Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways: A review

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Abstract

Colorectal carcinogenesis (CRC) imposes a major health burden in developing countries. It is the third major cause of cancer deaths. Despite several treatment strategies, novel drugs are warranted to reduce the severity of this disease. Adenomatous polyps in the colon are the major culprits in CRC and found in 45% of cancers, especially in patients 60 years of age. Inflammatory polyps are currently gaining attention in CRC, and a growing body of evidence denotes the role of inflammation in CRC. Several experimental models are being employed to investigate CRC in animals, which include the APCmin/+ mouse model, Azoxymethane, Dimethyl hydrazine, and a combination of Dextran sodium sulphate and dimethyl hydrazine. During CRC progression, several signal transduction pathways are activated. Among the major signal transduction pathways are p53, Transforming growth factor beta, Wnt/β-catenin, Delta Notch, Hippo signalling, nuclear factor erythroid 2-related factor 2 and Kelch-like ECH-associated protein 1 pathways. These signalling pathways collaborate with cell death mechanisms, which include apoptosis, necroptosis and autophagy, to determine cell fate. Extensive research has been carried out in our laboratory to investigate these signal transduction and cell death mechanistic pathways in CRC. This review summarizes CRC pathogenesis and the related cell death and signal transduction pathways.
Key words: Colorectal cancer; Cell death; Apoptosis; Autophagy; Inflammation; Hippo signalling; Nuclear factor erythroid 2-related factor 2; Wnt signalling

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Core tip: Colorectal carcinogenesis (CRC) imposes a major health burden. This review addresses the cell death mechanisms and major signal transduction pathways involved in CRC. Regulated cell death is important for maintaining normal homeostasis, and the dysregulation of cell death processes leads to a spectrum of diseases including cancer. It is interesting to note that cell death pathways collaborate with each other, so understanding the various cell death mechanisms are therefore essential. CRC is orchestrated by various signal transduction pathways, which are used as drug targets. This review highlights the key concepts concerning cell death mechanisms and signal transduction in CRC.

INTRODUCTION

Cancer is a dreadful disease caused to an anomalous growth of cells, which leads to an irregular balance of cell proliferation and death. Cell death is a physiological process where normal cells are regulated by “touch contact-inhibition”. However, proliferating tumor cells metastasize to distant sites and invade other tissues, often causing morbidity. In recent years, colorectal carcinogenesis (CRC) has imposed a major health burden in developing countries. CRC is the second highest cause of cancer deaths in women, and the third highest cause of cancer deaths in men. Due to environmental factors, a sedentary lifestyle and diet, the risk of CRC has been growing over the past few years. In many cases, the symptoms are not recognized by the individual. Although awareness via cancer screenings and the knowledge of therapy modalities has increased, the burden of CRC is much more pronounced in developing countries. The mortality rate of CRC is particularly high in Asian and African populations. Recently, mortality rates are declining in Western countries because of early screening and better treatment procedures. An increase in mortality has been reported in several Latin American countries, the Caribbean and Asia, likely due to inadequate health infrastructure and the lack of awareness about cancer screenings. It is well-known that dietary factors influence the incidences of CRC. Diets that are rich in fiber and that have low fat content tend to prevent CRC. The food stuffs we intake determine our quality of health. Fried foods, red meat, and processed foods all increase CRC risk.

ROLE OF POLyps IN COloRECTAL CANCer

The cells in the lining of the colon change morphologically and proliferate uncontrollably. Benign (non-cancerous) polyps are often found lining the bowels. They occur in several areas of the gastrointestinal tract, but predominantly arise in the colon. They appear as small protrusions in the lumen. As aging progresses, the number of polyps increases. Malignant polyps indicate an adenoma that appears benign. Adenomas are precursor lesions in CRC that arise through the adenoma-carcinoma sequence. CRC develops due to the formation of malignant neoplasms within the lining of the large intestine. Malignancy risk has been linked to the site, size, and histological characteristics of polyps. Polyps < 5 mm in diameter are harmless and pose an insignificant risk of malignancy, whereas those with a diameter > 25 mm pose a significant risk. Colonic polyps are aberrant growths that appears in the colon. Polyps, in principle, can be diagnosed by screening the colon via endoscopy or colonoscopy. Three types of colonic polyps include hyperplastic polyps, adenomatous polyps and malignant polyps. These small colorectal polyps vary in size, ranging from small (< 10 mm) to diminutive (< 6 mm), and develop into cancer in 3%-5% of cases. The larger polyps have a greater chance of developing into a tumor. Among polyps, the most common ones are adenomas, which have the potential to become cancerous and can be removed during screening tests. Hyperplastic polyps must be differentiated from adenomatous polyps, as they have less cancerous potential unless localized in the proximal colon. Inflammatory polyps are gaining attention and often contribute to ulcerative colitis. Ulcerative colitis therefore increases the overall risk of CRC. A recent article highlights the importance of both managing these complex polyps and resecting colonic tumors. It is known that 5% of all CRC cases are attributed to two specific inherited syndromes, which include hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis.

SYMPTOMS AND RISK FACTORS OF COloRECTAL CANCer

Common symptoms of CRC are rectal bleeding, significant changes in the colour of stool (especially dark or black-colored stools), irregular bowel habits, pain or discomfort in the lower abdomen, weakness or fatigue, and certain types of anemias. Several risk factors are thought to cause CRC. Age is a major risk factor. About 90% of CRC patients are above the age of 50. The median age of CRC diagnosis is 68 in men and 72 in women. CRC risk also increases due to environmental
factors, which include consuming a diet rich in red meat and fat, poor intake of dietary fiber, sedentary lifestyle, obesity, diabetes mellitus, smoking and consumption of alcohol\cite{22,23}. One possible mechanism of diet-associated CRC is the production of heterocyclic amines during the cooking of meat, as well as higher levels of fecal bile acids\cite{24}. Conversely, the consumption of fish oil rich in omega 3 - fatty acids (Omega 3 PUFA) reduces CRC risk. Personal history of sporadic tumours is also known to increase the risk of CRC. A previous history of colonic polyps, small bowel, endometrial, breast or ovarian cancers are additional factors that contribute to CRC\cite{25,26}. In recent years, there has been an increasing interest in evaluating the genetic pathways that contribute to CRC. The current research trend has been diverted towards chromosome instability pathways, which correlate with sporadic CRC via mutations arising in K-ras, p53 and adenomatous polyposis coli (APC). The microsatellite instability pathway describes hereditary non-polyposis through frequent mutations in DNA mismatch repair pathway genes\cite{27,28}.

**STAGES OF COLORECTAL CANCER**

CRC is a horrendous disease that progresses gradually through three precisely-connected stages: Initiation - a process that alters the molecular message of the normal cell, promotion - aberrant signal transduction cascades and progression - phenotypically-altered, transformed cells. CRC can be divided into five stages, stage 0 to IV (Figure 1). Disease severity and the corresponding therapeutic options depend on the stage\cite{29}. Stage 0 can be characterized by a tumour at the region of the mucosa or inner lining of the colon. CRC stage I is when cancer cells grow in the mucosa, yet their invasive capacity is restricted to the muscular region and not present in the neighbouring tissues of the colon\cite{30}. Stage II can be subcategorized into three types based on invasive growth into: the walls of the colon, the muscular layer of abdomen lining, and nearby tissues\cite{31}. Depending upon the growth of the cancer, stage III can be further divided into three types. During this stage, the cancer grows into the inner lining of the colonic muscular layer and forms lymph nodules in surrounding tissues. Based on the number of nodule formations, this stage can be named IIIA, IIIB or IIC. Stage IV describes the worst stage of the disease where the cancer has spread to distant parts of the body, such as the liver, lungs, etc.\cite{32}.

**MURINE MODELS OF COLORECTAL CANCER**

Basic CRC research using animal models has grown\cite{33,34}. 

*Figure 1  Different stages during the progression of colorectal carcinogenesis. Stage 0: The cancerous cells grow within the inner lining of the mucosa; Stage I: The cancerous cells grow throughout the mucosa and submucosa. The cancerous growth invades into the muscular layer of the colon; Stage II: The cancerous growth penetrates through the wall of the colon without spreading to neighbouring tissues or lymph nodes; Stage III: The cancerous growth penetrates through layers of muscle into the serosa, the layer of visceral peritoneum. The cancer begins to spread to the lymph nodes; Stage IV: A tumour nodule forms in the tissue surrounding the colon, cancer cells appear within the lymph nodes, and the cancer begins to metastasize.*
Especially in recent times, animal models have contributed towards our understanding of CRC pathogenesis and yielded insights into the development of novel chemotherapeutic drugs. In spite of this, murine models have become a key tool in understanding the effects of genetic modifications that occur during the process of CRC formation.[35,36] Researchers have developed and modified murine models of CRC, which is a resource with immense potential. Murine models have been segregated into three different classifications, namely genetically-modified, Western diet-induced, and chemically-induced models[37].

**APC^min/+ mouse model**

Studies over the past few decades involving preclinical CRC research utilize the APC^min/+ mouse[38]. The APC^min/+ mouse is a genetically-engineered model of mouse colon carcinogenesis. When these mice reach the age of 4 wk old, they spontaneously develop tumors in the intestine and colon. It is a well-known phenomenon that about 80% of CRCs arise due to mutations in the APC gene. Researchers removed one allele of the APC gene, thus creating the APC^min/+ mouse model. The APC^min/+ model of intestinal/colorectal cancer has been extensively studied in the context of developing novel chemotherapeutic drugs[39,40].

**Dimethyl hydrazine and azoxymethane**

Azoxymethane (AOM) and 1,2 dimethyl hydrazine (DMH) are the two notorious chemical carcinogens used to induce and study CRC in rat and mouse models[41,42]. AOM and DMH are alkylating agents that produce free radicals that bind to DNA and cause mutations. These accumulating mutations will develop into tumours. These agents are injected either intraperitoneally (i.p.) or subcutaneously (s.c.) into animals for several weeks to induce colonic tumors[43]. Detailed analysis of colonic tumours from these chemically-induced rodents harbour mutations in the β-catenin gene, which is quite similar to Human Non Polyposis Colorectal Cancer[44]. In our laboratory, we extensively use this model to develop many natural chemotherapeutic agents[45].

**DSS/DMH model of ulcerative colitis-induced CRC**

Chronic inflammatory bowel disease, where the colon is extensively injured over a prolonged period of time due to inflammation, increases the risk of CRC. The most common forms of inflammatory bowel disease are ulcerative colitis and Crohn's disease[46]. A combination of Dextran sodium sulfate (DSS) and DMH are now used to induce CRC in Fisher rats[47]. A single dose of AOM and three cycles of 2% DSS in drinking water for seven days results in tumor formation within 8 wk. These AOM/DSS or DMH/DSS mouse models are largely used by researchers to screen drugs.

**N-methyl-N-nitro-N-nitrosoguanidine and N-methyl-N-nitrosourea**

Chemically-induced N-methyl N-nitro-N-nitrosoguani-
feature of these mesenchymal cells is resistance to cellular senescence and apoptosis. Mesenchymal cells are characterized by the enhanced expression of extracellular proteases and transcription factors, such as snail, slug and twist, which activate the cells to produce collagen, fibronectin, vimentin, α-smooth muscle actin (α-SMA), et al. Interestingly, the shift from an epithelial to mesenchymal state is complex. Upon triggering by mediators, these events begin with the dissolution of cell-cell adhesion, which results in the loss of microvilli and cilia at the apical surface of epithelial cells. At this stage, cytoskeletal reorganization takes place, which releases α-smooth muscle actin and matrix metalloproteinases. These secreted matrix metalloproteinases degrade the extracellular matrix, which facilitates the dissolution of cells from the basement membrane and allows cells to move along the matrix.

EMT plays a key role in the spreading of cancer throughout distant parts of the body. Newly-produced cells by EMT display several properties associated with cancer metastasis. Reports suggest that EMT cells can avoid cellular senescence by inhibiting tumour-suppressor proteins. Furthermore, research evidence shows that high levels of vimentin in EMT cells makes these cells more resistant to chemotherapeutic drugs. The mechanism of EMT in colorectal cancer metastasis is depicted in Figure 2. The mechanism of EMT is considered to be complex because of the heterogeneity within this population. Interestingly, not all epithelial cells in a mutated epithelium undergo EMT. Moreover, not all EMT cells facilitate metastasis. Several environmental factors as well as signalling cascades regulate these mechanisms of EMT. A successful metastasis is achieved through the involvement of another mechanism called mesenchymal-to-epithelial transition. The invasive mesenchymal cells produced by EMT travel through systemic circulation and anchor themselves in other distant parts. For this, cells must regain their epithelial features and thereby undergo a mesenchymal-to-epithelial transition. The modulation of cells between EMT and mesenchymal-to-epithelial transition states facilitates cancer metastasis.

Interestingly, E-cadherin, a hallmark for EMT, is reported as a biomarker for colorectal cancer. Recently, a research group reported that the silencing of ubiquitin-specific protease 47, a deubiquitinating enzyme, augments the proteasomal degradation of Snail, the transcription factor involved in EMT, to prevent the progression of colorectal cancer. A molecular genetic approach towards the involvement of EMT in colorectal cancer revealed that the epithelial nature of colon cancer cells might be sensitive to several drugs, including Src, Notch, and epidermal growth factor receptor inhibitors. Further studies are warranted to identify novel regulators of EMT in order to find novel cellular targets of colorectal cancer.

CELL DEATH IN COLORECTAL CANCER: “CUTS TWO WAYS” PROCESS FROM WOMB TO TOMB

Although Carl Vogt reported the incidence of cell death in metamorphic toads in 1842, the mechanisms of cell death was recognized in the middle of the 19th century. However, research attempts have yet to come out with a clear picture of the phenomena of cell death, and confusions still remain between the alternative forms of cell death. As an essential physiological process required to maintain tissue homeostasis, the different modalities of cell death are intensively studied. The decision of a cell to live or die is important and can be the determining factor in the progression of cancers. Chemotherapies targeting cell death mechanisms are highly encouraged in order to prevent cancer progression and metastasis. Dysregulated cell death signalling cascades are considered to be fundamental to the progression and worsening of CRC. Considering this notion, a conceptual understanding of the involvement of different modes of cell death in colon carcinogenesis and its progression would shed light on novel cellular targets against colorectal cancer.

Death-triggering environmental cues in the colorectum

The urogenital system and hindgut, which include the colon and rectum, begin to divide in the 4th week of human gestation and become separate units by the 7th week. Cell death, particularly apoptosis in the mesenchyme, plays a predominant role in this process. Research evidence shows that apoptotic cells are concentrated in the mesenchyme of the terminal rectum during the formation of the anal canal in the 7th week of gestation. A number of developmental regulatory signalling molecules such as Wnt 5a, Cdx1, Hoxd-13, Tcf4 and Shh actively participate in the up- and downregulation of apoptotic cell death during the formation of the colorectum. Interestingly, researchers have reported the decisive role of autophagy in the activation of cellular signals that are required for the phagocytic engulfment of apoptotic cells during embryonic development. Yet another research group has reported that alternative cell death mechanisms such as autophagy, cornification, entosis, and necroptosis exist when apoptosis machinery fails during embryogenesis. Previous reports clearly point out that cell death mechanisms are not only important in shaping the embryo, but also for maintaining adult tissue homeostasis, and can therefore be considered as key machinery from womb to tomb.

TYPES AND CHARACTERIZATION OF CELL DEATH

According to the 2018 nomenclature committee on cell death, all cell death processes taken together can be
classified into fourteen or more subgroups based on their morphological characteristics, enzymological criteria, functional phases, and immunological reactions. These subgroups include apoptosis, necrosis, necroptosis[83], ferroptosis[84], pyroptosis[85], parthanatos[86], entosis[87], NETosis[88], autophagy[89], and mitotic catastrophe[90]. Genetically-programmed mechanisms for the targeted eradication of permanently-damaged and destructive cells or organs are collectively termed as regulated cell death mechanisms. The major classifications of different cell death modalities with each of their functional aspects are depicted in Figure 3.

**Targeting cell death in colorectal cancer: implications for therapy**

An interesting finding about cancer is that several genes that are responsible for cancer development are very much active during embryogenesis and fetal development, particularly regulating embryonic growth and organ formation. These genetic programs remain silent throughout the rest of the life of an organism; however, they are turned on in cells during cancer formation[91]. The genetic paradigm of colorectal cancer reveals that APC or Iβ-catenin is responsible for the initial changes in normal mucosa that form dysplastic aberrant crypt foci. COX-2 mainly regulates the formation of early adenomas, and K-RAS regulates the formation of intermediate adenomas. CPC4/SMAD4 is responsible for late adenomas and p53 is majorly responsible for carcinomas[92]. During these sequential events from benign polyp formation to adenomas and finally carcinomas, cell death plays an essential role.

A low rate of apoptosis in the base of the crypt, where stem cells are expected to reside, is fundamental to the function of the normal intestine. It is interesting to note that epithelial cells residing in the villi of the small intestine and colon are resistant to apoptosis[93]. Changes in the expression patterns of several apoptotic proteins during the transformation of adenomas into carcinomas reveal the importance of apoptosis during colon cancer progression[94]. Since 70% of reported CRCs are associated with mutations in the tumour suppressor p53 gene, the transition from adenomas to carcinomas in the colorectal region is considered to involve a mechanism whereby apoptosis machinery fails[95]. Therefore, chemotherapies intended to stimulate apoptosis in colon cells would be central to controlling disease progression[96]. With this notion, our laboratory is interested in elucidating the apoptosis-inducing effect of certain phytochemicals in order to eradicate cancer cells and provide protection against CRC progression. We have provided evidence that the bioflavonoid luteolin has strong anti-proliferative activity. Luteolin inhibits the Wnt/β-catenin signalling cascade, which induces apoptosis and cell cycle growth arrest in the G2/M phase in HCT-15 colon cancer cells[97]. In addition, azoxymethane induces colon carcinogenesis in BALB/c mice[98]. Our reports suggest that apoptosis is an efficient parameter in preventing malignant transformation since it eradicates harmful cells. On the contrary, apoptosis can also promote cancer growth by preventing the removal of certain genetic variants that have a high potential to induce malignancy. Yet another interesting hypothesis about cancer is that tumour tissues possess a higher apoptotic index than normal tissues. Notably, a higher apoptotic index in tissue indicates more a malignant tumour[99]. Therefore, apoptosis can be considered as a double-edged sword in cancer progression. However, the
Figure 3 Different modalities of cell death. Unpredictable perturbations in the extracellular or intracellular microenvironments of a cell can activate several signal transduction cascades that ultimately lead to various forms of cell death.

Type I cell death: apoptosis
- The extrinsic pathway of apoptosis is mediated by Fas-associated death domain protein (FADD). Caspase 8, in turn, triggers caspase 3 and 7, which then activates caspase 9. Both intrinsic and mitochondrial pathways of apoptosis are mediated through the inhibition of anti-apoptotic Bcl2, which in turn activates Bax/Bak and induces release of cytochrome c from the mitochondria. The activation of caspase 9 in the apoptosome induces apoptotic cell death.

Type II cell death: autophagy
- Autophagy is an active lysosomal degradative flux, which can be divided into three distinct types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy involves four different steps: initiation, autophagosome nucleation, phagosome expansion and completion, and autolysosome docking. The tightly-regulated autophagy machinery is mediated through several autophagy-related (Atg) molecules.

Regulated necrosis/necroptosis: regulated necrosis is mediated through the interaction of receptor interacting protein 1 (RIP1) with RIP3 upon caspase 8 inhibition. RIP3 and mixed-lineage kinase domain-like (MLKL) are phosphorylated and assembled into complex IIb, which is then translocated to the plasma membrane to mediate membrane permeabilization. Ferroptosis: this regulated form of cell death is driven by the loss of glutathione peroxidase 4 (GPX4) activity, a lipid repair enzyme, followed by the accumulation of lipid hydroperoxides. Autosis: a plasma membrane Na+/K+-dependent autophagy form of cell death. Entosis: internalized cells undergo entotic cell death through the formation of entotic vacuoles, which is mediated by autophagy proteins like Vps34, etc.

Pyroptosis: a caspase-dependent cell death mechanism that is an intermediary variation of apoptosis and necrosis. Caspase 1 is activated by the NLRP3 inflammasome, which activates the inflammatory cytokines interleukin 1β and interleukin 18, which in turn mediate the lytic cycle.
mechanism linking a high apoptotic rate with increased cancer cell proliferation and metastasis needs to be further elucidated.

Apart from apoptosis, other cell death modes are also gaining attention in cancer research in order to find better therapeutic targets. From this point of view, the pro-and anti-metastatic effects of autophagy have been studied in several cancers including brain, liver, pancreas, colon etc. Several signalling cascades are known to regulate autophagy. Among these, PI3K/Akt/mammalian target of rapamycin (mTOR) is an important signalling pathway that acts as a checkpoint in autophagy and promotes cancer progression. Interestingly, PI3K/Akt hyperactivation, PIK3CA mutations, and both PTEN mutations and deletions have been reported in the incidence of CRC\(^1\). Autophagy is reported as an anti-metastatic mechanism in the early stages of cancer metastasis by preventing both the infiltration of inflammatory cells as well as tumour cell necrosis, thus helps reduce cancer cell invasion and metastasis. However, autophagy may act as a promoter of metastasis during advanced cancer stages by enhancing EMT, cell survival and metastasis\(^1\). Moreover, high expression of LC3II, which is a key regulator of autophagosome nucleation and is known to downregulate Beclin 1, has been reported in the advanced stages of CRC\(^2\). This research evidence points out that autophagy machinery influences all stages of cancer progression, including initiation, proliferation and metastasis, while its effect on inhibiting or promoting cancer metastasis seems to be context-dependent.

Targeted therapies for necroptosis, a caspase-independent, receptor-interacting protein kinase-mediated form of regulated cell death, has recently been postulated as a novel strategy for cancer prevention. Very few reports are available concerning the role of necroptosis in regulating CRC progression. Moriwaki and colleagues have shown a significant downregulation in RIPK1 and RIPK3 expression in colon cancer tissues when compared with normal colon tissues\(^3\). Interestingly, dimethyl fumarate, an approved drug for the treatment of multiple sclerosis, is reported to induce necroptosis through the depletion of glutathione in colon cancer cells\(^4\). Colon cancer cell resistance against the 5-fluorouracil drug is sensitized by the usage of pan-caspase inhibitors, which facilitate 5-fluorouracil-induced necroptosis in CRC cells\(^5\). However, more research should be conducted to identify the possible regulatory role of necroptosis in the prevention of CRC. Altogether, these reports shed a limelight on colon cancer research by revealing a promising therapeutic target against cancer progression.

**SIGNALLING PATHWAYS IN COLORECTAL CANCER**

The development of colorectal involves various signalling pathways that regulate cellular proliferation, differentiation and immortalization. Signalling activation of Wnt/β-catenin, inactivation of transforming growth factor β (TGFβ) and epidermal growth factor receptor, and mutation in k-ras signalling all play a vital role in the progression of CRC\(^6,7\).

### Wnt/β-catenin signalling in colon cancer

Wnt signalling plays divergent biological roles, such as regulating cellular homeostasis and maintaining cell self-renewal throughout embryogenesis and adulthood. This pathway particularly promotes intestinal epithelial proliferation and differentiation of the intestinal crypt\(^8\). In the presence of Wnt ligand, the receptor frizzled inhibits the phosphorylation of Glycogen synthase kinase-3 beta, thus impeding the degradation of β-catenin by ubiquitins. Accumulated cytoplasmic β-catenin translocates to the nucleus and transcribes target genes (Figure 4). The activity of this signalling pathway depends on the cellular localization of β-catenin. Among 90% of colonic tumours have a mutation in the APC and β-catenin genes\(^9\). Mutations in the cluster region of APC leads to the generation of truncated protein, which fails to prevent complex formation. This mutational dysregulation in Wnt signalling stabilizes cytoplasmic β-catenin, and its nuclear translocation promotes β-catenin-dependent transcription of Wnt target genes, which therein contributes to CRC progression\(^10\). Nuclear β-catenin favours peripheral cellular changes that impact cell adhesion and migration. Interestingly, Wnt signalling is necessary for the initial activation of intestinal stem cells. This plays a crucial role not only for stem cell maintenance but also for crypt homeostasis. Research evidence shows that experimental ablation of Wnt signalling in cells leads to the specific loss of proliferative crypts\(^11,12\).

### PI3K/Akt/mTOR signalling in colorectal cancer

PI3K/Akt/mTOR is the second most frequently mutated oncogenic signalling network in human cancers. The dysregulation of PI3K is observed in almost 30% of human cancers, making this signalling cascade an important therapeutic target in controlling cancer progression\(^13\). The involvement of PI3K/Akt/mTOR signalling in colon carcinogenesis has been intensively studied. Overexpression of p-Akt and impaired expression of PTEN, a tumor suppressor negative regulator of Akt, have been reported in 70% of colorectal cancer patients\(^14\). The carotenoid Lycopene has been reported to suppress leptin-mediated cell invasion in CRC HT-29 cells through the inhibition of Akt phosphorylation\(^15\). Yet another research group has reported that aspirin, an inhibitor of mTOR and activator of AMP-activated protein kinase, induces autophagy and protects against the progression of colorectal cancer\(^16\).

### TGFβ / Smad signalling in colorectal cancer

TGFβ and related bone morphogenetic proteins belong to the family of cytokines involved in the governing of various cellular processes, including proliferation, differentiation, and apoptosis\(^17\). The TGFβ superfamily
of cytokines contains many proteins, including TGFβ1, TGFβ2, TGFβ3, and activins. TGFβ conducts its signals via numerous intracellular signalling molecules, including the Smad family of proteins, mainly Smads 2 and 3[118,119]. TGFβ enhances the expression of several fibrogenic and pro-inflammatory cytokines, such as platelet-derived growth factor, tumor necrosis factor α or interleukin 1β, and promotes the development and progression of the fibrotic reaction[120]. Three major isoforms of TGFβ have been identified in mammals, namely TGFβ1, TGFβ2, and TGFβ3. In general, TGFβ is secreted in an inactivated form through its attachment to a latent TGFβ-binding protein[121]. The downstream regulation of TGFβ signalling is activated upon ligand binding to type II receptors, which phosphorylates the type I receptor, which then further phosphorylates Smads 2 and 3. The phosphorylated Smads heterodimerize with Smad4 and translocate into the nucleus to promote gene transcription (Figure 5)[122]. TGFβ plays a dual role in early cancer progression. TGFβ can perform as a tumor-suppressor pathway in normal colon epithelial cells by regulating cell proliferation and apoptosis. In later stages of cancer, however, TGFβ promotes cell migration by increasing EMT events and suppressing the immune response[123,124]. The involvement of TGFβ signalling in CRC was described earlier[125-127].

Epidermal growth factor receptor and Ras-Raf-MEK-ERK signalling
Epidermal growth factor receptor, a membrane-bound receptor tyrosine kinase, plays a vibrant role in the development and progression of many cancers. Ligand-activated receptors form homo and heterodimers with the other ErbB family members and autophosphorylate their tyrosine residues[128]. Once ligand binds to the receptor, it triggers the activation of downstream signalling such as Ras, MAPK, ERK, NFκB and PI3K/Akt. These pathways are very critical to CRC development. The overexpression of epidermal growth factor receptor and its ligands correlates with the development of human cancer and its poor prognosis[129].

P53 AND COLORECTAL CANCER
p53 is well known gene for its tumor suppressor role and is one of the most mutated genes in all forms of human cancer. Activation of the p53 DNA damage stress response induces DNA repair and regulates the cell cycle to prevent oncogenic mutation[130]. Alteration of p53 signalling in colon cancer, which results in the loss of apoptosis and cellular checkpoints while altering genetic integrity, ultimately leads to malignancy. Accumulation of mutations in cancer-related genes, such as K-ras, p53 and APC, instigates the transition from normal epithelium to adenomatous to colorectal cancer[131].

NOTCH SIGNALLING IN COLORECTAL CANCER
In mammals, the major components of Notch signalling include five ligands (Delta like ligands 1, 3 and 4, and Jagged 1 and 2 (Stetter-like ligands)), four Notch
receptors (Notch 1-4), and several downstream target genes. Signal-transduction is initiated by the interaction of a notch ligand that is present on one cell with the transmembrane Notch receptor that is present on a neighbouring cell. This binding interaction activates metalloproteases that cleave the transmembrane domain of the Notch receptor, resulting in the release of the constitutively-active Notch intracellular domain. Translocation of this domain to the nucleus regulates transcriptional complexes to induce the expression of target genes (Figure 6).

Although currently available reports provide little information about cell-specific functions of Notch signalling in CRC when compared with other solid tumours, aberrant activation of Notch signalling has been reported in CRC. In a recent study, the superior therapeutic effect of targeting both Notch and MAPK signalling on colon cancer growth, as well as its role in regulating tumor cell plasticity, has been reported. Notch signalling has been reported to induce cellular resistance to chemotherapeutic drugs. It was demonstrated that Notch signalling is significantly upregulated in SW480 cells that are resistant to the experimentally-generated Regorafenib drug, a multikinase inhibitor. Interestingly, the inhibition of Notch signalling in resistant cells restored their sensitivity to Regorafenib, thus suggesting the important role of Notch in promoting resistance to chemotherapeutic drugs. The dysregulation of Notch signalling in colon cancer metastasis has been studied in detail. These reports strongly suggest the importance of Notch signalling in the pathogenesis and progression of CRC.

**Nrf2/Keap signalling in colorectal cancer**

Oxidative stress is denoted as an imbalance between oxidant production and antioxidant defences, where oxidants dominate and lead to cellular dysfunction and tissue damage. Oxidative stress caused by harmful reactive oxygen species are involved in colorectal cancer. Reactive oxygen species cause cellular damage, leading to the progression of many diseases such as cancers, fibrosis, neurodegenerative disorders etc. In turn, cells possess detoxification genes (Phase II) and antioxidant genes to counterbalance the lethal effects of reactive oxygen species. In many disease settings, NF-E2-related factor 2 (Nrf2), which is a basic leucine zipper transcription factor, plays a crucial role in protecting tissues against free radical-mediated insults including carcinogens, drugs, inflammation, etc. Nrf2 is a member of the Cap-N-collar transcription factor family. It recognizes the antioxidant response element in the promoter of target genes. Under basal conditions, Nrf2 is restricted to the cytoplasm by Kelch like ECH associated protein 1. Kelch like ECH associated protein 1 is critical, as it serves as a linker protein substrate between the Cul3-based E3-ubiquitin ligase complex and Nrf2, leading to the ubiquitination and proteosomal degradation of Nrf2. Certain conditions, such as the induction of the antioxidant response element, promote the detachment of Nrf2 from its partner Kelch like ECH associated protein 1, thereby facilitating the translocation of Nrf2 to the nucleus. Inside the nucleus, Nrf2 dimerizes and associates with small Maf proteins, leading to the binding of Nrf2 to antioxidant response elements, which...
therein promotes transcriptional activation of these genes. In colorectal cancer, the chemopreventive effect of many drugs greatly depends on this signalling [142-144].

**Hippo signalling and colorectal cancer**

The origin of the hippo pathway began with observations in *Drosophila melanogaster* flies with concomitant mutations that led to tissue overgrowth [145]. Hippo signalling has gained attention in cancer biology because of its crosstalk with oncogenic signalling pathways [146]. Yes associated protein 1 is the key transcriptional regulator of the Hippo pathway. This protein, along with its partner PDZ-binding domain taffazin, orchestrate the Hippo pathway [147]. In principle, hippo signalling plays an important role in the regulation of tissue homeostasis, development, regeneration, and cancer [148]. Three protein components in mammals are depicted: Mammalian Ste 2 like kinase 1 and 2, and large tumor suppressor kinase 1 and 2. These kinases phosphorylate Yes associated protein 1 and PDZ-binding domain taffazin, which leads to their nuclear exclusion and ubiquitin-mediated proteosomal degradation in the cytoplasm, thus promoting the suppression of Yes associated protein 1/ PDZ-binding domain taffazin-targeted genes [149,150]. Recently, a huge body of evidence suggests the critical role of Hippo signalling in CRC [151,152]. The Hippo signalling pathway has been reported to crosstalk with other signalling pathways [153,154].

**MiRNAs AND COLORECTAL CANCER**

Over the years, several molecular mechanisms have been identified to be involved in CRC [155]. In recent years, the discovery of microRNAs (miRNAs) has attracted considerable attention in different disease conditions. An understanding of the roles of miRNAs in development and disease, especially in cancer, have made miRNAs both an attractive tool and novel therapeutic target [156]. Generally, miRNAs are non-coding RNAs that are 20-24 nucleotides in length and were classified into Oncomirs, including the tumor-suppressor miRNAs that are related to cancer. According to recent research relating miRNAs and cancer, miRNAs impact several vital processes such as the cell cycle, proliferation, differentiation, metabolism, and apoptosis [157]. It was reported that miRNAs such as miR-21, miR-181b1, miR-101, the let7 family, miR-133b, and miR-126 were dysregulated in CRC [158,159]. Recently, miR-760 was found to suppress human colorectal cancer growth by targeting BATF3/AP-1/cyclinD1 signalling [160]. MiR-422a acts as a tumor-suppressor in colorectal cancer, and its expression is limited to CRC tumours. Increasing the expression of miR-422a could inhibit CRC cell growth and promote cell apoptosis in colorectal cancer cells. It was also reported that miR-422a restricts colorectal cancer by inhibiting the p38/MAPK pathway [161]. Therefore, miRNAs are emerging as potential targets in CRC.

**CONCLUSION**

Research attempts to develop more effective therapies against CRC progression are of outstanding importance, as the effectiveness of mono-therapeutic approaches in CRC treatment are very limited. However, combinational...
therapies are gaining attention due to their ability to manipulate certain signalling cascades and induce different modalities of cell death to prevent cancer metastasis. The regulation of both cell signalling pathways and cell death represents a promising tool to improve patient responses to chemotherapy. When the normal orchestra of cellular signalling is dysregulated, cells become pathological and ultimately decide whether to die or survive. A subset of novel signalling pathways, and their association with colorectal cancer progression and metastasis, was discussed in this review. A better understanding of anticancer agents that target these cellular pathways and induce cell death modalities will hopefully provide more insights into the complicated molecular mechanisms that underlie colorectal cancer, thus facilitating the development of more effective treatments.

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