metabolism supporting tumour growth and chemoresistance (Barisciano et al., 2020). Interestingly, a recent study has shown the colorectal tumour-derived exosomes could activate hepatic stellate cells in the liver to enhance lactate metabolism of tumour cells via the IL-6/STAT3 pathway to confer the resistance of SN38 (active metabolite of irinotecan) (Li et al., 2020a; Li et al., 2020b). Hence, this indicates a novel mechanism in which the tumour-derived exosomes are involved in regulating the metabolic reprogramming between the tumour cells and the microenvironment to promote drug resistance (Li et al., 2020a; Li et al., 2020b). Previous studies suggest that hypoxia-induced metabolic reprogramming of CRC can be reversed by targeting valine catabolism and the inhibition of PTEN/AKT/HIF1α signalling pathway to interfere with energy production in CRC (Wang et al., 2018; Shan et al., 2019). Alternative strategies to tackle metabolic heterogeneity in CRC warrant further investigation, given that the signalling mechanisms that contribute to metabolic reprogramming in CRC are complex.

Given the increasing complexity of molecular networks in multidrug-resistant CRC, multi-omics approaches encompassing genomics, epigenomics, transcriptomics,
proteomics and metabolomics are applied to facilitate cancer biomarker discovery and guide cancer treatment strategies (Tong et al., 2016; Satoh et al., 2017; Ressa et al., 2018; Ishaque et al., 2018). Integrated multi-omics analyses of CRC cell lines have reported genetic and epigenetic alterations in the molecular landscape for CRC carcinogenesis such as (i) the identification of BRCA1-centred gene-miRNA-protein regulatory network as the main driver for liver metastasis of CRC and chemoresistance (Gerovska et al., 2020), (ii) co-occurrence of genetic alteration events in CRC that affects drug response (Zhou et al., 2020), (iii) heterogeneous Wnt/β-catenin activity that supports Runt-related transcription factor 2 (RUNX2)-based epigenetic regulation of EMT as the molecular implication for poor survival of CRC patients and failure of anti-cancer therapy (Yi et al., 2020), and (iv) the characterisation of CRC patients’ drug response patterns based on differential DNA methylation profiles in CRC stem cell populations (Visone et al., 2019). To better understand the relationship between immune landscape in the TME and drug efficacy against CRC, computational methods such as (i) the development of artificial intelligence platform to predict immunological responses to ICB therapy in MSI-H tumour (Cao et al., 2020) and (ii) the reconstruction of the intercellular network according to consensus molecular subtypes of CRC (Lee et al., 2020), have enabled the selection of better treatment options for individuals resistant to immunotherapy. Comprehensive analysis of multi-omics data such as metagenomic and metabolomic has also reported the role of gut microbiota in CRC progression and their influences on the DNA methylome of CRC, implying that the metabolic output of gut microbiota and the host’s epigenetic signatures could be important diagnostic targets for CRC management (Yachida et al., 2019; Sobhani et al., 2019; Zouggar, Haebe & Benoit, 2020).

Cancer biopsy-based bulk analysis of CRC is gradually replaced by patient-derived cancer organoid (PDCO) to study therapy resistance in vitro. This is because PDCO can recapitulate tumour heterogeneity in the patient tumour which potentiates the study of CRC at the single-cell level (Jeppesen et al., 2017; Chen et al., 2018c; Pasch et al., 2019; Demmers et al., 2020). However, limitations such as the time and cost to grow the organoids as well as limited amount of organoids available prompts the shift of focus to cancer tissue-originated spheroid (CTOS) as an alternative method for measuring chemotherapeutic heterogeneity and high-throughput drug screening for CRC patients (Jeppesen et al., 2017; Kondo et al., 2019). Technical advancement to improve the study of tumour heterogeneity in the spatial context is exemplified by RNA-based in situ hybridisation which complements the current genetic method to ease the detection of rare subclones in CRC (Baker et al., 2017). Non-invasive methods such as comprehensive genotyping of circulating tumour DNA (ctDNA) and integrated multi-omics data analyses for gene alteration events relating to drug responses, are also useful in identifying druggable mutational targets for personalising cancer medicine (Cao et al., 2019; Zhou et al., 2020). Besides improving on experimental methods to better understand tumour heterogeneity in CRC, the application of modern bioinformatic practice (e.g., reference component analysis of single-cell transcriptomes) and machine learning algorithm (e.g., deep learning for the prediction of treatment efficacy on CRC patients) are equally important to the management of increasingly complex cancer
research data which influences cancer treatment policy (Li et al., 2017; Skrede et al., 2020; Vera-Yunca et al., 2020).

CONCLUSIONS

Therapy resistance in CRC remains a major obstacle to CRC management due to alterations in the molecular landscape that drive the survival of cancer cells. In particular, dysregulation of MAPK pathway, PI3K/PKB pathway, Wnt/β-catenin pathway and Notch pathway are frequently reported to induce resistance to anti-cancer drugs targeting CRC cells. On the other hand, other signal transduction pathways such as TGFβ/Smad, BMP and Hedgehog pathways have also been implicated in the development of therapeutic resistance in CRC but are not well studied yet. The complexity of drug resistance mechanisms is further widened by pre-existing genetic heterogeneity in CRC and cellular components of the TME (e.g., stromal cells, immune cells and gut bacteria) which results in the evolution of drug-resistant tumour subclones. To address this problem, integrated multi-omics data analysis using modern computational methods, three-dimensional cell culture model and other robust experimental methods are needed to identify new cancer biomarkers and drug targets for CRC treatment. Despite the effort in combating multidrug-resistant CRC, further studies are warranted to generate quality results for better cancer care delivery.

DISCLAIMER

Most experimental findings discussed this review are derived from studies using laboratory-based cancer cell lines. Hence, the results should be interpreted with caution and be further validated in animal models and human clinical studies.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding
This work is supported by the Fundamental Research Grant Scheme (FRGS/1/2019/SKK08/UKM/03/5) awarded by the Ministry of Higher Education, Malaysia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures
The following grant information was disclosed by the authors:
The Fundamental Research Grant Scheme awarded by the Ministry of Higher Education, Malaysia: FRGS/1/2019/SKK08/UKM/03/5.

Competing Interests
The authors declare there are no competing interests.

Author Contributions
• Yeelon Yeoh performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
Teck Yew Low and Nadiah Abu conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

Pey Yee Lee conceived and designed the experiments, performed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.

Data Availability
The following information was supplied regarding data availability:

There are no raw data

REFERENCES

Ahmed M, Hussain AR, Siraj AK, Uddin S, Al-Sanea N, Al-Dayel F, Al-Assiri M, Beg S, Al-Kuraya KS. 2015. Co-targeting of Cyclooxygenase-2 and FoxM1 is a viable strategy in inducing anticancer effects in colorectal cancer cells. *Molecular Cancer* 14:1–14 DOI 10.1186/s12943-015-0406-1.

Ahronian LG, Sennott EM, Van Allen EM, Wagle N, Kwak EL, Faris JE, Godfrey JT, Nishimura K, Lynch KD, Mermel CH, Lockerman EL, Kalsy A, Gurski JM, Bahl S, Anderka K, Green LM, Lennon NJ, Huynh TG, Mino-Kenudson M, Getz G, Dias-Santagata D, Iafrate AJ, Engelman JA, Garraway LA, Corcoran RB. 2015. Clinical acquired resistance to RAF inhibitor combinations in BRAF-mutant colorectal cancer through MAPK pathway alterations. *Cancer Discovery* 5:358–367 DOI 10.1158/2159-8290.CD-14-1518.

Alessi DR, James SR, Downes CP, Holmes AB, Gaffney PRJ, Reese CB, Cohen P. 1997. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Bα. *Current Biology* 7:261–269 DOI 10.1016/s0960-9822(06)00122-9.

Allegra CJ, Jessup JM, Somerfield MR, Hamilton SR, Hammond EH, Hayes DF, McAllister PK, Morton RF, Schilsky RL. 2009. American society of clinical oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *Journal of Clinical Oncology* 27:2091–2096 DOI 10.1200/JCO.2009.21.9170.

Andrew AS, Parker S, Anderson JC, Rees JR, Robinson C, Riddle B, Butterly LF. 2018. Risk factors for diagnosis of colorectal cancer at a late stage: a population-based study. *Journal of General Internal Medicine* 33:2100–2105 DOI 10.1007/s11606-018-4648-7.

Angius A, Pira G, Scanu AM, Uva P, Sotgiu G, Saderi L, Manca A, Serra C, Uleri E, Piu C, Caocci M, Ibba G, Zinellu A, Cesaraccio MR, Sanges F, Muroni MR, Dolei A, Cossu-Rocca P, De Miglio MR. 2019. Microrna-425-5p expression affects BRAF/RAS/MAPK pathways in colorectal cancers. *International Journal of Medical Sciences* 16:1480–1491 DOI 10.7150/ijms.35269.

Aoki K, Aoki M, Sugai M, Harada N, Miyoshi H, Tsukamoto T, Mizoshita T, Tatsumatsu M, Seno H, Chiba T, Oshima M, Hsieh CL, Taketo MM. 2007. Chromosomal...
instability by β-catenin/TCF transcription in APC or β-catenin mutant cells. *Oncogene* **26**:3511–3520 DOI 10.1038/sj.onc.1210141.

Arango D, Wilson AJ, Shi Q, Corner GA, Arañes MJ, Nicholas C, Lesser M, Mariadason JM, Augenlicht LH. 2004. Molecular mechanisms of action and prediction of response to oxaliplatin in colorectal cancer cells. *British Journal of Cancer* **91**:1931–1946 DOI 10.1038/sj.bjc.6602215.

Artavanis-Tsakonas S, Rand MD, Lake RJ. 1999. Notch signaling: cell fate control and signal integration in development. *Science* **284**:770–776 DOI 10.1126/science.284.5415.770.

Backer JM. 2016. The intricate regulation and complex functions of the Class III phosphoinositide 3-kinase Vps34. *Biochemical Journal* **473**:2251–2271 DOI 10.1042/BCJ20160170.

Baharudin R, Mutalib NSAb, Othman SN, Sagap I, Rose IM, Mokhtar NM, Jamal R. 2017. Identification of predictive DNA methylation biomarkers for chemotherapy response in colorectal cancer. *Frontiers in Pharmacology* **8** DOI 10.3389/fphar.2017.00047.

Baker SJ, Fearon ER, Nigro JM, Hamilton SR, Preisinger AC, Jessup JM, Vantuinen P, Ledbetter DH, Barker DF, Nakamura Y, White R, Vogelstein B. 1989. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* **244**:217–221 DOI 10.1126/science.2649981.

Baker AM, Huang W, Wang XMM, Jansen M, Ma XJ, Kim J, Anderson CM, Wu X, Pan L, Su N, Luo Y, Domingo E, Heide T, Sottoriva A, Lewis A, Beggs AD, Wright NA, Rodriguez-Justo M, Park E, Tomlinson I, Graham TA. 2017. Robust RNA-based in situ mutation detection delineates colorectal cancer subclonal evolution. *Nature Communications* **8**:1998 DOI 10.1038/s41467-017-02295-5.

Baretti M, Personeni N, Destro A, Santoro A, Rimassa L. 2020. miR-27a is a master regulator of metabolic reprogramming and chemoresistance in colorectal cancer. *British Journal of Cancer* **122**:1354–1366 DOI 10.1038/s41416-020-0773-2.

Belli V, Matrone N, Napolitano S, Migliardi G, Cottino F, Bertotti A, Trusolino L, Martinelli E, Morgillo F, Ciardiello D, De Falco V, Giunta EF, Bracale U, Ciardiello F, Troiani T. 2019. Combined blockade of MEK and PI3KCA as an effective anti-tumor strategy in HER2 gene amplified human colorectal cancer models. *Journal of Experimental and Clinical Cancer Research* **38**:236 DOI 10.1186/s13046-019-1230-z.

Bendell JC, Atreya CE, André T, Tabernero J, Gordon MS, Bernards R, Van Cutsem E, Tejpar S, Sidhu R, Go WY, Allred A, Motwani M, Suttle BB, Wu Y, Hoos A,
Orford KW, Corcoran RB, Schellens JH. 2014. Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAF V600E mutated colorectal cancer (CRC). Journal of Clinical Oncology 32:3515–3515 DOI 10.1200/jco.2014.32.15_suppl.3515.

Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen Y-J, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Garrido-Laguna I, Grem JL, Grothey A, Hochster HS, Hoffe S, Hu S, Freedman-Cass DA. 2018. NCCN guidelines insights: colon cancer, version 2.2018. Journal of the National Comprehensive Cancer Network 16:359–369 DOI 10.6004/jnccn.2018.0021.

Berlin J, Posey J, Tchekmedjian S, Hu E, Chan D, Malik I, Yang L, Amado RG, Randolph Hecht J. 2007. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. Clinical Colorectal Cancer 6:427–432 DOI 10.3816/CCC.2007.n.011.

Bian Z, Zhang J, Li M, Feng Y, Yao S, Song M, Qi X, Fei B, Yin Y, Hua D, Huang Z. 2017. Long non-coding RNA LINC00152 promotes cell proliferation, metastasis, and confers 5-FU resistance in colorectal cancer by inhibiting miR-139-5p. Oncogenesis 6:395 DOI 10.1038/s41389-017-0008-4.

Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, De Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralowski P. 2009. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. Journal of Clinical Oncology 27:663–671 DOI 10.1200/JCO.2008.20.8397.

Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic I, Daban A, Bardet E, Beny A, Ollier JC. 2006. Chemotherapy with preoperative radiotherapy in rectal cancer. New England Journal of Medicine 355:1114–1123 DOI 10.1056/NEJMoa060829.

Boyer J, Mclean EG, Aroori S, Wilson P, Mcculla A, Carey PD, Longley DB, Johnston PG, Carey PDeclan, Longley DB, Johnston PG. 2004. Characterization of p53 Wild-type and null isogenic colorectal cancer cell lines resistant to 5-Fluorouracil, Oxaliplatin, and Irinotecan. Clinical Cancer Research 10:2158–2167 DOI 10.1158/1078-0432.CCR-03-0362.

Bray SJ. 2006. Notch signalling: a simple pathway becomes complex. Nature Reviews Molecular Cell Biology 7:678–689 DOI 10.1038/nrm2009.

Bruun J, Kryeziu K, Eide PW, Moosavi SH, Eilertsen IA, Langerud J, Røsk B, Totland MZ, Brunsell TH, Pellinen T, Saarela J, Bergsland CH, Palmer HG, Brudvik KW, Guren T, Dienstmann R, Guren MG, Nesbakken A, Bjornbeth BA, Sveen A, Lothe RA. 2020. Patient-derived organoids from multiple colorectal cancer liver metastases reveal moderate intra-patient pharmacotranscriptomic heterogeneity. Clinical Cancer Research 26:4107–4119 DOI 10.1158/1078-0432.CCR-19-3637.

Cancer Research UK. 2019. CT colonography | Tests and scans | Cancer Research UK. Available at https://www.cancerresearchuk.org/about-cancer/cancer-in-general/tests/ct-colonography (accessed on 22 May 2020).
Cao W, Xu Y, Chang L, Gong Y, Li L, Mo X, Zhang X, Lin G, Zhou J, Liu D, Yi Y, Dai P, Zhu C, Liu T, Chu Y, Guan Y, Chen Y, Wang J, Xia X, Yang L, Yi X, Cheng Y. 2019. Genotyping of circulating tumor DNA reveals the clinically actionable mutation landscape of advanced colorectal cancer. *Molecular Cancer Therapeutics* 18:1158–1167 DOI 10.1158/1535-7163.MCT-18-1247.

Cao R, Yang F, Ma SC, Liu L, Zhao Y, Li Y, Wu DH, Wang T, Lu WJ, Cai WJ, Zhu HB, Guo XJ, Lu YW, Kuang JJ, Huan WJ, Tang WM, Huang K, Huang J, Yao J, Dong ZY. 2020. Development and interpretation of a pathomics-based model for the prediction of microsatellite instability in Colorectal Cancer. *Theranostics* 10:11080–11091 DOI 10.7150/thno.49864.

Carethers JM. 2008. Review: systemic treatment of advanced colorectal cancer: tailoring therapy to the tumor. *Therapeutic Advances in Gastroenterology* 1:33–42 DOI 10.1177/1756283X08093607.

Cargnello M, Roux PP. 2011. Activation and Function of the MAPKs and Their Substrates, the MAPK-Activated Protein Kinases. *Microbiology and Molecular Biology Reviews* 75:50–83 DOI 10.1128/mmbbr.00031-10.

Castro-Piedras I, Sharma M, Den Bakker M, Molehin D, Martinez EG, Vartak D, Pruitt WM, Deitrick J, Almodovar S, Pruitt K. 2018. DVL1 and DVL3 differentially localize to CYP19A1 promoters and regulate aromatase mRNA in breast cancer cells. *Oncotarget* 9:35639–35654 DOI 10.18632/oncotarget.26257.

Chang F, Lee JT, Navolanic PM, Steelman LS, Shelton JG, Blalock WL, Franklin RA, McCubrey JA. 2003. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: a target for cancer chemotherapy. *Leukemia* 17:590–603 DOI 10.1038/sj.leu.2402824.

Chen G, Gao C, Gao X, Zhang DH, Kuan SF, Burns TF, Hu J. 2018a. Wnt/β-catenin pathway activation mediates adaptive resistance to BRAF inhibition in colorectal cancer. *Molecular Cancer Therapeutics* 17:806–813 DOI 10.1158/1535-7163.MCT-17-0561.

Chen XQ, Jiang J, Wang XT, Zhang CL, Ji AY, Chen XJ. 2018b. Role and mechanism of Dvl13 in the esophageal squamous cell carcinoma. *European Review for Medical and Pharmacological Sciences* 22:7716–7725 DOI 10.26355/eurrev-201811-16393.

Chen HY, Lang YD, Lin HN, Liu YR, Liao CC, Nana AW, Yen Y, Chen RH. 2019. miR-103/107 prolong Wnt/β-catenin signaling and colorectal cancer stemness by targeting Axin2. *Scientific Reports* 9:9687 DOI 10.1038/s41598-019-41053-z.

Chen KY, Srinivasan T, Lin C, Tung KL, Gao Z, Hsu DS, Lipkin SM, Shen X. 2018c. Single-cell transcriptomics reveals heterogeneity and drug response of human colorectal cancer organoids. In: *Proceedings of the annual international conference of the IEEE engineering in medicine and biology society, EMBS 2018-July*. 2378–2381 DOI 10.1109/EMBC.2018.8512784.

Chung AS, Wu X, Zhuang G, Ng H, Kasman I, Zhang J, Vernes JM, Jiang Z, Meng YG, Peale FV, Ouyang W, Ferrara N. 2013. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. *Nature Medicine* 19:1114–1123 DOI 10.1038/nm.3291.
Corcoran RB, Atreya CE, Falchook GS, Infante JR, Hamid O, Messersmith WA, Daud A, Kwak EL, Ryan D, Kurzrock R, Sun P, Cunningham EA, Orford KW, Motwani M, Bai Y, Patel K, Venook AP, Kopetz S. 2014. Phase 1-2 trial of the BRAF inhibitor dabrafenib (D) plus MEK inhibitor trametinib (T) in BRAF V600 mutant colorectal cancer (CRC): updated efficacy and biomarker analysis. Journal of Clinical Oncology 32:3517–3517 DOI 10.1200/jco.2014.32.15_suppl.3517.

Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, Brown RD, Pelle P Della, Dias-Santagata D, Hung KE, Flaherty KT, Piris A, Wargo JA, Settleman J, Mino-Kenudson M, Engelman JA. 2012. EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discovery 2:227–235 DOI 10.1158/2159-8290.CD-11-0341.

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. 2004. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. New England Journal of Medicine 351:337–345 DOI 10.1056/NEJMoa033025.

Danielsen SA, Eide PW, Nesbakken A, Guren T, Leithe E, Lothe RA. 2015. Portrait of the PI3K/AKT pathway in colorectal cancer. Biochimica et Biophysica Acta - Reviews on Cancer 1855:104–121 DOI 10.1016/j.bbcan.2014.09.008.

Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JWC, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Wooster R, Futreal PA. 2002. Mutations of the BRAF gene in human cancer. Nature 417:949–954 DOI 10.1038/nature00766.

De Angelis ML, Zeuner A, Policicchio E, Russo G, Bruselles A, Signore M, Vitale S, De Luca G, Pilozzi E, Boe A, Stassi G, Ricci-Vitiani L, Amoreo CA, Pagliuca A, Francescangeli F, Tartaglia M, De Maria R, Baiocchi M. 2016. Cancer stem cell-based models of colorectal cancer reveal molecular determinants of therapy resistance. Stem Cells Translational Medicine 5:511–523 DOI 10.5966/sctm.2015-0214.

De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, De Braud F, Wilson C, Morvan F, Bonetti A. 2000. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. Journal of Clinical Oncology 18:2938–2947 DOI 10.1200/JCO.2000.18.16.2938.

De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeras KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinar F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C,
Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S. 2010. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. The Lancet Oncology 11:753–762 DOI 10.1016/S1470.

Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. 2019. Colorectal cancer. The Lancet 394:1467–1480 DOI 10.1016/S0140-6736(19)32319-0.

Demmers LC, Kretzschmar K, Van Hoeck A, Bar-Epräim YE, van den Toorn HWP, Koomen M, Van Son G, Van Gorp J, Pronk A, Smakman N, Cuppen E, Clevers H, Heck AJR, Wu W. 2020. Single-cell derived tumor organoids display diversity in HLA class I peptide presentation. Nature Communications 11:5338 DOI 10.1038/s41467-020-19142-9.

Di J, Yang H, Wang Z, Yang J, Gao P, Jiang B, Su X. 2019. Clonality and heterogeneity of metachronous colorectal cancer. Molecular Carcinogenesis 58:447–457 DOI 10.1002/mc.22947.

Díaz LA, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA, Kinzler KW, Oliner KS, Vogelstein B. 2012. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature 486:537–540 DOI 10.1038/nature11219.

Díaz-Maroto NG, Garcia-Vicién G, Polcaro G, Bañuls M, Albert N, Villanueva A, Molleví DG. 2021. The blockade of tumoral il1ß-mediated signaling in normal colonic fibroblasts sensitizes tumor cells to chemotherapy and prevents inflammatory caf activation. International Journal of Molecular Sciences 22:4960 DOI 10.3390/ijms22094960.

Díaz-Maroto NG, Sañz-Pamplona R, Berdiel-Acer M, Cimas FJ, García E, Gonçalves-Ribeiro S, Albert N, Garcia-Vicien G, Capella G, Moreno V, Salazar R, Villanueva A, Molleví VG. 2019. Noncanonical TGFβ pathway relieves the blockade of IL1ß/TGFβ-mediated crosstalk between tumor and stroma: TGFBR1 and TAK1 inhibition in colorectal cancer. Clinical Cancer Research 25:4466–4479 DOI 10.1158/1078-0432.CCR-18-3957.

Dimitriou N, Griniatsos J. 2015. Complete mesocolic excision: techniques and outcomes. World Journal of Gastrointestinal Oncology 7:383–388 DOI 10.4251/wjgo.v7.i12.383.

Dosset M, Vargas TR, Lagrange A, Boidot R, Végran F, Roussey A, Chalmin F, Dondaine I, Paul C, Marie-Joseph EL, Martin F, Ryffel B, Borg C, Adotévi O, Ghiringhelli F, Apetoh L. 2018. PD-1/PD-L1 pathway: an adaptive immune resistance mechanism to immunogenic chemotherapy in colorectal cancer. OncoImmunology 7:e1433981 DOI 10.1080/2162402X.2018.1433981.

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Grua G, Awad L, Rougier P. 2000. Irinotecan combined with fluorouracil compared with fluorouracil alone. as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. The Lancet 355:1041–1047 DOI 10.1016/S0140-6736(00)02034-1.
Duong HQ, Nemazanyy I, Rambow F, Tang SC, Delaunay S, Tharun L, Florin A, Buttner R, Vandaele D, Close P, Marine JC, Shostak K, Chariot A. 2018. The endosomal protein CEMIP links WNT signaling to MEK1âĂŞERK1/2 activation in selumetinib-resistant intestinal organoids. Cancer Research 78:4533–4548 DOI 10.1158/0008-5472.CAN-17-3149.

Durrant DE, Morrison DK. 2018. Targeting the Raf kinases in human cancer: the Raf dimer dilemma. British Journal of Cancer 118:3–8 DOI 10.1038/bjc.2017.399.

Endo E, Okayama H, Saito K, Nakajima S, Yamada L, Ujiie D, Kase K, Fujita S, Endo H, Sakamoto W, Saito M, Saze Z, Momma T, Ohki S, Mimura K, Kono K. 2020. A TGFb-dependent stromal subset underlies immune checkpoint inhibitor efficacy in DNA mismatch repair-deficient/microsatellite instability-high colorectal cancer. Molecular Cancer Research 18:1402–1413 DOI 10.1158/1541-7786.MCR-20-0308.

Falasca M, Maffucci T. 2012. Regulation and cellular functions of class II phosphoinositide 3-kinases. Biochemical Journal 443:587–601 DOI 10.1042/BJ20120008.

Fang JY, Richardson BC. 2005. The MAPK signalling pathways and colorectal cancer. The Lancet Oncology 6:322–327 DOI 10.1016/S1470-2045(05)70168-6.

Fearon ER, Vogelstein B. 1990. A genetic model for colorectal tumorigenesis. Cell 61:759–767 DOI 10.1016/0092-8674(90)90186-I.

Frattini M, Saletti P, Romagnani E, Martin V, Molinari F, Ghisletta M, Camponovo A, Etienne LL, Cavalli F, Mazzucchelli L. 2007. PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. British Journal of Cancer 97:1139–1145 DOI 10.1038/sj.bjc.6604009.

Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. 2017. The PI3K pathway in human disease. Cell 170:605–635 DOI 10.1016/j.cell.2017.07.029.

Galofré C, Geyik ÖG, Asensio E, Wangsa D, Hirsch D, Parra C, Saez J, Mollà M, Yüce Z, Castells A, Ried T, Camps J. 2020. Tetraploidy-associated genetic heterogeneity confers chemo-radiotherapy resistance to colorectal cancer cells. Cancer 12:1118 DOI 10.3390/cancers12051118.

Gao C, Chen YG. 2010. Dishevelled: the hub of Wnt signaling. Cellular Signalling 22:717–727 DOI 10.1016/j.cellsig.2009.11.021.

Gao Z, Fu P, Yu Z, Zhen F, Gu Y. 2019. Comprehensive analysis of lncRNA-miRNA- mRNA network ascertains prognostic factors in patients with colon cancer. Technology in Cancer Research & Treatment 18:1533033819853237 DOI 10.1177/1533033819853237.

Gao J, Liu J, Fan D, Xu H, Xiong Y, Wang Y, Xu W, Wang Y, Cheng Y, Zheng G. 2011. Up-regulated expression of Notch1 and Jagged1 in human colon adenocarcinoma. Pathologie Biologie 59:298–302 DOI 10.1016/j.pathbio.2010.11.001.

Gao J, Shi L, Zhao H, Chen J, Xiong L, He Q, Chen T, Roszik J, Bernatchez C, Woodman S, Chen P, Hwu P, Allison J, Futreal A, Wargo J, Sharma P. 2016. Loss of IFN-γ pathway genes in tumor cells as a mechanism of resistance to Anti-CTLA-4 therapy. Cell 167:397–404 DOI 10.1016/j.cell.2016.08.069.
Gao F, Zhang Y, Wang S, Liu Y, Zheng L, Yang J, Huang W, Ye Y, Luo W, Xiao D. 2014. Hes1 is involved in the self-renewal and tumourigenicity of stem-like cancer cells in colon cancer. *Scientific Reports* **4**:1–9 DOI 10.1038/srep03963.

Gerlach JP, Emmink BL, Nojima H, Kranenburg O, Maurice MM. 2014. Wnt signalling induces accumulation of phosphorylatedβ-catenin in two distinct cytosolic complexes. *Open Biology* **4**:140120 DOI 10.1098/rsob.140120.

Gerovska D, Larrinaga G, Solano-Iturria JD, Márquez J, Gallastegi PG, Khatib AM, Poschmann G, Stühler K, Armesto M, Lawrie CH, Badiola I, Araúzo-Bravo MJ. 2020. An integrative omics approach reveals involvement of BRCA1 in hepatic metastatic progression of colorectal cancer. *Cancer* **12**:1–24 DOI 10.3390/cancers12092380.

Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KLR, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW, Ware JA, Wright SH, Wah Yee S, Zamek-Gliszczynski MJ, Zhang L. 2010. Membrane transporters in drug development. *Nature Reviews Drug Discovery* **9**:215–236 DOI 10.1038/nrd3028.

Giulianotti PC, Coratti A, Angelini M, Sbrana F, Cecconi S, Balestracci T, Caravagllos G. 2003. Robotics in general surgery: personal experience in a large community hospital. *Archives of Surgery* **138**:777–784 DOI 10.1001/archsurg.138.7.777.

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. 2004. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *Journal of Clinical Oncology* **22**:23–30 DOI 10.1200/JCO.2004.09.046.

Gongora C, Vezzio-Vie N, Tuduri S, Denis V, Causse A, Auzanneau C, Collod-Beroud G, Coquelle A, Pasero P, Pourquier P, Martineau P, Del Rio M. 2011. New Topoisomerase I mutations are associated with resistance to camptothecin. *Molecular Cancer* **10**:1–13 DOI 10.1186/1476-4598-10-64.

Greaves N, Nicholson J. 2011. Single incision laparoscopic surgery in general surgery: a review. *Annals of the Royal College of Surgeons of England* **93**:437–440 DOI 10.1308/003588411X590358.

Guo Y, Xiong BH, Zhang T, Cheng Y, Ma L. 2016. XELOX vs. FOLFOX in metastatic colorectal cancer: An updated meta-analysis. *Cancer Investigation* **34**:94–104 DOI 10.3109/07357907.2015.1104689.

Gupta AK, Brenner DE, Turgeon DK. 2008. Early detection of colon cancer: new tests on the horizon. *Molecular Diagnosis and Therapy* **12**:77–85 DOI 10.1007/BF03256273.

Gurjao C, Liu D, Hofree M, ALDubayan SH, Wakiro I, Su MJ, Felt K, Gjni E, Brais LK, Rotem A, Rosenthal MH, Rozenblatt-Rosen O, Rodig S, Ng K, Van Allen EM, Corsello SM, Ogino S, Regev A, Nowak JA, Giannakis M. 2019. Intrinsic resistance to immune checkpoint blockade in a mismatch repair–deficient colorectal cancer. *Cancer Immunology Research* **7**:1230–1236 DOI 10.1158/2326-6066.CIR-18-0683.

Häfner MF, Debus J. 2016. Radiotherapy for colorectal cancer: current standards and future perspectives. *Visceral Medicine* **32**:172–177 DOI 10.1159/000446486.
Hamada T, Nowak JA, Ogino S. 2017. PIK3CA mutation and colorectal cancer precision medicine. *Oncotarget* 8:22305–22306 DOI 10.18632/oncotarget.15724.

Han P, Li JW, Zhang BM, Lv Jc, Li YM, Gu XY, Yu ZW, Jia YH, Bai XF, Li L, Liu YL, Cui BB. 2017. The lncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/β-catenin signaling. *Molecular Cancer* 16:9 DOI 10.1186/s12943-017-0583-1.

Hatzivassiliou G, Song K, Yen I, Brandhuber BJ, Anderson DJ, Alvarado R, Ludlam MJC, Stokoe D, Gloor SL, Vigors G, Morales T, Aliagas I, Liu B, Sideris S, Hoeflich KP, Jaiswal BS, Sideris S, Koeppen H, Belvin M, Friedman LS, Malek S. 2010. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature* 464:431–435 DOI 10.1038/nature08833.

Hawkins PT, Stephens LR. 2016. Emerging evidence of signalling roles for PI(3,4)P2 in Class I and II PI3K-regulated pathways. *Biochemical Society Transactions* 44:307–314 DOI 10.1042/BST20150248.

He T, Zhang M, Zheng R, Zheng S, Linghu E, Herman JG, Guo M. 2017. Methylation of SLFN11 is a marker of poor prognosis and cisplatin resistance in colorectal cancer. *Epigenomics* 9:849–862 DOI 10.2217/epi-2017-0019.

He L, Zhu H, Zhou S, Wu T, Wu H, Yang H, Mao H, SekharKathera C, Janardhan A, Edick AM, Zhang A, Hu Z, Pan F, Guo Z. 2018. Wnt pathway is involved in 5-FU drug resistance of colorectal cancer cells. *Experimental and Molecular Medicine* 50:1–12 DOI 10.1038/s12276-018-0128-8.

Health NI. 2020. Colonoscopy | MedlinePlus. Available at [https://medlineplus.gov/colonoscopy.html](https://medlineplus.gov/colonoscopy.html) (accessed on 22 May 2020).

Heinemann V, Weikersthal LF von, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes H-G, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S. 2014. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. *The Lancet Oncology* 15:1065–1075 DOI 10.1016/S1470-2045(14)70330-4.

Hemmings BA. 1997. Akt signaling: linking membrane events to life and death decisions. *Science* 275:628–630 DOI 10.1126/science.275.5300.628.

Hemmings BA, Restuccia DF. 2012. PI3K-PKB/Akt pathway. *Cold Spring Harbor Perspectives in Biology* 4:a011189 DOI 10.1101/cshperspect.a011189.

Herrera M, Llorens C, Rodríguez M, Herrera A, Ramos R, Gil B, Candia A, Larriba MJ, Garre P, Earl J, Rodríguez-Garrote M, Caldés T, Bonilla F, Carrato A, García-Barberán V, Peña C. 2018. Differential distribution and enrichment of non-coding RNAs in exosomes from normal and Cancer-associated fibroblasts in colorectal cancer. *Molecular Cancer* 17:114 DOI 10.1186/s12943-018-0863-4.

Hiraki M, Nishimura J, Takahashi H, Wu X, Takahashi Y, Miyo M, Nishida N, Uemura M, Hata T, Takemasa I, Mizushima T, Soh JW, Doki Y, Mori M, Yamamoto H. 2015. Concurrent targeting of KRAS and AKT by MiR-4689 is a novel treatment
against mutant KRAS colorectal cancer. *Molecular Therapy - Nucleic Acids* 4:e231 DOI 10.1038/mtna.2015.5.

Hou Z, Sun L, Xu F, Hu F, Lan J, Song D, Feng Y, Wang J, Luo X, Hu J, Wang G. 2020. Blocking histone methyltransferase SETDB1 inhibits tumorigenesis and enhances cetuximab sensitivity in colorectal cancer. *Cancer Letters* 487:63–73 DOI 10.1016/j.canlet.2020.05.029.

Hu PS, Li T, Lin JF, Qiu MZ, Wang DS, Liu ZX, Chen ZH, Yang LP, Zhang XL, Zhao Q, Chen YX, Lu YX, Wu QN, Pu HY, Zeng ZL, Xie D, Ju HQ, Luo HY, Xu RH. 2020. VDR–SOX2 signaling promotes colorectal cancer stemness and malignancy in an acidic microenvironment. *Signal Transduction and Targeted Therapy* 5:183 DOI 10.1038/s41392-020-00230-7.

Hu T, Li Z, Gao CY, Cho CH. 2016. Mechanisms of drug resistance in colon cancer and its therapeutic strategies. *World Journal of Gastroenterology* 22:6876–6889 DOI 10.3748/wjg.v22.i30.6876.

Hu JL, Wang W, Lan XL, Zeng ZC, Liang YS, Yan YR, Song FY, Wang FF, Zhu XH, Liao WJ, Liao WT, Ding YQ, Liang L. 2019. CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. *Molecular Cancer* 18:91 DOI 10.1186/s12943-019-1019-x.

Huan L, Guo T, Wu Y, Xu L, Huang S, Xu Y, Liang L, He X. 2020. Hypoxia induced LUCAT1/PTBP1 axis modulates cancer cell viability and chemotherapy response. *Molecular Cancer* 19:11 DOI 10.1186/s12943-019-1122-z.

Huang S, Armstrong EA, Benavente S, Chinnaiyan P, Harari PM. 2004. Dual-agent molecular targeting of the epidermal growth factor receptor (EGFR): combining anti-EGFR antibody with tyrosine kinase inhibitor. *Cancer Research* 64:5355–5362 DOI 10.1158/0008-5472.CAN-04-0562.

Ikenoue T, Kanai F, Hikiba Y, Obata T, Tanaka Y, Imamura J, Ohto M, Jazag A, Guleng B, Tateishi K, Asaoka Y, Matsumura M, Kawabe T, Omata M. 2005. Functional analysis of PIK3CA gene mutations in human colorectal cancer. *Cancer Research* 65:4562–4567 DOI 10.1158/0008-5472.CAN-04-4114.

International Agency for Research on Cancer. 2020. Cancer Today. Available at https://gco.iarc.fr/today/home (accessed on 24 February 2021).

Ishaque N, Abba ML, Hauser C, Patil N, Paramasivam N, Huebschmann D, Leupold JH, Balasubramanian GP, Kleinheinz K, Toprak UH, Hutter B, Benner A, Shavinskaya A, Zhou C, Gu Z, Kerssemakers J, Marx A, Moniuszko M, Kozlowski M, Reszec J, Niklinski J, Eils J, Schlesner M, Eils R, Brors B, Allgayer H. 2018. Whole genome sequencing puts forward hypotheses on metastasis evolution and therapy in colorectal cancer. *Nature Communications* 9:4782 DOI 10.1038/s41467-018-07041-z.

Ishiguro H, Okubo T, Kuwabara Y, Kimura M, Mitsui A, Sugito N, Ogawa R, Katada T, Tanaka T, Shiozaki M, Mizoguchi K, Samoto Y, Matsuo Y, Takahashi H, Takiguchi S. 2017. NOTCH1 activates the Wnt/β-catenin signaling pathway in colon cancer. *Oncotarget* 8:60378–60389 DOI 10.18632/oncotarget.19534.
Iveson TJ, Sobrero AF, Yoshino T, Souglakos I, Ou FS, Meyers JP, Shi Q, Grothey A, Saunders MP, Labianca R, Yamanaka T, Boukouvinas I, Hollander NH, Galli F, Yamazaki K, Georgoulas V, Kerr R, Oki E, Lonardi S, Harkin A, Rosati G, Paul J. 2021. Duration of Adjuvant Doublet Chemotherapy (3 or 6 months) in Patients With High-Risk Stage II Colorectal Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 39:631–641 DOI 10.1200/JCO.20.01330.

Jackstadt R, Van Hooff SR, Leach JD, Cortes-Lavaud X, Lohuis JO, Ridgway RA, Wouters VM, Roper J, Kendall TJ, Roxburgh CS, Horgan PG, Nixon C, Nourse C, Gunzer M, Clark W, Hedley A, Yilmaz OH, Rashid M, Bailey P, Biankin AV, Campbell AD, Adams DJ, Barry ST, Steele CW, Medema JP, Sansom OJ. 2019. Epithelial NOTCH signaling rewires the tumor microenvironment of colorectal cancer to drive poor-prognosis subtypes and metastasis. *Cancer Cell* 36:319–336e7 DOI 10.1016/j.ccell.2019.08.003.

Janda CY, Waghray D, Levin AM, Thomas C, Garcia KC. 2012. Structural basis of Wnt recognition by frizzled. *Science* 336:59–64 DOI 10.1126/science.1222879.

Jansson MD, Lund AH. 2012. MicroRNA and cancer. *Molecular Oncology* 6:590–610 DOI 10.1016/j.molonc.2012.09.006.

Jeantet M, Tougeron D, Tachon G, Cortes U, Archambaut C, Fromont G, Karayan-Tapon L. 2016. High intra-and inter-tumoral heterogeneity of RAS mutations in colorectal cancer. *International Journal of Molecular Sciences* 17 DOI 10.3390/ijms17122015.

Jeppesen M, Hagel G, Glenthoj A, Vainer B, Ibsen P, Harling H, Thastrup O, Jørgensen LN, Thastrup J. 2017. Short-term spheroid culture of primary colorectal cancer cells as an in vitro model for personalizing cancer medicine. *PLOS ONE* 12:e0183074 DOI 10.1371/journal.pone.0183074.

Jing S, Miao D, Wang M, Lv J, Wang Y, Tong J. 2019. MiR-30-5p suppresses cell chemoresistance and stemness in colorectal cancer through USP22/Wnt/β-catenin signaling axis. *Journal of Cellular and Molecular Medicine* 23:630–640 DOI 10.1111/jcmm.13968.

Jin Y, Wang M, Hu H, Huang Q, Chen Y, Wang G. 2018. Overcoming stemness and chemoresistance in colorectal cancer through miR-195-5p-modulated inhibition of notch signaling. *International Journal of Biological Macromolecules* 117:445–453 DOI 10.1016/j.ijbiomac.2018.05.151.

Jonker DJ, O’Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC, Van Hazel G, Wierzbicki R, Langer C, Moore MJ. 2007. Cetuximab for the treatment of colorectal cancer. *New England Journal of Medicine* 357:2040–2048 DOI 10.1056/NEJMoa071834.

Kadioglu O, Saeed M, Mahmoud N, Azawi S, Mrasek K, Liehr T, Effert H. 2021. Identification of potential novel drug resistance mechanisms by genomic and transcriptomic profiling of colon cancer cells with p53 deletion. *Archives of Toxicology* 95 DOI 10.1007/s00204-021-02979-4.
Kafka A, Tomas D, Lechpammer M, Gabud T, Pažanin L, Pečina-Šlaus N. 2017. Expression levels and localizations of DVL3 and sFRP3 in glioblastoma. Disease Markers 2017:9253495 DOI 10.1155/2017/9253495.

Kahlert C, Kalluri R. 2013. Exosomes in tumor microenvironment influence cancer progression and metastasis. Journal of Molecular Medicine 91:431–437 DOI 10.1007/s00109-013-1020-6.

Kalloo AN. 2007. Natural orifice transluminal endoscopic surgery (NOTES). Gastroenterology & Hepatology 3:183–184.

Kang S, Bader AG, Vogt PK. 2005. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proceedings of the National Academy of Sciences of the United States of America 102:802–807 DOI 10.1073/pnas.0408864102.

Katoh M. 2017. Canonical and non-canonical WNT signaling in cancer stem cells and their niches: cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). International Journal of Oncology 51:1357–1369 DOI 10.3892/ijo.2017.4129.

Kavuri SM, Jain N, Galimi F, Cottino F, Leto SM, Migliardi G, Searleman AC, Shen W, Monsey J, Trusolino L, Jacobs SA, Bertotti A, Bose R. 2015. HER2 activating mutations are targets for colorectal cancer treatment. Cancer Discovery 5:832–841 DOI 10.1158/2159-8290.CD-14-1211.

Khan A, Ahmed E, Elareer N, Junejo K, Steinhoff M, Uddin S. 2019. Role of miRNA-Regulated cancer stem cells in the pathogenesis of human malignancies. Cell 8:840 DOI 10.3390/cells8080840.

Kim EK, Choi EJ. 2010. Pathological roles of MAPK signaling pathways in human diseases. Biochimica et Biophysica Acta 1802:396–405 DOI 10.1016/j.bbadis.2009.12.009.

Kim A, Lee JE, Lee SS, Kim C, Lee SJ, Jang WS, Park S. 2013. Coexistent mutations of KRAS and PIK3CA affect the efficacy of NVP-BEZ235, a dual PI3K/MTOR inhibitor, in regulating the PI3K/MTOR pathway in colorectal cancer. International Journal of Cancer 133:984–996 DOI 10.1002/ijc.28073.

Kim BR, Oh SC, Lee DH, Kim JL, Lee SY, Kang MH, Lee S Il, Kang S, Joung SY, Min BW. 2015. BMP-2 induces motility and invasiveness by promoting colon cancer stemness through STAT3 activation. Tumor Biology 36:9475–9486 DOI 10.1007/s13277-015-3681-y.

Klein CE, Gupta E, Reid JM, Atherton PJ, Sloan HC, Ratain MJ, Kastrissios H. 2002. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clinical Pharmacology and Therapeutics 72:638–647 DOI 10.1067/mcp.2002.129502.

Komiy Y, Habas R. 2008. Wnt signal transduction pathways. Organogenesis 4:68–75 DOI 10.4161/org.4.2.5851.

Kondo J, Ekawa T, Endo H, Yamazaki K, Tanaka N, Kukita Y, Okuyama H, Okami J, Imamura F, Ohue M, Kato K, Nomura T, Kohara A, Mori S, Dan S, Inoue M. 2019. High-throughput screening in colorectal cancer tissue-originated spheroids. Cancer Science 110:345–355 DOI 10.1111/cas.13843.
Kretzschmar K, Clevers H. 2017. Wnt/β-catenin signaling in adult mammalian epithelial stem cells. *Developmental Biology* 428:273–282 DOI 10.1016/j.ydbio.2017.05.015.

Kubiniok P, Lavoie H, Therrien M, Thibault P. 2017. Time-resolved phosphoproteome analysis of paradoxical RAF activation reveals novel targets of ERK. *Molecular and Cellular Proteomics* 16:663–679 DOI 10.1074/mcp.M116.065128.

Kukcinaviciute E, Jonusiene V, Sasnauskiene A, Dabkeviciene D, Eidenaitė E, Lau-rinavicius A. 2018. Significance of Notch and Wnt signaling for chemoresistance of colorectal cancer cells HCT116. *Journal of Cellular Biochemistry* 119:5913–5920 DOI 10.1002/jcb.26783.

Kuo T, Cho CD, Halsey J, Wakelee HA, Advani RH, Ford JM, Fisher GA, Sikic BI. 2005. Phase II study of gefitinib, fluorouracil, leucovorin, and oxaliplatin therapy in previously treated patients with metastatic colorectal cancer. *Journal of Clinical Oncology* 23:5613–5619 DOI 10.1200/JCO.2005.08.359.

Kwon JJ, Willy JA, Quirin KA, Wek RC, Korc M, Yin XM, Kota J. 2016. Novel role of miR-29a in pancreatic cancer autophagy and its therapeutic potential. *Oncotarget* 7:1635–17650 DOI 10.18632/oncotarget.11928.

Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, Arnold D, Group EGW. 2013. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 24:164–172.

Laurent-Puig P, Cayre A, Manceau G, Buc E, Bachet JB, Lecomte T, Rougier P, Lievre A, Landi B, Boige V, Ducreux M, Ychou M, Bibeau F, Bouché O, Reid J, Stone S, Penault-Llorca F. 2009. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *Journal of Clinical Oncology* 27:5924–5930 DOI 10.1200/JCO.2008.21.6796.

Lazzari L, Corti G, Picco G, Isella C, Montone M, Arcela P, Durinikova E, Zanella ER, Novara L, Barbosa F, Cassingena A, Cancelliere C, Medico E, Sartore-Bianchi A, Siena S, Garnett MJ, Bertotti A, Trusolino L, Di Nicolantonio F, Linnebacher M, Bardelli A, Arena S. 2019. Patient-derived xenografts and matched cell lines identify pharmacogenomic vulnerabilities in colorectal cancer. *Clinical Cancer Research* 25:6243–6259 DOI 10.1158/1078-0432.CCR-18-3440.

Lee HO, Hong Y, Etioglu HE, Cho YB, Pomella V, VandenBosch B, Vanhecke J, Verbandt S, Hong H, Min JW, Kim N, Eum HH, Qian J, Boeckx B, Lambrechts D, Tsantoulis P, De Hertogh G, Chung W, Lee T, An M, Shin HT, Joung JG, Jung MH, Ko G, Wirapati P, Kim SH, Kim HC, Yun SH, Tan IBH, Ranjan B, Lee WY, Kim TY, Choi JK, Kim YJ, Prabhakar S, Tejpar S, Park WY. 2020. Lineage-dependent gene expression programs influence the immune landscape of colorectal cancer. *Nature Genetics* 52:594–603 DOI 10.1038/s41588-020-0636-z.

Li H, Courtois ET, Sengupta D, Tan Y, Chen KH, Goh JJI, Kong SL, Chua C, Hon LK, Tan WS, Wong M, Choi PJ, Wee LJK, Hillmer AM, Tan IB, Robson P, Prabhakar S. 2017. Reference component analysis of single-cell transcriptomes elucidates cellular heterogeneity in human colorectal tumors. *Nature Genetics* 49:708–718 DOI 10.1038/ng.3818.
Li N, Kang Y, Wang L, Huff S, Tang R, Hui H, Agrawal K, Gonzalez GM, Wang Y, Patel SP, Rana TM. 2020b. ALKBH5 regulates anti–PD-1 therapy response by modulating lactate and suppressive immune cell accumulation in tumor microenvironment. *Proceedings of the National Academy of Sciences of the United States of America* **117**:20159–20170 DOI 10.1073/PNAS.1918986117.

Li JL, Sainson RCA, Oon CE, Turley H, Leek R, Sheldon H, Bridges E, Shi W, Snell C, Bowden ET, Wu H, Chowdhury PS, Russell AJ, Montgomery CP, Poulsom R, Harris AL. 2011. DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy in vivo. *Cancer Research* **71**:6073–6083 DOI 10.1158/0008-5472.CAN-11-1704.

Li F, Zhan L, Dong Q, Wang Q, Wang Y, Li X, Zhang Y, Zhang J. 2020a. Tumor-derived exosome-educated hepatic stellate cells regulate lactate metabolism of hypoxic colorectal tumor cells via the IL-6/STAT3 pathway to confer drug resistance. *OncoTargets and Therapy* **13**:7851–7864 DOI 10.2147/OTT.S253485.

Liao W, Overman MJ, Boutin AT, Shang X, Zhao D, Dey P, Li J, Wang G, Lan Z, Li J, Tang M, Jiang S, Ma X, Chen P, Katkhuda R, Korphaisarn K, Chakravarti D, Chang A, Spring DJ, Chang Q, Zhang J, Maru DM, Maeda DY, Zebala JA, Kopetz S, Wang YA, De Pinho RA. 2019. KRAS-IRF2 axis drives immune suppression and immune therapy resistance in colorectal cancer. *Cancer Cell* **35**:559–572 DOI 10.1016/j.ccell.2019.02.008.

Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, Côté JF, Tomasic G, Penna C, Ducreux M, Rougier P, Renault–Llorca F, Laurent-Puig P. 2006. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Research* **66**:3992–3995 DOI 10.1158/0008-5472.CAN-06-0191.

Lippert TH, Ruoff HJ, Volm M. 2008. Intrinsic and acquired drug resistance in malignant tumors: the main reason for therapeutic failure. *Arzneimittel-Forschung/Drug Research* **58**:261–264 DOI 10.1055/s-0031-1296504.

Liu X, Lv X, Yang Q, Jin H, Zhou W, Fan Q. 2018. MicroRNA-29a functions as a tumor suppressor and increases cisplatin sensitivity by targeting NRAS in lung cancer. *Technology in Cancer Research and Treatment* **17**:15330381875890 DOI 10.1177/153303818758905.

Liu H, Yin Y, Hu Y, Feng Y, Bian Z, Yao S, Li M, You Q, Huang Z. 2016. miR-139-5p sensitizes colorectal cancer cells to 5-fluorouracil by targeting NOTCH-1. *Pathology Research and Practice* **212**:643–649 DOI 10.1016/j.prp.2016.04.011.

Liu G, Zhou JP, Dong M. 2019. Down-regulation of miR-543 expression increases the sensitivity of colorectal cancer cells to 5-Fluorouracil through the PTEN/PI3K/AKT pathway. *Bioscience Reports* **39**:BSR20190249 DOI 10.1042/BSR20190249.

Loeb LA, Kohn BF, Loubet-Senear KJ, Dunn YJ, Ahn EH, O’Sullivan JN, Salk JJ, Bronner MP, Beckman RA. 2019. Extensive subclonal mutational diversity in human colorectal cancer and its significance. *Proceedings of the National Academy of Sciences of the United States of America* **116**:26863–26872 DOI 10.1073/pnas.1910301116.

Lotti F, Jarrar AM, Pai RK, Hitomi M, Lathia J, Mace A, Gantt GA, Sukhdeo K, DeVecchio J, VasANJI A, Leahy P, Hjelmeland AB, Kalady MF, Rich JN. 2013. Chemotherapy activates cancer-associated fibroblasts to maintain colorectal...
cancer-initiating cells by IL-17A. *Journal of Experimental Medicine* **210**:2851–2872 DOI 10.1084/jem.20131195.

Lu W, Yu W, He J, Liu W, Yang J, Lin X, Zhang Y, Wang X, Jiang W, Luo J, Zhang Q, Yang H, Peng S, Yi Z, Ren S, Chen J, Siwko S, Nussinov R, Cheng F, Zhang H, Liu M. 2021. Reprogramming immunosuppressive myeloid cells facilitates immunotherapy for colorectal cancer. *EMBO Molecular Medicine* **13**:e12798 DOI 10.15252/emmm.202012798.

Lu Y, Zhao X, Liu Q, Li C, Graves-Deal R, Cao Z, Singh B, Franklin JL, Wang J, Hu H, Wei T, Yang M, Yeatman TJ, Lee E, Saito-Diaz K, Hinger S, Patton JG, Chung CH, Emmrich S, Klusmann JH, Fan D, Coffey RJ. 2017. LncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/β-catenin signaling. *Nature Medicine* **23**:1331–1341 DOI 10.1038/nm.4424.

Luo Q, Wei C, Li X, Li J, Chen L, Huang Y, Song H, Li D, Fang L. 2014. MicroRNA-195-5p is a potential diagnostic and therapeutic target for breast cancer. *Oncology Reports* **31**:1096–1102 DOI 10.3892/or.2014.2971.

Ma B, Gao P, Wang H, Xu Q, Song Y, Huang X, Sun J, Zhao J, Luo J, Sun Y, Wang Z. 2017. What has preoperative radio(chemo)therapy brought to localized rectal cancer patients in terms of perioperative and long-term outcomes over the past decades? A systematic review and meta-analysis based on 41, 121 patients. *International Journal of Cancer* **141**:1052–1065 DOI 10.1002/ijc.30805.

Ma Y, Yang Y, Wang F, Moyer MP, Wei Q, Zhang P, Yang Z, Liu W, Zhang H, Chen N, Wang H, Qin H. 2016. Long non-coding RNA CCAL regulates colorectal cancer progression by activating Wnt/β-catenin signalling pathway via suppression of activator protein 2α. *Gut* **65**:1494–1504 DOI 10.1136/gutjnl-2014-308392.

Macrae FA. 2016. Colorectal cancer: epidemiology, risk factors, and protective factors - UpToDate. Available at https://www.uptodate.com/contents/colorectal-cancer-epidemiology-risk-factors-and-protective-factors (accessed on 30 April 2020).

Mahalakshmi R, Husayn Ahmed P, Mahadevan V. 2018. HDAC inhibitors show differential epigenetic regulation and cell survival strategies on p53 mutant colon cancer cells. *Journal of Biomolecular Structure and Dynamics* **36**:938–955 DOI 10.1080/07391102.2017.1302820.

Majidinia M, Darband SG, Kaviani M, Nabavi SM, Jahanban-Esfahan R, Yousefi B. 2018. Cross-regulation between Notch signaling pathway and miRNA machinery in cancer. *DNA Repair* **66–67**:30–41 DOI 10.1016/j.dnarep.2018.04.002.

Manning BD, Cantley LC. 2007. AKT/PKB signaling: navigating Downstream. *Cell* **129**:1261–1274 DOI 10.1016/j.cell.2007.06.009.

Margolin DA, Silinsky J, Grimes C, Spencer N, Aycock M, Green H, Cordova J, Davis NK, Driscoll T, Li L. 2011. Lymph node stromal cells enhance drug-resistant colon cancer cell tumor formation through SDF-1α/CXCR4 paracrine signaling. *Neoplasia* **13**:874–886 DOI 10.1593/neo.11324.

Martinelli E, Morgillo F, Troiani T, Ciardiello F. 2017. Cancer resistance to therapies against the EGFR-RAS-RAF pathway: the role of MEK. *Cancer Treatment Reviews* **53**:61–69 DOI 10.1016/j.ctrv.2016.12.001.
Meropol NJ, Gold PJ, Diasio RB, Andria M, Dhami M, Godfrey T, Kovatich AJ, Lund KA, Mitchell E, Schwarting R. 2006. Thymidine phosphorylase expression is associated with response to capecitabine plus irinotecan in patients with metastatic colorectal cancer. *Journal of Clinical Oncology* 24:4069–4077 DOI 10.1200/JCO.2005.05.2084.

Mesange P, Bouygues A, Ferrand N, Sabbah M, Escargueil AE, Savina A, Chibaudel B, Tournigand C, Andre T, De Gramont A, Larsen AK. 2018. Combinations of bevacizumab and erlotinib show activity in colorectal cancer independent of ras status. *Clinical Cancer Research* 24:2548–2558 DOI 10.1158/1078-0432.CCR-17-3187.

Miron G, Perna S, Shukla A, Marfe G. 2016. Involvement of Notch-1 in resistance to regorafenib in colon cancer cells. *Journal of Cellular Physiology* 231:1097–1105 DOI 10.1002/jcp.25206.

Misale S, Di Nicolantonio F, Sartore-Bianchi A, Siena S, Bardelli A. 2014. Resistance to Anti-EGFR therapy in colorectal cancer: From heterogeneity to convergent evolution. *Cancer Discovery* 4:1269–1280 DOI 10.1158/2159-8290.CD-14-0462.

Mohamed SY, Kaf RM, Ahmed MM, Elwan A, Ashour HR, Ibrahim A. 2019. The prognostic value of cancer stem cell markers (Notch1, ALDH1, and CD44) in primary colorectal carcinoma. *Journal of Gastrointestinal Cancer* 50:824–837 DOI 10.1007/s12029-018-0156-6.

Molgora M, Esaulova E, Vermi W, Hou J, Chen Y, Luo J, Brioschi S, Bugatti M, Omodei AS, Ricci B, Fronick C, Panda SK, Takeuchi Y, Gubin MM, Faccio R, Cell M, Gilfillan S, Unanue ER, Artyomov MN, Colonna M. 2020. TREM2 modulation remodels the tumor myeloid landscape enhancing Anti-PD-1 immunotherapy. *Cell* 182:886–900 DOI 10.1016/j.cell.2020.07.013.

Molinari C, Marisi G, Passardi A, Matteucci L, De Maio G, Ulivi P. 2018. Heterogeneity in colorectal cancer: a challenge for personalized medicine? *International Journal of Molecular Sciences* 19:3733–3750 DOI 10.3390/ijms19123733.

Moon SU, Kang MH, Sung JH, Kim JW, Lee JO, Kim YJ, Lee KW, Bang SM, Lee JS, Kim JH. 2015. Effect of Smad3/4 on chemotherapeutic drug sensitivity in colorectal cancer cells. *Oncology Reports* 33:185–192 DOI 10.3892/or.2014.3582.

Morrison DK. 2012. MAP kinase pathways. *Cold Spring Harbor Perspectives in Biology* 4:a011254 DOI 10.1101/cshperspect.a011254.

Muluhngwi P, Alizadeh-Rad N, Viittitow SL, Kalbfleisch TS, Klinge CM. 2017. The miR-29 transcriptome in endocrine-sensitive and resistant breast cancer cells. *Scientific Reports* 7:5205 DOI 10.1038/s41598-017-05727-w.

Murga C, Laguinge L, Wetzker R, Cuadrado A, Gutkind JS. 1998. Activation of Akt/protein kinase B by G protein-coupled receptors: a role for α and β γ subunits of heterotrimERIC G proteins acting through phosphatidylinositol-3-OH kinase γ. *Journal of Biological Chemistry* 273:19080–19085 DOI 10.1074/jbc.273.30.19080.

Negri F, Bozzetti C, Pedrazzi G, Azzoni C, Bottarelli L, Squadrilli A, Lagrasta C, Tammagnini I, Bisagni A, Ragazzi M, Porzio R, Tomasello G, Mori D, Leonardi F, Gnetti
L, Crafa P, Sala R, Cascinu S. 2019. High levels of Notch intracellular cleaved domain are associated with stemness and reduced bevacizumab efficacy in patients with advanced colon cancer. Oncology Reports 42:2750–2758 DOI 10.3892/or.2019.7349.

Negri FV, Crafa P, Pedrazzi G, Bozzi G, Lagrasta C, Gardini G, Tamagnini I, Bisagni A, Azzoni C, Bottarelli L, Graiani G, Romano I, Porzio R, Bacchini GP, Paties C, Tomasello G, Marchetti G, Fanello S, Pinto C, Sala R, Ardizzoni A. 2015. Strong Notch activation hinders bevacizumab efficacy in advanced colorectal cancer. Future Oncology 11:3167–3174 DOI 10.2217/fon.15.218.

Ning Z, Wang A, Liang J, Xie Y, Liu J, Feng L, Yan Q, Wang Z. 2014. USP22 promotes the G1/S phase transition by upregulating FoxM1 expression via β-catenin nuclear localization and is associated with poor prognosis in stage II pancreatic ductal adenocarcinoma. International Journal of Oncology 45:1594–1608 DOI 10.3892/ijo.2014.2531.

Nisar S, Hashem S, Macha MA, Yadav SK, Muralitharan S, Therachiyl I, Sageena G, Al-Naemi H, Haris M, Bhat AA. 2020. Exploring dysregulated signaling pathways in cancer. Current Pharmaceutical Design 26:429–445 DOI 10.2174/1381612826666200115095937.

Normanno N, Rachiglio AM, Lambiase M, Martinelli E, Fenizia F, Esposito C, Roma C, Troiani T, Rizzi D, Tatangelo F, Botti G, Maiello E, Colucci G, Ciardiello F, Giuliani F, Simone G, Febbraro A, Tommaselli E, Cinieri S, Criscuolo M, Rinaldi A, Bordonaro R, Manusia M, Romito S, Bufo P, CartenĂĄ G, Biglietto M, Nappi O, Montesarchio E, Micheli P, Nasti G, Chiocchini N, Iannaccone A, Russo A, Cabibi D, Barone C, Rindi G, Tonini G, Onetti Muda A, Perrone G, Latiano T, Graziano P, Piscitelli S, Sebastio A. 2015. Heterogeneity of KRAS, NRAS, BRAF and PIK3CA mutations in metastatic colorectal cancer and potential effects on therapy in the CAPRI GOIM trial. Annals of Oncology 26:1710–1714 DOI 10.1093/annonc/mdv176.

Oddo D, Sennott EM, Barault L, Valtorta E, Arena S, Cassingena A, FilicuottO G, Marzolla G, Elez E, Van Geel RMJM, Bartolini A, Crisafulli G, Boscaro V, Godfrey JT, Buscharino M, Cancelliere C, Linnebach M, Corti G, Truini M, Siravegna G, Grasselli J, Gallicchio M, Bernards R, Schellens JH, Tabernero J, Engelman JA, Sartore-Bianchi A, Bardelli A, Siena S, Corcoran RB, Di Nicolantonio F. 2016. Molecular landscape of acquired resistance to targeted therapy combinations in BRAF-mutant colorectal cancer. Cancer Research 76:4504–4515 DOI 10.1158/0008-5472.CAN-16-0396.

Okkenhaug K. 2013. Signaling by the phosphoinositide 3-kinase family in immune cells. Annual Review of Immunology 31:675–704 DOI 10.1146/annurev-immunol-032712-095946.

Påhlman L. 1997. Improved survival with preoperative radiotherapy in resectable rectal cancer. New England Journal of Medicine 336:980–987 DOI 10.1056/NEJM199704033361402.

Pai SG, Carneiro BA, Chae YK, Costa RL, Kalyan A, Shah HA, Helenowski I, Rademaker AW, Mahalingam D, Giles FJ. 2017. Correlation of tumor mutational burden
and treatment outcomes in patients with colorectal cancer. *Journal of Gastrointestinal Oncology* 8:858–866 DOI 10.21037/jgo.2017.06.20.

Park SH, Jo MJ, Kim BR, Jeong YA, Na YJ, Kim JL, Jeong S, Yun HK, Kim DY, Kim BG, Kang SH, Oh SC, Lee DH. 2019. Sonic hedgehog pathway activation is associated with cetuximab resistance and EPHB3 receptor induction in colorectal cancer. *Theranostics* 9:2235–2251 DOI 10.7150/thno.30678.

Parker WB, Cheng YC. 1990. Metabolism and mechanism of action of 5-fluorouracil. *Pharmacology and Therapeutics* 48:381–395 DOI 10.1016/0163-7258(90)90056-8.

Pasch CA, Favreau PF, Yueh AE, Babiarz CP, Gillette AA, Sharick JT, Karim MR, Nickel KP, De Zeeuw AK, Sprackling CM, Emmerich PB, De Stefanis RA, Pitera RT, Payne SN, Korkos DP, Clipson L, Walsh CM, Miller D, Carchman EH, Burkard ME, Lemmon KK, Matkowskyj KA, Newton MA, Ong IM, Bassetti MF, Kimple RJ, Skala MC, Deming DA. 2019. Patient-derived cancer organoid cultures to predict sensitivity to chemotherapy and radiation. *Clinical Cancer Research* 25:5376–5387 DOI 10.1158/1078-0432.CCR-18-3590.

Pelullo M, Nardozza F, Zema S, Quaranta R, Nicoletti C, Besharat ZM, Felli MP, Cerbelli B, D’Amati G, Palermo R, Capalbo C, Talora C, Marcotullio I Di, Giannini G, Checquolo S, Screpanti I, Bellavia D. 2019. Kras/ADAM17-dependent Jag1-ICD reverse signaling sustains colorectal cancer progression and chemoresistance. *Cancer Research* 79:5575–5586 DOI 10.1158/0008-5472.CAN-19-0145.

Peng X, Luo Z, Kang Q, Deng D, Wang Q, Peng H, Wang S, Wei Z. 2015. FOXQ1 mediates the crosstalk between TGF-Î² and Wnt signaling pathways in the progression of colorectal cancer. *Cancer Biology and Therapy* 16:1099–1109 DOI 10.1080/15384047.2015.1047568.

Petrelli F, Labianca R, Zaniboni A, Lonardi S, Galli F, Rulli E, Rosati G, Corallo S, Ronzoni M, Cardellino GGG, Mattioli R, Mambrini A, Ciuflfreda L, Banzi M, Pusceddu V, Maiello E, Zampino M, Zagonel V, Marchetti P, Corsi D, Rimassa L, Cinieri S, Sobrero A. 2020. Assessment of Duration and Effects of 3 vs 6 Months of Adjuvant Chemotherapy in High-Risk Stage II Colorectal Cancer: A Subgroup Analysis of the TOSCA Randomized Clinical Trial. *JAMA Oncology* 6:547–551 DOI 10.1001/jamaoncol.2019.6486.

Picardo F, Romanelli A, Muinelo-Romay L, Mazza T, Fusilli C, Parrelia P, Barbazán J, López-López R, Barbano R, De Robertis M, Taffon C, Bordoni V, Agrati C, Costantini M, Ricci F, Graziano P, Maiello E, Muscarella LA, Fazio VM, Poeta ML. 2019. Diagnostic and prognostic value of B4GALT1 hypermethylation and its clinical significance as a novel circulating cell-free DNA biomarker in colorectal cancer. *Cancer* 11:1598 DOI 10.3390/cancers11101598.

Piletič K, Kunej T. 2016. MicroRNA epigenetic signatures in human disease. *Archives of Toxicology* 90:2405–2419 DOI 10.1007/s00204-016-1815-7.

Pirker R, Pereira JR, Szczesna A, Pawel Jvon, Krzakowski M, Ramlau R, Vynnychenko I, Park K, Yu CT, Ganul V, Roh JK, Bajetta E, O’Byrne K, De Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U. 2009. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer
(FLEX): an open-label randomised phase III trial. *The Lancet* **373**:1525–1531 DOI 10.1016/S0140-6736(09)60569-9.

Po A, Citarella A, Catanzaro G, Besharat ZM, Trocchianesi S, Gianno F, Sabato C, Moretti M, De Smaele E, Vacca A, Fiori ME, Ferretti E. 2020. Hedgehog-GLI signaling promotes chemoresistance through the regulation of ABC transporters in colorectal cancer cells. *Scientific Reports* **10**:13988 DOI 10.1038/s41598-020-70871-9.

Porcellini E, Laprovitera N, Riefolo M, Ravaioli M, Garajova I, Ferracin M. 2018. Epigenetic and epitranscriptomic changes in colorectal cancer: diagnostic, prognostic, and treatment implications. *Cancer Letters* **419**:84–95 DOI 10.1016/j.canlet.2018.01.049.

Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, Beijersbergen RL, Bardelli A, Bernards R. 2012. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* **483**:100–104 DOI 10.1038/nature10868.

Rai A, Greening DW, Chen M, Xu R, Ji H, Simpson RJ. 2019. Exosomes Derived from Human Primary and Metastatic Colorectal Cancer Cells Contribute to Functional Heterogeneity of Activated Fibroblasts by Reprogramming Their Proteome. *Proteomics* **19**:e1800148 DOI 10.1002/pmic.201800148.

Ramirez M, Rajaram S, Steininger RJ, Osipchuk D, Roth MA, Morinishi LS, Evans L, Ji W, Hsu C-H, Thurler K, Wei S, Zhou A, Koduru PR, Posner BA, Wu LF, Altschuler SJ. 2016. Diverse drug-resistance mechanisms can emerge from drug-tolerant cancer persister cells. *Nature Communications* **7**:10690 DOI 10.1038/ncomms10690.

Raskov H, Søby JH, Troelsen J, Bojesen RD, Gøgenur I. 2020. Driver gene mutations and epigenetics in colorectal cancer. *Annals of Surgery* **271**:75–85 DOI 10.1097/SLA.0000000000003393.

Rasmussen MH, Jensen NF, Tarpgaard LS, Qvortrup C, Rømer MU, Stenvang J, Hansen TP, Christensen LL, Lindebjerg J, Hansen F, Jensen BV, Hansen TF, Pfeiffer P, Brünner N, Orntoft TF, Andersen CL. 2013. High expression of microRNA-625-3p is associated with poor response to first-line oxaliplatin based treatment of metastatic colorectal cancer. *Molecular Oncology* **7**:637–646 DOI 10.1016/j.molonc.2013.02.016.

Rasmussen MH, Lyskjaer I, Jersie-Christensen RR, Tarpgaard LS, Primdal-Bengtson B, Nielsen MM, Pedersen JS, Hansen TP, Hansen F, Olsen JV, Pfeiffer P, Ørntoft TF, Andersen CL. 2016. MiR-625-3p regulates oxaliplatin resistance by targeting MAP2K6-p38 signalling in human colorectal adenocarcinoma cells. *Nature Communications* **7**:12436–12436 DOI 10.1038/ncomms12436.

Rawla P, Sunkara T, Barsouk A. 2019. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* **14**:89–103 DOI 10.5114/pg.2018.81072.

Raymond E, Faivre S, Woynarowski JM, Chaney SG. 1998. Oxaliplatin: mechanism of action and antineoplastic activity. *Seminars in Oncology* **2**:4–12.

Ren J, Ding L, Zhang D, Shi G, Xu Q, Shen S, Wang Y, Wang T, Hou Y. 2018. Carcinoma-associated fibroblasts promote the stemness and chemoresistance of
colorectal cancer by transferring exosomal lncRNA H19. *Theranostics* 8:3932–3948 DOI 10.7150/thno.25541.

Rentsch M, Schiergens T, Khandoga A, Werner J. 2016. Surgery for colorectal cancer—Trends, developments, and future perspectives. *Visceral Medicine* 32:184–191 DOI 10.1159/000446490.

Ressa A, Bosdriesz E, De Ligt J, Mainardi S, Maddalo G, Prahallad A, Jager M, De La Fonteijn L, Fitzpatrick M, Groten S, Alтелaar AFM, Bernards R, Cuppen E, Wessels L, Heck AJR. 2018. A system-wide approach to monitor responses to synergistic BRAF and EGFR inhibition in colorectal cancer cells. *Molecular and Cellular Proteomics* 17:1892–1908 DOI 10.1074/mcp.RA117.000486.

Rezapour S, Hosseinzadeh E, Marofi F, Hassanzadeh A. 2019. Epigenetic-based therapy for colorectal cancer: Prospect and involved mechanisms. *Journal of Cellular Physiology* 234:19366–19383 DOI 10.1002/jcp.28658.

Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, Taylor G, Barrett JH, Quirke P. 2009. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. *Journal of Clinical Oncology* 27:5931–5937 DOI 10.1200/JCO.2009.22.4295.

Rimassa L, Bozzarelli S, Pietrantonio F, Cordio S, Lonardi S, Toppo L, Zaniboni A, Bordonaro R, Di Bartolomeo M, Tomasello G, Dadduzio V, Tronconi MC, Piombo C, Giordano L, Gloghini A, Di Tommaso L, Santoro A. 2019. Phase II study of tivantinib and cetuximab in patients with KRAS wild-type metastatic colorectal cancer with acquired resistance to EGFR inhibitors and emergence of MET overexpression: lesson learned for future trials with EGFR/MET dual inhibition. *Clinical Colorectal Cancer* 18:125–132 DOI 10.1016/j.clcc.2019.02.004.

Rodilla V, Villanueva A, Obrador-Hevia A, Robert-Moreno À, Fernández-Majada V, Grilli A, López-Bigas N, Bellora N, Albà MM, Torres F, Duñach M, Sanjuán X, Gonzalez S, Gridley T, Capella G, Bigas A, Espinosa L. 2009. Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America* 106:6315–6320 DOI 10.1073/pnas.0813221106.

Russo M, Crisafulli G, Sogari A, Reilly NM, Arena S, Lamba S, Bartolini A, Amadio V, Magri A, Novara L, Sarotto I, Nagel ZD, Piett CG, Amatu A, Sartore-Bianchi A, Siena S, Bertotti A, Trusolino L, Corigliano M, Gherardi M, Lagomarsino MC, Nicolantonio F Di, Bardelli A. 2019. Adaptive mutability of colorectal cancers in response to targeted therapies. *Science* 366:1473–1480 DOI 10.1126/science.aav4474.

Russo M, Siravegna G, Blaszkowsky LS, Corti G, Crisafulli G, Ahronian LG, Mussolin B, Kwak EL, Buscarino M, Lazzari I, Valtorta E, Truini M, Jessop NA, Robinson HE, Hong TS, Mino-Kenudson M, Di Nicolantonio F, Thabet A, Sartore-Bianchi A, Siena S, Iafrate J, Bardelli A, Corcoran RB. 2016. Tumor heterogeneity and Lesion-Specific response to targeted therapy in colorectal cancer. *Cancer Discovery* 6:147–153 DOI 10.1158/2159-8290.CD-15-1283.
Sakahara M, Okamoto T, Oyanagi J, Takano H, Natsume Y, Yamanaka H, Kusama D, Fusejima M, Tanaka N, Mori S, Kawachi H, Ueno M, Sakai Y, Noda T, Nagayama S, Yao R. 2019. IFN/STAT signaling controls tumorigenesis and the drug response in colorectal cancer. *Cancer Science* **110**:1293–1305 DOI 10.1111/cas.13964.

Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL. 2000. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *New England Journal of Medicine* **343**:905–914 DOI 10.1056/NEJM200009283431302.

Samuels Y, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, Willson JKV, Markowitz S, Kinzler KW, Vogelstein B, Velculesscove VE. 2004. High frequency of mutations of the PIK3CA gene in human cancers. *Science* **304**:554 DOI 10.1126/science.1096502.

Sansom OJ, Reed KR, Hayes AJ, Ireland H, Brinkmann H, Newton IP, Battle E, Simon-Assmann P, Clevers H, Nathke IS, Clarke AR, Winton DJ. 2004. Loss of Apc in vivo immediately perturbs Wnt signaling, differentiation, and migration. *Genes and Development* **18**:1385–1390 DOI 10.1101/gad.287404.

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. 2005. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science* **307**:1098–1101 DOI 10.1126/science.1106148.

Sartore-Bianchi A, Di Nicolantonio F, Michelatti M, Molinari F, De Dosso S, Saeletti P, Martini M, Cipani T, Marrapease G, Mazzucchelli L, Lamba S, Veronesi S, Frattini M, Bardelli A, Siena S. 2009. Multi-determinants analysis of molecular alterations for predicting clinical benefit to EGFR-targeted monoclonal antibodies in colorectal cancer. *PLOS ONE* **4**:e7287 DOI 10.1371/journal.pone.0007287.

Satoh K, Yachida S, Sugimoto M, Oshima M, Nakagawa T, Akamoto S, Tabata S, Saitoh K, Kato K, Sato S, Igarashi K, Aizawa Y, Kajino-Sakamoto R, Kojima Y, Fujishita T, Enomoto A, Hirayama A, Ishikawa T, Takeo MM, Kushida Y, Haba R, Okano K, Tomita M, Suzuki Y, Fukuda S, Aoki M, Soga T. 2017. Global metabolic reprogramming of colorectal cancer occurs at adenoma stage and is induced by MYC. *Proceedings of the National Academy of Sciences of the United States of America* **114**:E7697–E7706 DOI 10.1073/pnas.1710366114.

Schumacher D, Andrieux G, Boehnek K, Keil M, Silvestri A, Silvestrov M, Keilholz U, Haybaeck J, Erdmann G, Sachse C, Tempelin M, Hoffmann J, Boerries M, Schäfer R, Regenbrecht CRA. 2019. Heterogeneous pathway activation and drug response modelled in colorectal-tumor-derived 3D cultures. *PLOS Genetics* **15**:e1008076 DOI 10.1371/journal.pgen.1008076.

Seppälä TT, Böhm JP, Friman M, Lahtinen L, Väyrynen VM, Liipo TKE, Ristimäki AP, Kairaluoma MJ, Kellokumpu IH, Kuopio THI, Mecklin JP. 2015. Combination of microsatellite instability and BRAF mutation status for subtyping colorectal cancer. *British Journal of Cancer* **112**:1966–1975 DOI 10.1038/bjc.2015.160.

Shaik JP, Alanazi IO, Pathan AAK, Parine NR, Almadi MA, Azzam NA, Aljebreen AM, Alharbi O, Alanazi MS, Khan Z. 2020. Frequent activation of notch signaling...
pathway in colorectal cancers and its implication in patient survival outcome. *Journal of Oncology* 2020:6768942. DOI 10.1155/2020/6768942.

Shan Y, Gao Y, Jin W, Fan M, Wang Y, Gu Y, Shan C, Sun L, Li X, Yu B, Luo Q, Xu Q. 2019. Targeting HIBCH to reprogram valine metabolism for the treatment of colorectal cancer. *Cell Death and Disease* 10:618 DOI 10.1038/s41419-019-1832-6.

Shang S, Hua F, Hu ZW. 2017. The regulation of β-catenin activity and function in cancer: therapeutic opportunities. *Oncotarget* 8:33972–33989 DOI 10.18632/oncotarget.15687.

Shen H, Li L, Yang S, Wang D, Zhong S, Zhao J, Tang J. 2016. MicroRNA-29a contributes to drug-resistance of breast cancer cells to adriamycin through PTEN/AKT/GSK3β signaling pathway. *Gene* 593:84–90 DOI 10.1016/j.gene.2016.08.016.

Shen K, Mao R, Ma L, Li Y, Qiu Y, Cui D, Le V, Yin P, Ni L, Liu J. 2014. Post-transcriptional regulation of the tumor suppressor miR-139-5p and a network of miR-139-5p-mediated mRNA interactions in colorectal cancer. *FEBS Journal* 281:3609–3624 DOI 10.1111/febs.12880.

Shen Y, Tong M, Liang Q, Guo Y, Sun HQ, Zheng W, Ao L, Guo Z, She F. 2018. Epigenomics alternations and dynamic transcriptional changes in responses to 5-fluorouracil stimulation reveal mechanisms of acquired drug resistance of colorectal cancer cells. *Pharmacogenomics Journal* 18:23–28 DOI 10.1038/tpj.2016.91.

Sherwood LM, Parris EE, Folkman J. 1971. Tumor Angiogenesis: therapeutic Implications. *New England Journal of Medicine* 285:1182–1186 DOI 10.1056/NEJM197111182852108.

Shi L, Li X, Wu Z, Li X, Nie J, Guo M, Mei Q, Han W. 2018. DNA methylation-mediated repression of miR-181a/135a/302c expression promotes the microsatellite-unstable colorectal cancer development and 5-FU resistance via targeting PLAG1. *Journal of Genetics and Genomics* 45:205–214 DOI 10.1016/j.jgg.2018.04.003.

Shi X, Valizadeh A, Mir SM, Asemi Z, Karimian A, Majidina M, Safa A, Yosefi B. 2020. miRNA-29a reverses P-glycoprotein-mediated drug resistance and inhibits proliferation via up-regulation of PTEN in colon cancer cells. *European Journal of Pharmacology* 880:173138 DOI 10.1016/j.ejphar.2020.173138.

Siebel C, Lendahl U. 2017. Notch signaling in development, tissue homeostasis, and disease. *Physiological Reviews* 97:1235–1294 DOI 10.1152/physrev.00005.2017.

Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. 2017. Colorectal cancer statistics. 2017. *CA: A Cancer Journal for Clinicians* 67:177–193 DOI 10.3322/caac.21395.

Sitia I, Bonizzi A, Mazzucchelli S, Negri S, Sottani C, Grignani E, Rizzuto MA, Prosperi D, Sorrentino L, Morasso C, Allevi R, Severi M, Silva F, Truffi M, Corsi F. 2021. Selective targeting of cancer-associated fibroblasts by engineered h-ferritin nanocages loaded with navitoclax. *Cell* 10:328 DOI 10.3390/cells10020328.

Skrede OJ, De Raedt S, Kleppe A, Hveem TS, Liestøl K, Maddison J, Askaudrud HA, Pradhan M, Nesheim JA, Albrechtsen F, Farstad IN, Domingo E, Church DN, Nesbakken A, Shepherd NA, Tomlinson I, Kerr R, Novelli M, Kerr DJ, Danielsen
HE. 2020. Deep learning for prediction of colorectal cancer outcome: a discovery and validation study. *The Lancet* **395**:350–360 DOI 10.1016/S0140-6736(19)32998-8.

Sobhani I, Bergsten E, Couffin S, Amiot A, Nebbad B, Barau C, De’Angelis N, Rabot S, Canouï-Poitrine F, Mestivier D, Pédron T, Khazaie K, Sansonetti PJ. 2019. Colorectal cancer-associated microbiota contributes to oncogenic epigenetic signatures. *Proceedings of the National Academy of Sciences of the United States of America* **116**:24285–24295 DOI 10.1073/pnas.1912129116.

Soleimani A, Rahmani F, Ferns GA, Ryzhikov M, Avan A, Hassanian SM. 2019. Role of regulatory oncogenic or tumor suppressor miRNAs of PI3K/AKT signaling axis in the pathogenesis of colorectal cancer. *Current Pharmaceutical Design* **24**:4605–4610 DOI 10.2174/1381612825666190110151957.

Spranger S, Bao R, Gajewski T. 2015. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. *Nature* **523**:231–235 DOI 10.1038/nature14404.

Stigliano V, Sanchez-Mete L, Martayan A, Anti M. 2014. Early-onset colorectal cancer: a sporadic or inherited disease? *World Journal of Gastroenterology* **20**:12420–12430 DOI 10.3748/wjg.v20.i35.12420.

Su C-C, Lin Y-P, Cheng Y-J, Huang J-Y, Chuang W-J, Shan Y-S, Yang B-C. 2007. Phosphatidylinositol 3-Kinase/Akt activation by integrin-tumor matrix interaction suppresses fas-mediated apoptosis in T Cells. *The Journal of Immunology* **179**:4589–4597 DOI 10.4049/jimmunol.179.7.4589.

Sun L, Ke J, He Z, Chen Z, Huang Q, Ai W, Wang G, Wei Y, Zou X, Zhang S, Lan P, Hong C. 2017. HES1 promotes colorectal cancer cell resistance to 5-Fu by inducing of EMT and ABC transporter proteins. *Journal of Cancer* **8**:2802–2808 DOI 10.7150/jca.19142.

Swanton C. 2012. Intratumor heterogeneity: evolution through space and time. *Cancer Research* **72**:4875–4882 DOI 10.1158/0008-5472.CAN-12-2217.

Tabernero J, Chan E, Baselga J, Blay J-Y, Chau I, Hyman DM, Raje NS, Wolf J, Sirzen F, Veronese ML, Mitchell L, Hidalgo M. 2014. VE-BASKET, a Simon 2-stage adaptive design, phase II, histology-independent study in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m): activity of vemurafenib (VEM) with or without cetuximab (CTX) in colorectal cancer (CRC). *Journal of Clinical Oncology* **32**:3518–3518 DOI 10.1200/jco.2014.32.15_suppl.3518.

Taciak B, Pruszynska I, Kiraga L, Bialasek M, Krol M. 2018. Wnt signaling pathway in development and cancer. *Journal of Physiology and Pharmacology* **69**:185–196 DOI 10.26402/jpp.2018.2.07.

Taelman VF, Dobrowolski R, Plouhinec JL, Fuentealba LC, Vorwald PP, Gumper I, Sabatini DD, De Robertis EM. 2010. Wnt signaling requires sequestration of Glycogen Synthase Kinase 3 inside multivesicular endosomes. *Cell* **143**:1136–1148 DOI 10.1016/j.cell.2010.11.034.

Tang YA, Chen YF, Bao Y, Mahara S, Yatim SMJM, Oguz G, Lee PL, Feng M, Cai Y, Tan EY, Fong SS, Yang ZH, Lan P, Wu XJ, Yu Q. 2018. Hypoxic tumor microenvironment activates GLI2 via HIF-1α and TGF-β2 to promote chemoresistance in...
colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America* **115**:E5990–E5999 DOI 10.1073/pnas.1801348115.

Teng W, Kuan N, Lu TX, Hua D. 2017. Elevated expression of TrpC5 and GLUT1 is associated with chemoresistance in colorectal cancer. *Oncology Reports* **37**:1059–1065 DOI 10.3892/or.2016.5322.

Tong M, Zheng W, Li H, Li X, Ao L, Shen Y, Liang Q, Li J, Hong G, Yan H, Cai H, Li M, Guan Q, Guo Z. 2016. Multi-omics landscapes of colorectal cancer subtypes discriminated by an individualized prognostic signature for 5-fluorouracil-based chemotherapy. *Oncogenesis* **5**:e242–e242 DOI 10.1038/oncsis.2016.51.

Townley CA, Major P, Siu LL, Dancey J, Chen E, Pond GR, Nicklee T, Ho J, Hedley D, Tsao M, Moore MJ, Oza AM. 2006. Phase II study of erlotinib (OSI-774) in patients with metastatic colorectal cancer. *British Journal of Cancer* **94**:1136–1143 DOI 10.1038/sj.bjc.6603055.

Vaish V, Kim J, Shim M. 2017. Jagged-2 (JAG2) enhances tumorigenicity and chemoresistance of colorectal cancer cells. *Oncotarget* **8**:53262–53275 DOI 10.18632/oncotarget.18391.

Valvezan AJ, Zhang F, Diehl JA, Klein PS. 2012. Adenomatous Polyposis Coli (APC) regulates multiple signaling pathways by enhancing glycogen synthase kinase-3 (GSK-3) activity. *Journal of Biological Chemistry* **287**:3823–3832 DOI 10.1074/jbc.M111.323337.

Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chien CRC, Makhson A, D’Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Teijpar S, Schlichting M, Nipppgen J, Rougier P. 2009. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *New England Journal of Medicine* **360**:1408–1417 DOI 10.1056/NEJMoA0805019.

Van Kappel EC, Maurice MM. 2017. Molecular regulation and pharmacological targeting of the β-catenin destruction complex. *British Journal of Pharmacology* **174**:4575–4588 DOI 10.1111/bph.13922.

Van Schaeybroeck S, Kyula JN, Fenton A, Fenning CS, Sasazuki T, Shirasawa S, Longley DB, Johnston PG. 2011. Oncogenic Kras promotes chemotherapy-induced growth factor shedding via ADAM17. *Cancer Research* **71**:1071–1080 DOI 10.1158/0008-5472.CAN-10-0714.

Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S, Duval A, Carneiro F, Machado JC, Hamelin R, Seruca R. 2005. The prevalence of PIK3CA mutations in gastric and colon cancer. *European Journal of Cancer* **41**:1649–1654 DOI 10.1016/j.ejca.2005.04.022.

Vellinga T, Borovski T, De Boer V, Fatrai S, Van Schelven S, Trumpi K, Verheem A, Snoeren E, Emmink B, Koster J, Rinkes I, Kranenburg O. 2015. SIRT1/PGC1α-Dependent Increase in Oxidative Phosphorylation Supports Chemotherapy Resistance of Colon Cancer. *Clinical Cancer Research* **21**:2870–2879 DOI 10.1158/1078-0432.CCR-14-2290.

Venook AP. 2005. Epidermal growth factor receptor-targeted treatment for advanced colorectal carcinoma. *Cancer* **103**:2435–2446 DOI 10.1002/cncr.21123.
Vera-Yunca D, Girard P, Parra-Guillen ZP, Munafo A, Trocóniz IF, Terranova N. 2020. Machine learning analysis of individual tumor lesions in four metastatic colorectal cancer clinical studies: linking tumor heterogeneity to overall survival. *AAPS Journal* 22:58 DOI 10.1208/s12248-020-0434-7.

Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. 2008. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *New England Journal of Medicine* 359:1116–1127 DOI 10.1056/NEJMoa0802656.

Visone R, Bacalini MG, Franco S Di, Ferracin M, Colorito ML, Pagotto S, Laprovitera N, Licastro D, Marco M Di, Scavo E, Bassi C, Saccenti E, Nicotra A, Grzes M, Garagnani P, Laurenzi V De, Valeri N, Mariani-Costantini R, Negrini M, Stassi G, Veronese A. 2019. DNA methylation of shelf, shore and open sea CpG positions distinguish high microsatellite instability from low or stable microsatellite status colon cancer stem cells. *Epigenomics* 11:587–604 DOI 10.2217/epi-2018-0153.

Vinson KE, George DC, Fender AW, Bertrand FE, Sigounas G. 2016. The Notch pathway in colorectal cancer. *International Journal of Cancer* 138:1835–1842 DOI 10.1002/ijc.29800.

Vitiello PP, Cardone C, Martini G, Ciardiello D, Belli V, Matrone N, Barra G, Napolitano S, Corte CDella, Turano M, Furia M, Troiani T, Morgillo F, De Vita F, Ciardiello F, Martinelli E. 2019. Receptor tyrosine kinase-dependent PI3K activation is an escape mechanism to vertical suppression of the EGFR/RAS/MAPK pathway in KRAS-mutated human colorectal cancer cell lines. *Journal of Experimental and Clinical Cancer Research* 38:41 DOI 10.1186/s13046-019-1035-0.

Wan PTC, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, Jones CM, Marshall CJ, Springer CJ, Barford D, Marais R, Project CG, Jones CM, Marshall CJ, Springer CJ, Barford D, Marais R. 2004. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* 116:855–867 DOI 10.1016/S0092-8674(04)00215-6.

Wan ML, Wang Y, Zeng Z, Deng B, Zhu BS, Cao T, Li YK, Xiao J, Han Q, Wu Q. 2020. Colorectal cancer (CRC) as a multifactorial disease and its causal correlations with multiple signaling pathways. *Bioscience Reports* 40:20200265 DOI 10.1042/BSR20200265.

Wang Q, Chen X, Jiang Y, Liu S, Liu H, Sun X, Zhang H, Liu Z, Tao Y, Li C, Hu Y, Liu D, Ye D, Liu Y, Wang M, Zhang X. 2020b. Elevating H3K27me3 level sensitizes colorectal cancer to oxaliplatin. *Journal of Molecular Cell Biology* 12:125–137 DOI 10.1093/jmcb/mjz032.

Wang L, Hui H, Agrawal K, Kang Y, Li N, Tang R, Yuan J, Rana TM. 2020a. m 6 A RNA methyltransferases METTL3/14 regulate immune responses to anti-PD-1 therapy. *The EMBO Journal* 39 DOI 10.15252/embj.2020104514.

Wang X, Ghareeb WM, Zhang Y, Yu Q, Lu X, Huang Y, Huang S, Sun Y, Chi P. 2019. Hypermethylated and downregulated MEIS2 are involved in stemness properties and...
oxaliplatin-based chemotherapy resistance of colorectal cancer. *Journal of Cellular Physiology* **234**:18180–18191 DOI 10.1002/jcp.28451.

Wang Q, Shi YL, Zhou K, Wang LL, Yan ZX, Liu YL, Xu LL, Zhao SW, Chu HL, Shi TT, Ma QH, Bi J. 2018. PIK3CA mutations confer resistance to first-line chemotherapy in colorectal cancer. *Cell Death and Disease* **9**:739 DOI 10.1038/s41419-018-0776-6.

Wang X, Zhang H, Chen X. 2019. Drug resistance and combating drug resistance in cancer. *Cancer Drug Resistance* **2**:141–160 DOI 10.20517/cdr.2019.10.

Wang X, Zhang H, Yang H, Bai M, Ning T, Deng T, Liu R, Fan Q, Zhu K, Li J, Zhan Y, Ying G, Ba Y. 2020c. Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer. *Molecular Oncology* **14**:539–555 DOI 10.1002/1878-0261.12629.

Weber S, Koschade SE, Hoffmann CM, Dubash TD, Giessler KM, Dieter SM, Herbst F, Glimm H, Ball CR. 2019. The notch target gene HEYL modulates metastasis forming capacity of colorectal cancer patient-derived spheroid cells in vivo. *BMC Cancer* **19**:1181 DOI 10.1186/s12885-019-6396-4.

Wee Z, Liu HT. 2002. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Research* **12**:9–18 DOI 10.1038/sj.cr.7290105.

Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S. 2006. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nature Reviews Drug Discovery* **5**:835–844 DOI 10.1038/nrd2130.

Wolpin BM, Mayer RJ. 2008. Systemic treatment of colorectal cancer. *Gastroenterology* **134**:1296–1310 DOI 10.1053/j.gastro.2008.02.098.

Woolston A, Khan K, Spain G, Barber LJ, Griffiths B, Gonzalez-Exposito R, Hornsteiner I, Punta M, Patil Y, Newey A, Mansukhani S, Davies MN, Furness A, Sclafani F, Peckitt C, Jiménez M, Kouvelakis K, Ranftl R, Begum R, Rana I, Thomas J, Bryant A, Quezada S, Wotherspoon A, Khan N, Fotiadis N, Marafioti T, Powles T, Lise S, Calvo F, Guettler S, Loga K von, Rao S, Watkins D, Starling N, Chau I, Sadanandam A, Cunningham D, Gerlinger M. 2019. Genomic and transcriptomic determinants of therapy resistance and immune landscape evolution during Anti-EGFR treatment in colorectal cancer. *Cancer Cell* **36**:35–50 DOI 10.1016/j.ccell.2019.05.013.

Wu G, Huang H, Abreu JG, He X. 2009. Inhibition of GSK3 phosphorylation of β-catenin via phosphorylated PPPSPXS motifs of Wnt coreceptor LRP6. *PLOS ONE* **4** DOI 10.1371/journal.pone.0004926.

Xie YH, Chen YX, Fang JY. 2020a. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduction and Targeted Therapy* **5**:22 DOI 10.1038/s41392-020-0116-z.

Xie M, He CS, Wei SH, Zhang L. 2013. Notch-1 contributes to epidermal growth factor receptor tyrosine kinase inhibitor acquired resistance in non-small cell
lung cancer in vitro and in vivo. *European Journal of Cancer* **49**:3559–3572 DOI 10.1016/j.ejca.2013.07.007.

Xie ZY, Wang FF, Xiao ZH, Liu SF, Tang SL, Lai YL. 2020b. Overexpressing microRNA-34a overcomes ABCG2-mediated drug resistance to 5-FU in side population cells from colon cancer via suppressing DLL1. *Journal of Biochemistry* **167**:557–564 DOI 10.1093/jb/mvaa012.

Xu JM, Wang Y, Wang YL, Wang Y, Liu T, Ni M, Li MS, Lin L, Ge FJ, Gong C, Gu JY, Jia R, Wang HF, Chen YL, Liu RR, Zhao CH, Tan ZL, Jin Y, Zhu YP, Ogino S, Qian ZR. 2017. PIK3CA mutations contribute to acquired cetuximab resistance in patients with metastatic colorectal cancer. *Clinical Cancer Research* **23**:4602–4616 DOI 10.1158/1078-0432.CCR-16-2738.

Xu Z, Zhang Y, Xu M, Zheng X, Lin M, Pan J, Ye C, Deng Y, Jiang C, Lin Y, Lu X, Chi P. 2019. Demethylation and overexpression of CSF2 are involved in immune response, chemotherapy resistance, and poor prognosis in colorectal cancer. *OncoTargets and Therapy* **12**:11255–11269 DOI 10.2147/OTT.S216829.

Yachida S, Mizutani S, Shiroma H, Shiba S, Nakajima T, Sakamoto T, Watanabe H, Masuda K, Nishimoto Y, Kubo M, Hosoda F, Rokutani H, Matsumoto M, Takamura H, Yamada M, Matsuda T, Iwasaki M, Yamaji T, Yachida T, Soga T, Kurokawa K, Toyoda A, Ogura Y, Hayashi T, Hatakeyama M, Nakagama H, Saito Y, Fukuda S, Shibata T, Yamada T. 2019. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nature Medicine* **25**:968–976 DOI 10.1038/s41591-019-0458-7.

Yadav VK, Huang YJ, George TA, Wei PL, Sumitra MR, Ho CL, Chang TH, Wu ATH, Huang HS. 2020. Preclinical evaluation of the novel small-molecule msi-n1014 for treating drug-resistant colon cancer via the lgr5/β-catenin/mir-142-3p network and reducing cancer-associated fibroblast transformation. *Cancer* **12**:1–15 DOI 10.3390/cancers12061590.

Yamada T, Matsuda A, Takahashi G, Iwai T, Takeda K, Ueda K, Kuriyama S, Koizumi M, Shinji S, Yokoyama Y, Ohta R, Yoshida H. 2020. Emerging RAS, BRAF, and EGFR mutations in cell-free DNA of metastatic colorectal patients are associated with both primary and secondary resistance to first-line anti-EGFR therapy. *International Journal of Clinical Oncology* **25**:1523–1532 DOI 10.1007/s10147-020-01691-0.

Yarden Y, Pines G. 2012. The ERBB network: at last, cancer therapy meets systems biology. *Nature Reviews Cancer* **12**:553–563 DOI 10.1038/nrc3309.

Yi H, Li G, Long Y, Liang W, Cui H, Zhang B, Tan Y, Li Y, Shen L, Deng D, Tang Y, Mao C, Tian S, Cai Y, Zhu Q, Hu Y, Chen W, Fang L. 2020. Integrative multiomics analysis of a colon cancer cell line with heterogeneous Wnt activity revealed RUNX2 as an epigenetic regulator of EMT. *Oncogene* **39**:5152–5164 DOI 10.1038/s41388-020-1351-z.

Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, Ercan D, Rogers A, Roncalli M, Takeda M, Fujisaka Y, Philips J, Shimizu T, Maenishi O, Cho Y, Sun J, Destro A, Taira K, Takeda K, Okabe T, Swanson J, Itoh H, Takada M, Lifshits E, Okuno K, Engelman JA, Shivdasani RA, Nishio K, Fukuoka M,
Varella-Garcia M, Nakagawa K, Jänne PA. 2011. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Science Translational Medicine* 3:99ra86 DOI 10.1126/scitranslmed.3002442.

Yoon HH, Shi Q, Heying EN, Muranyi A, Bredno J, Ough F, Djililvand A, Clements J, Bowermaster R, Liu WW, Barnes M, Alberts SR, Shannugam K, Sinicrope FA. 2019. Intertumoral heterogeneity of CD3⁺and CD8⁺T-cell densities in the microenvironment of DNA mismatch-repair–deficient colon cancers: implications for prognosis. *Clinical Cancer Research* 25:125–133 DOI 10.1158/1078-0432.CCR-18-1984.

Yu TC, Guo F, Yu Y, Sun T, Ma D, Han J, Qian Y, Kryczek I, Sun D, Nagarsheth N, Chen Y, Chen H, Hong J, Zou W, Fang JY. 2017. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. *Cell* 170:548–563 DOI 10.1016/j.cell.2017.07.008.

Yu J, Hu D, Cheng Y, Guo J, Wang Y, Tan Z, Peng J, Zhou H. 2021. Lipidomics and transcriptomics analyses of altered lipid species and pathways in oxaliplatin-treated colorectal cancer cells. *Journal of Pharmaceutical and Biomedical Analysis* 200:114077 DOI 10.1016/j.jpba.2021.114077.

Yuan LL, Li I, Liu JN, Mei J, Lei CJ. 2018. Down-regulation of miR-29a facilitates apoptosis of colorectal carcinoma cell SW480 and suppresses its Paclitaxel resistance. *European Review for Medical and Pharmacological Sciences* 22:5499–5507 DOI 10.26355/eurrev_201809_15810.

Yue B, Cai D, Liu C, Fang C, Yan D. 2016. Linc00152 functions as a competing endogenous RNA to confer oxaliplatin resistance and holds prognostic values in colon cancer. *Molecular Therapy* 24:2064–2077 DOI 10.1038/mt.2016.180.

Yue B, Liu C, Sun H, Liu M, Song C, Cui R, Qiu S, Zhong M. 2018. A positive feed-forward loop between LncRNA-CYTOR and Wnt/β-Catenin signaling promotes metastasis of colon cancer. *Molecular Therapy* 26:1287–1298 DOI 10.1016/j.ymthe.2018.02.024.

Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, Ukaegbu CL, Brais LK, McNamara PG, Mayer RJ, Schrag D, Meyerhardt JA, Ng K, Kidd J, Singh N, Hartman AR, Wenstrup RJ, Syngal S. 2017. Cancer susceptibility gene mutations in individuals with colorectal cancer. *Journal of Clinical Oncology* 35:1086–1095 DOI 10.1200/JCO.2016.71.0012.

Zhang L, Castanaro C, Luan B, Yang K, Fan L, Fairhurst JL, Rafique A, Potocky TB, Shan J, Delfino FJ, Shi E, Huang T, Martin JH, Chen G, MacDonald D, Rudge JS, Thurston G, Daly C. 2014a. ERBB3/HER2 signaling promotes resistance to EGFR blockade in head and neck and colorectal cancer models. *Molecular Cancer Therapeutics* 13:1345–1355 DOI 10.1158/1535-7163.MCT-13-1033.

Zhang L, Dong Y, Zhu N, Tsai H, Zhao Z, Wu CW, Wang K, Zheng S, Ng SSM, Chan FKL, Sung JJY, Yu J. 2014b. MicroRNA-139-5p exerts tumor suppressor function by targeting NOTCH1 in colorectal cancer. *Molecular Cancer* 13:1–12 DOI 10.1186/1476-4598-13-124.

Zhang C, Li C, Chen X, Zhou Y, Yin B, Ni R, Zhang Y, Liu J. 2017a. Overexpression of dishevelled 2 is involved in tumor metastasis and is associated with poor prognosis.
in hepatocellular carcinoma. *Clinical and Translational Oncology* 19:1507–1517 DOI 10.1007/s12094-017-1697-z.

Zhang K, Li M, Huang H, Li L, Yang J, Feng L, Gou J, Jiang M, Peng L, Chen L, Li T, Yang P, Yang Y, Wang Y, Peng Q, Dai X, Zhang T. 2017b. Dishevelled1-3 contribute to multidrug resistance in colorectal cancer via activating Wnt/β-catenin signaling. *Oncotarget* 8:115803–115816 DOI 10.18632/oncotarget.23253.

Zou ZZ, Nie PP, Li YW, Hou BX, Rui-Li, Shi XP, Ma ZK, Han BW, Luo XY. 2017. Synergistic induction of apoptosis by salinomycin and gefitinib through lysosomal and mitochondrial dependent pathway overcomes gefitinib resistance in colorectal cancer. *Oncotarget* 8:22414–22432 DOI 10.18632/oncotarget.5628.

Zhao Q, Zhuang K, Han K, Tang H, Wang Y, Si W, Yang Z. 2020. Silencing DVL3 defeats MTX resistance and attenuates stemness via Notch Signaling Pathway in colorectal cancer. *Pathology Research and Practice* DOI 10.1016/j.prp.2020.152964.

Zhong S, Li W, Chen Z, Xu J, Zhao J. 2013. MiR-222 and miR-29a contribute to the drug-resistance of breast cancer cells. *Gene* 531:8–14 DOI 10.1016/j.gene.2013.08.062.

Zhou Y, Cheng X, Zhang F, Chen Q, Chen X, Shen Y, Lai C, Kota VG, Sun W, Huang Q, Yuan Y, Wang J, Lai M, Zhang D. 2020. Integrated multi-omics data analyses for exploring the co-occurring and mutually exclusive gene alteration events in colorectal cancer. *Human Mutation* 41:1588–1599 DOI 10.1002/humu.24059.

Zougar A, Haebe JR, Benoit YD. 2020. Intestinal microbiota influences dna methylome and susceptibility to colorectal cancer. *Gene* 11:1–6 DOI 10.3390/genes11070808.