Review Article

2b or Not 2b: How Opposing FGF Receptor Splice Variants Are Blocking Progress in Precision Oncology

Richard J. Epstein,1,2 Li Jun Tian,1 and Yan Fei Gu1

1New Hope Cancer Center, Beijing United Hospital, 9-11 Jiangtai West Rd, Chaoyang, Beijing 100015, China
2Garvan Institute of Medical Research and UNSW Clinical School, 84 Victoria St, Darlinghurst 2010 Sydney, Australia

Correspondence should be addressed to Richard J. Epstein; richard.epstein@ufh.com.cn

Received 1 April 2021; Accepted 21 April 2021; Published 3 May 2021

Academic Editor: Chandra Singh

Copyright © 2021 Richard J. Epstein et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

More than ten thousand peer-reviewed studies have assessed the role of fibroblast growth factors (FGFs) and their receptors (FGFRs) in cancer, but few patients have yet benefited from drugs targeting this molecular family. Strategizing how best to use FGFR-targeted drugs is complicated by multiple variables, including RNA splicing events that alter the affinity of ligands for FGFRs and hence change the outcomes of stromal-epithelial interactions. The effects of splicing are most relevant to FGFR2; expression of the FGFR2b splice isoform can restore apoptotic sensitivity to cancer cells, whereas switching to FGFR2c may drive tumor progression by triggering epithelial-mesenchymal transition. The differentiating and regulatory actions of wild-type FGFR2b contrast with the proliferative actions of FGFR1 and FGFR3, and may be converted to mitogenicity either by splice switching or by silencing of tumor suppressor genes such as CDH1 or PTEN. Exclusive use of small-molecule pan-FGFR inhibitors may thus cause nonselective blockade of FGFR2 isoforms with opposing actions, undermining the rationale of FGFR2 drug targeting. This splice-dependent ability of FGFR2 to switch between tumor-suppressing and -driving functions highlights an unmet oncologic need for isoform-specific drug targeting, e.g., by antibody inhibition of ligand-FGFR2c binding, as well as for more nuanced molecular pathology prediction of FGFR2 actions in different stromal-tumor contexts.

1. Introduction

Fibroblast growth factor receptors (FGFRs) are a family of transmembrane enzymes that coordinate ligand-dependent paracrine signaling between epithelial and stromal cells during embryonic development or adult adaptive responses [1–4]. Ten canonical secreted fibroblast growth factors (FGF1-10) activate four FGF receptor tyrosine kinases (FGFR1-4), and a dozen other FGFs comprise either circulating endocrine (e.g., FGF19) or nonsignaling intracellular (iFGF) peptides [5–7]; a fifth FGFR homolog lacking a catalytic domain acts as a ligand-sequestering decoy protein [8]. Binding of FGFs to heparan sulfate proteoglycans (HSPGs) and other noncanonical coreceptors in the extracellular matrix further complicates the in vivo dynamics of FGFR activation [9–11]. In addition, mutations affecting extracellular N-glycosylation sites can affect ligand binding and receptor function even when the amino acid substitution has no structural consequence [12]. FGF1- and FGF2-unglycosylated ligands, formerly termed acidic and basic FGF, activate numerous FGFR splice variants, whereas other FGFs tend to be more specific in their binding affinity. Ancient phylogenetic conservation of these diverse receptors and ligands implies important functional differences [13], precluding generalizations as to what constitutes prototypical FGF/FGFR actions across a vast spectrum of health and disease contexts [14].

Reflecting this complexity, the challenge of targeting a wide range of FGF-related genetic aberrations in human cancers [15–17] has proven more daunting than once hoped [18]. A key obstacle has been the rapid acquisition of drug resistance by tumors with FGFR aberrations [19], perhaps reflecting the high adaptivity of FGF signaling due to intracellular signaling fluxes [20–23], HSPG-ligand
interplay [11], and splicing affecting any of the extracellular [24], kinase [25], juxtamembrane [26], or carboxyterminal [27] receptor domains. A related stumbling block has concerned frequent disconnects between FGFR-targetable genetic anomalies and their cellular; hence, therapeutic [28], sequelae [29]: for example, FGFR1-amplified squamous lung cancers [30] and FGFR3-mutant urothelial cancers [31], respond better than unselected cases to FGFR inhibitors, but survival benefits remain elusive [32, 33]. The finding that FGFR2-fused cholangiocarcinomas respond more durably is an advance [34], but resistance still hampers progress [35, 36]. These issues have led to FGFRs acquiring a problematic status in the personalised oncology space [37, 38], with FGFR defects arguably predicting drug resistance more reliably than survival gains [39–42].

Improving the value of FGFR-targeted anticancer treatments may therefore require closer attention to the underlying biology [43–45], including development of strategies to minimise the usual dose-limiting ocular and hyperphosphatemic toxicities of FGFR blockade [46]. To this end, the following perspective focuses on one such receptor, FGFR2, and its epithelial and mesenchymal splice isoforms, FGFR2b and FGFR2c.

## 2. Main Text

### 2.1. FGFR2 in Embryogenesis

The regulatory effects of FGFRs 1–3 are diversified by tissue-specific FGFR mRNA splicing events that determine ligand-binding specificity. This process is of most relevance to the FGFR2 gene which, unlike the other three FGFR genes, contains an open reading frame that has been invaded by large introns [47], implying a critical effect of splicing on transcriptomic regulation [48]. At least nine FGFR2 splice variants are reported, expression of which varies even within the same tumor type [24], while FGFR2 contains at least one and perhaps as many as three [49] more exons than other FGFRs [47]. Splicing of the FGFR2 third immunoglobulin-like domain produces either epithelial-specific IIIb (FGFR2-IIIb, i.e., FGFR2b, formerly keratinocyte growth factor receptor, KGFR/K-Sam) or mesenchymal IIIc (FGFR2c, Bek) receptors. FGFR2b is activated by mesenchymal FGFR7 (keratinocyte growth factor, KGF1) or FGFR10 (KGF2) [3] and also by FGFR3 or FGFR22, whereas mesenchymal FGFR2c responds to numerous ectodermal ligands including FGFs 2, 4, 6, 8, 9, 17, and 18.

#### 2.1.1. FGFR2 RNA Splicing in Morphogenetic Patterning

Splice switching between FGFR heteroisoforms is fundamental to normal development [50]. Two-way crosstalk between mesenchymal FGF ligands and epithelial FGFR2b balances the counteractivation of mesenchymal FGFR2c by epithelial FGFs, with such interactions underlying both physiological and pathological stromal-epithelial communication [51, 52]. Epithelial FGFR2b splice variants are expressed by ectodermal and endodermal tissues, including skin (keratinocytes, hair follicles, and sebocytes) and viscera (e.g., gut epithelium), in which context this isoform typically plays a prodifferentiating or -apoptotic role in response to FGF7/KGF or FGF10/KGF2 [53–57]. Knockout of the FGFR2b receptor or ligand expression leads to nonlethal congenital defects of hypospadias, anorectal malformations, glindular aplasia, or intestinal atresia [58–60], consistent with a role in epithelial patterning. In contrast, pan-FGFR2 gene targeting manifests with lethal mesenchymal and bone defects, suggesting a more decisive role for FGFR2c than for FGFR2b in determining fetal viability [61].

#### 2.1.2. Germline FGFR2 Hyperactivation Syndromes

Illustrative of the morphologic effects of FGF signaling, the craniosynostoses are congenital syndromes in which constitutive kinase activity associated with FGFR2 missense mutations manifests with premature skull bone fusion, facial dysmorphism, cognitive dysfunction, and limb abnormalities. These phenotypes reflect accelerated mesenchymal apoptosis and/or differentiation [62], pathogenetically distinguishing them from the FGFR3-mutant germline ciliopathies, achondroplasia, and thanatophoric dysplasia [63].

The common craniosynostoses are Apert and Crouzon syndromes; the latter arises due to mutations causing overexpression of FGFR2c [64], consistent with its predominantly mesenchymal phenotype and its corresponding paucity of epithelial (e.g., skin) stigmata. In contrast, Apert-type FGFR2 mutations, two-thirds of which comprise Ser252Trp missense substitutions affecting the extracellular domain, extend the ligand responsiveness of FGFR2b to FGFR2c ligands [65, 66], causing a severe phenotype with combined epithelial and mesenchymal defects [67]. Premature osteogenic differentiation due to Apert mutations is blocked by soluble nonsignaling FGFR2 fragments containing the same mutation [68], confirming enhanced ligand affinity as the mechanism of receptor hyperactivation [69].

#### 2.1.3. FGFR2b-Dependent Phenotypes

The mesenchymal bone and cartilage stigmata of Apert syndrome arise via mutant FGFR2-induced upregulation of prodifferentiation p38-MAPK signaling [70]. However, the trademark epithelial presentation of this syndrome—extensive early-onset acne—is associated with induction of proinflammatory IL-1 further downstream [71, 72]. A direct genotype-phenotype relationship between acne and FGFR2 expression has been confirmed in postzygotic FGFR2 mosaics and in segmental acneniform nevi [73–75].

FGFR2b-activating ligands are inducible by the embryonic morphogen retinoic acid [76, 77] leading over time to FGFR2 downregulation [78]. It is via this pathway that retinoids, including the potent congener isotretinoin, improve both Apert and nonsyndromic acne [79, 80]. The same pharmacologic FGFR2-blocking mechanism likely causes the dysmorphogenetic teratogenicity of this drug, as well as of thalidomide [81].

#### 2.2. Acne: A Clinical Window into FGFR2b Action

The FGFR2 inducibility of epithelial acne—whether sporadic (ligand-induced) or in Apert syndrome (constitutive)—is
attributable to hyperactivation of FGFR2b [71]. Relevant to cancer control, acne is inducible not only by Apc- or mutagenic FGFR2 activation but also by epidermal growth factor receptor (EGFR) inactivation, either by homozygous knockout [82] or targeted drug inhibition [83]. This raises the hypothesis that FGFR2 plays a key intermediary role in both the skin toxicity and antitumor efficacy of EGFR-blocking drugs.

2.2.1. FGFR2b-Inducible Acne following EGFR Signal Blockade. The folliculitis-like toxicities associated with EGFR blockade for diseases such as colorectal cancer (CRC) [83, 84] correlate with therapeutic efficacy, whereas tumoral resistance to these drugs is predicted by activating KRAS or BRAF mutations that make EGFR signaling redundant; in KRAS/BRAF-wild-type colon cancers, resistance to EGFR blockade may likewise arise from mutations upregulating FGFR2 function [85–87]. The targeted drug resistance associated in this context with FGFR2 overexpression is also predictive of poor tumor response to chemotherapy and radiotherapy [88], suggesting the concurrence of heterologous suppressor gene losses that impair apoptosis and thereby permit FGFR2 upregulation in these tumors (see below).

Pharmacologic EGFR inhibition in nonresistant CRCs is associated with compensatory FGFR2-induced p38/MAPK upregulation [72, 89] that induces the downstream proinflammatory mesenchymal mitogen IL-1α [90–94] which in turn promotes both sporadic acne [95] and iatrogenic folliculitis [96, 97]. Since IL-1 can also trigger cancer cell death [98, 99], the linked tumorigenic and acnegenic effects of EGFR blockade in such patients could reflect the same mechanism: namely, loss of negative feedback by (active) EGFR, leading by default to bypass upregulation of FGFR2b [100]. This bypass mechanism is reminiscent of c-RAF activation-induced skin toxicity that occurs when melanoma patients receive BRAF inhibitors [101]. Consistent with this, prevention of EGFR inhibitor-induced acne by skin irradiation is attributable to FGFR2 downregulation [102]; FGF7-activated FGFR2b causes TGFA-induced EGFR signaling [103], completing a homeostatic FGFR2-EGFR control loop. Drug inhibition of EGFR signaling may thus release a feedback constraint on FGFR2b which manifests off-target as IL1-mediated skin toxicity [71], predicting on-target tumor response.

A key nexus for FGF and EGF signaling is the phosphotyrosine-independent binding of the adaptor protein FRS2α to FGFR juxtamembrane sequences via its PTB domain [104]. Ligand-dependent FGFR activation causes FRS2α tyrosine-196 phosphorylation which triggers SH2 domain binding of Grb2 (or the tyrosine phosphatase SHP2), activating the mitogenic Ras-Raf-MEK-ERK (p42-MAPK) pathway [105] and driving proliferation of mesenchymal tissues expressing FGFR2c [106, 107]. EGF abrogates FGF-inducible FRS2α phosphorylation in an ERK-dependent manner [108], implicating FRS2α as a negative regulatory node in this EGF/FGF signaling network [109].

2.2.2. FGFR2b as a Mediator of Androgenic Acne and Alopecia. The causes of FGFR2b-induced acne are not only genetic or iatrogenic but also androgenic. Expression of FGFR2b-specific ligands FGF7 [110] and FGF10 [59] is androgen dependent, with androgen-induced upregulation of FGFR1 [111] being implicated in the pathogenesis of adolescent acne [79]. In the rare seborrhea-acne-hirsutism-alopoea (SAHA) syndrome [112], acne responds equally well to isotretinoin (which downregulates FGFR2b) and antiandrogens (which block transactivation of FGF7/10) [113]. This latter syndromic association between androgens, FGFR2, acne, and alopecia raises the intriguing hypothesis that in addition to FGFR2b-induced inflammatory folliculitis, androgen-dependent FGFR2b proapoptotic signaling could be involved in the pathogenesis of male-pattern baldness.

Consistent with this, dominant-negative EGFR-silenced transgenic mice exhibit striking hair follicle necrosis due to failure of catagen entry [114]. Since EGFR drives follicle proliferation and blocks differentiation [82] whereas FGFR2b promotes follicle differentiation [115, 116], increased androgen-inducible FGFR2b signaling in the presence of sustained EGF exposure [117] could trigger follicle autophagy and hair loss, raising novel treatment strategies. Indeed, both FGF7 [118–120] and FGF10 [121] are implicated as driving telogen/agenan transition during hair growth in vivo, though whether this is accompanied by FGFR2b downregulation (vs. sustained activation) remains unclear. These observations highlight that FGFR2 action is best understood in the context of ambient signaling by other hormones and cytokines, and suggest how FGFR2b-specific drug inhibitors—whether systemic or topical (e.g., photodynamic therapy [122])—could improve therapy of nonmalignant diseases.

2.3. FGFR2b in Tumor Suppression. Common hardwired cancer-associated FGFR genotypes include FGFR1 amplification (e.g., in lung cancers, uveal melanomas, low-grade gliomas, or drug-refractory breast cancers [39, 123, 124]), FGFR3 mutations (e.g., in superficial papillary urothelial cancers [125, 126]), and FGFR2 gene fusions (especially in fluke-negative intrahepatic cholangiocarcinomas [127]). Unlike FGFR1 and FGFR3—firmly implicated as oncogenic drivers in tumor invasion and proliferation [128–130]—wild-type FGFR2b often acts in a tumor-suppressive manner to promote differentiation or apoptosis [131–136], with FGFR2b downregulation mirroring FGFR1 upregulation during progression or epithelial-mesenchymal transition (EMT) [137–142]. Restoration of FGFR2b signaling may also enhance the chemosensitivity [143] and radiosensitivity [144] of treatment-refractory cancer cells by lowering apoptotic threshold.

2.3.1. Regulatory Functions of FGFR2b. The FGFR2 gene is structurally distinguished among FGFRs by having a promoter CpG island enabling epigenetic transexpression, e.g., in neoplasms of the pituitary [145, 146] or bladder [131]. Methylation-induced transcriptional FGFR2
downregulation is thus associated with poorer prognosis in hepatocellular carcinoma [147] and bladder cancer [131], analogous to functional losses caused by FGFR2 deletion in glioblastomas [148], or loss of FGFR2 heterozygosity in osteosarcomas [149].

Conversely, immunohistochemical FGFR2b expression is positively associated with well-differentiated morphology and inversely with Ki-67 in normal colorectal mucosa and CRCs [150]. The prodifferentiation and procoagulant effects of FGFR2b [151, 152] have been linked to certain effector steps, most notably including autophagy mediated by JNK1 [153, 154]. Additional downstream pathways in this tumor-suppressive context include Cbl-dependent ubiquitin downregulation of Lyn and Fyn kinases [155] and/or bystander effects on FGFR3-expressing stromal cells [156].

2.3.2. Functional Alterations due to FGFR2 Gene Splicing. Splice-dependent insertion of a juxtamembrane domain VT (valine-threonine; VT+) dipeptide enables FRS2α binding, enhancing Raf-ERK signaling [26]. Epithelial FGFR2b with splice-dependent loss of this dipeptide (VT−) would thus be predicted to lose mitogenic Grb2-Ras-Raf-ERK signaling [157] but not C-terminal Tyr-766 PLC-γ activation or proinflammatory/apoptotic p38-MAPK/IL-1 and JNK signaling. Alternatively, FGFR2b receptors could be converted to oncogenicity by C-terminal truncations that abolish Tyr-770 PI3K docking [27], leading to faster receptor internalisation and upregulated FRS2α signaling [158].

Spliceosomal dysregulation may switch FGFR2b to FGFR2c, altering ligand binding and driving dedifferentiation [159] or EMT [160], e.g., during progression of hormone-dependent -resistant cancers [161, 162], or associated with constitutive FGFR activation in HPV16 E5-induced neoplasia [163]. The more tumorigenic role of FGFR2c relative to FGFR2b [164] is clear, with FGFR2c overexpression correlating with tumor growth and metastasis [52, 133, 165, 166]. In contrast, the relationship of FGFR2b overexpression to vascular invasion, for example, is reported as positive in some clinical contexts [167] and negative in others [147], suggesting unmeasured confounding variables. Splice switching from FGFR2b to FGFR2c has been reported in 90% of clear-cell renal carcinomas, whereas less-aggressive lesions such as oncocytomas continue to express FGFR2b [159].

2.4. FGFR2b in Oncogenesis. Activating FGFR2 missense mutations or amplifications can occur in cancers of the stomach, breast, lung, endometrium, and ovary [168], and overexpression of the FGFR2b-specific ligand FGF10 is linked to worse prognosis in breast cancer [169]. However, cancer occurrences in the mutant-activated FGFR2 craniosynostoses appear confined to rare cases associated with chromosomal losses [170]. This discrepancy suggests that FGFR2-mutant syndromes lack heterologous regulatory defects in the germline akin to those that permit uncontrolled FGFR2 activation in somatic tumors [171, 172], such as TP53 loss [173].

2.4.1. FGFR2 in Carcinogenesis Associated with Inflammatory Bowel Disease. Relevant to this, FGFR2 may play a causal role in the natural history of CRCs arising from inflammatory bowel disease (IBD): the p38 pathway downstream of FGFR2b drives the chronic inflammatory phenotypes of ulcerative colitis and Crohn’s disease [174, 175], with colitis-associated tumors characterised by gain-of-function FGFR2 aberrations [172, 176] such as have been reported in fewer than 2% of sporadic CRC [177]. Furthermore, activating FGFR2 mutations occur in non-dysplastic colorectal mucosa from ulcerative colitis patients, together with defects of the E-cadherin-encoding suppressor gene CDH1 [178]. Colonic inflammation mediated by overexpression of proapoptotic FGFR2 may thus select for loss-of-function CDH1 defects, in turn permitting mutagenic fixation of FGFR2 hyperactivation.

2.4.2. FGFR2b and E-Cadherin/CDH1 in Diffuse Gastric Cancers. The proapoptotic effects of normal ligand-inducible FGFR2 activation depend on cadherin-dependent epithelial cell adhesion [179]. FGFR2b signaling may induce p38-dependent expression of CDH1 and its product E-cadherin, leading to tumor suppression [180]. Splice switching from FGFR2b to FGFR2c reverses these effects via alternative upregulation of the stromal adhesion molecule N-cadherin, with this FGFR2b-downregulating splicing change contributing to loss of E-cadherin expression and EMT [160, 181].

In contrast, tumors driven by amplified FGFR2 in which wild-type FGFR2b is the overexpressed isoform [182] tend to occur within tissues that are E-cadherin-deficient. The prototype example is diffuse gastric cancer defined by CDH1 gene loss [183, 184], which suggests that lack of E-cadherin enables FGFR2b to drive cell growth and invasion without apoptosis [185]. Small-molecule FGFR2 inhibitors may temporarily control such E-cadherin-deficient cancers [186] due to nonselective FGFR2c cross-inhibition; however, such treatments also select for EMT-driven drug resistance [187]. In gastric cancers already associated with EMT, TWIST repressor protein upregulation leads to further E-cadherin downregulation [188], accelerating epithelial dedifferentiation, FGFR2c overexpression, and tissue invasion [189].

2.4.3. FGFR2b and PTEN in Endometrial Cancers. Acquired genetic changes disrupting the PTEN tumor suppressor pathway represent another frequent cancer-associated source of apoptotic resistance. Such defects often occur in low-immunogenicity hormone-driven tumors such as breast and prostate cancer [190] and permit overexpression of the PIK3CA gene which in turn activates antiapoptotic signaling via the phosphatidylinositol-3′kinase (PI3K)-AKT-mTOR pathway [191]. In postpubertal females, proapoptotic signaling is central to hormone-dependent endometrial decidualization during menstruation; consistent
with this, another hormonally induced human tumor subtype—endometrioid endometrial cancers—exhibits PTEN loss and/or PI3K over-signaling in 90% of cases, often associated with Apert-like FGFR2 mutations [135, 192] that upregulate FGFR2c [193]. The idea that increased FGFR2 signaling confers a growth advantage which depends on PTEN-defective apoptotic defects is supported by experiments showing that co-inhibition of FGFR2 [194] and PI3K [195] restores growth control. Overexpression of EMT-promoting FGFR2c [133] confers a worse prognosis in PTEN-defective endometrial carcinoma [196], whereas non-endometrioid endometrial cancers with wild-type PTEN lose E-cadherin expression en route to EMT [197]. These disparate tumor trajectories show how the pro-apoptotic function of FGFR2 may be converted to tumorigenicity by a variety of epistatic suppressor gene defects [135].

Relevant to brain tumors, the 10q26.13 FGFR2 chromosomal locus is sited adjacent to the WDR1 tumor suppressor gene [198] near the PTEN deletion site at 10q23.31 and the methylatable (repressible) MGMT suppressor gene promoter at 10q26.3 [199] which predicts chemotherapy response and natural history [200–202]. Deletion of PTEN leads to mTORC1-induced upregulation of the FGFR2b ligand FGF10, promoting tumor outgrowth [203]. PTEN deletion may also trigger upregulation of the FGFR2c ligand FGF18 and downregulation of FGFR2 repressor SPRY2 [204]. FGFR2 actions thus vary as a dynamic function of PTEN pathway signaling integrity, in some ways paralleling the above relationship with CDH1/E-cadherin.

2.4.4. FGFR2b and ΔNp63α in Squamous and Colorectal Cancers. The p53 family of stress-responsive cell-cycle control proteins includes p63 and p73. Like FGFR2, the TP63 gene family plays key roles in craniofacial morphogenesis [205], skin differentiation, and apoptosis [206]. Epithelial barrier integrity is dependent upon the expression of wild-type p63 [207] which in turn regulates epithelial-mesenchymal crosstalk via induction of FGFR2b [208]. A mechanistic link between these pathways is supported by molecular correlates of AEC (ankylolobphenaron-ectodermal-clefting, Hay–Wells) syndrome, in which germline loss-of-function TP63 mutations are associated with pathologically high FGFR2b expression accompanied by failure of epithelial differentiation [209].

Like FGFR2, several TP63 gene isoforms (α, β, and γ) are regulated by differential splicing. Two p63α isoforms are transcribed from different promoters: a pro-apoptotic transcriptionally activating (TA) isoform that includes an N-terminal transactivation domain, called TAp63α, which is the main p63 isoform expressed in normal colon and overexpressed in CRC [210]—in which context it exerts a tumor-suppressive effect [211]—and a dominant-negative p53-inhibitory N-terminal-truncated (ΔN) isoform lacking the transactivation domain, called ANp63α, which is the main isoform in keratinocytes [212]. Activating FGFR2 mutations or amplifications [213] or FGFR2b ligand overexpression [214] often occur in tumors lacking TAp63 protein due to ANp63 substitution [206, 215], particularly squamous cancers [210, 216, 217]. Like FGFR2c [52] but not FGFR2b [54], ΔNp63α suppresses JNK-dependent differentiation and apoptosis in an ERK-dependent manner [218], and its overexpression confers a poor prognosis upon urothelial cancers [219] which release exosomes that trigger EMT in adjacent urothelium [220], creating positive feedback between FGFR2c and ANp63α [52, 216]. In the colon, TAp63α represses EGFR expression, leading to feedback upregulation of pro-apoptotic TP53 that normally transactivates the EGFR gene via a promoter response element lacking in TP63 [221]. Anticancer drug-induced EGFR kinase silencing may thus cause CRC response via a compensatory FGFR2b-mediated JNK1 and IL-1 signal which occurs against a background of p53 upregulation and TAp63α expression.

2.5. FGFR2 in Anticancer Therapy. Amongst the ligand-inducible FGFRs, only FGFR4—genetic aberrations of which, compared with FGFRs 1–3, are seldom implicated as tumorigenic drivers—has sufficient divergence in its kinase structure to enable selective small-molecule inhibition [222], e.g., by drugs such as BLU9931 [223]. Since homozygous FGFR4 gene knockout causes no phenotypic loss of viability or fertility [224], this gene may have regulatory (tumor-suppressor) rather than mitogenic (oncogenic) properties [225]. For oncologic purposes, then, drugs inhibiting FGFRs 1–3 may be considered “pan”-FGFR inhibitors, and many inhibitors so defined—including TAS-120 [226], AZD4547, CPL304110 [227], BGJ398 (infragitinib) [228], and Debio 1347 [229]—have already been tested in trials [230]. The term “receptor nonselectivity” may therefore be better applied to drugs that cross-inhibit multiple receptor tyrosine kinases, such as VEGFR2, PDGFRβ, CSF1R, FLT3, and KIT, and which include broad-spectrum partial FGFR antagonists such as dovitinib, ponatinib, and lenvatinib [38].

2.5.1. Clinically Effective FGFR Inhibitors. Two drugs have so far been FDA-approved for tumors expressing targetable genetic aberrations of FGF signaling, and both are small-molecule pan-FGFR inhibitors. The first is erdafitinib, which is licensed for patients with advanced bladder cancers expressing either FGFR3 or FGFR2 aberrations [231]. A phase II trial reported response rates of 40% and progression-free survival of 5.5 months, with best and worst response rates in FGFR3-mutant vs. FGFR2/3-fused bladder tumors, respectively [31, 232]. Adverse events were frequent, often grade 3 or higher, and mandated close monitoring [233]. Despite this promising evidence of efficacy in trials [234], immunotherapies have to date largely outcompeted FGFR-based approaches for second-line palliation of platinum-refractory urothelial cancer [235].

For unresectable intrahepatic cholangiocarcinomas expressing FGFR2 gene fusions or similar rearrangements, the FDA has approved pemigatinib, an FGFR1-3 inhibitor earlier approved for orphan treatment of hematologic malignancies with PDGFR or JAK2 aberrations [236]. In FGFR2-fused or -rearranged tumors, 35–40% responded to pemigatinib; however, all tumors with nonfusion FGFR2
2.5.2. Strategies to Improve Patient Benefit. Given the above evidence for tumor-suppressive activity of FGFR2b, one key strategic concern should be that empirical use of small-molecule pan-FGFR kinase antagonists cross-inhibiting multiple receptors [241] may directly select for resistance. Primary resistance may be predetermined in some cases by de novo regulatory defects affecting proapoptotic genes such as TP53 or CDKN2A; acquired resistance to FGFR-targeted drug therapies may also supervene via selectable changes, including not only new gain-of-function FGFR mutations [35] but also transmodulatory crosstalk [23, 242], targeting errors due to splice-dependent signaling variations [243, 244], and/or multistep loss-of-function tumor suppressor pathway derangements such as those affecting CDH1 or PTEN. Since knockdown of wild-type FGFR2b promotes cell dedifferentiation [54, 245], drugs including this isoform in their inhibitory spectrum could accelerate resistance [181].

More customised approaches to the dose-limiting toxicities of FGF(R)-targeted drugs should improve therapeutic ratios. A distinctive toxicity of this drug class is hyperphosphatemia due to increased renal tubular phosphate reabsorption, which affected 70% of patients in trials of small-molecule FGFR inhibitors [46]. Since hypophosphatemia is induced by FGF23 but not by other ligands for FGFR1 [246]—the main phosphate-regulating FGFR—cotreatment with recombinant FGF23 is one approach that could, in theory, mitigate this toxicity.

This illustrates that one strategy for improving the therapeutic index of FGF(R)-targeted drugs is combination therapies [247–249], i.e., network-based regimens that reflect the interactive mesh-like regulation of FGF signaling [45, 250]. For example, missense mutations causing combined activation of FGFR2 and VEGFR2 occur together in a subset of CRCs [177], raising the possibility of dual therapy. On a cautionary note, however, relatively few combinations of targeted drugs with other medications have so far proven to be game-changers.

2.5.3. Better Personalisation of FGFR2-Targeted Therapies. An ideal dataset to predict FGFR2-targeted drug success would include not only the specific actionable FGFR2-related aberration (e.g., fusion, missense mutation, and amplification) but also quantification of the pattern of FGFR2b vs. FGFR2c expression by the tumor itself; pathway fingerprinting of other non-targeted receptor tyrosine kinase (e.g., EGFR, VEGFR, or other FGFRs) signaling, whether up- or downregulated, within the tumor and stroma, e.g., by using phosphoantibody profiling; and tumor suppressor gene aberrations implicated in either FGFR2 function switching (such as CDH1, PTEN, and TP63; see above) or disease prognosis (e.g., TP53 or CDKN2A [237]).

Strategies beyond small-molecule pan-FGFR inhibitors are needed [18, 251], and newer approaches offer hope [28, 252]. The importance of separately targeting FGFR2b and FGFR2c has been recognized by researchers for over a decade [253]. An example of isoform-specific FGF signaling inhibition is bemarituzumab (FPA144), a monoclonal antibody that targets FGFR2b and prevents ligand binding; either FGFR2b immunohistochemistry or FGFR2 amplification by ctDNA has been used for patient selection and trial eligibility [254, 255]. Antibodies specific for the extracellular domain of FGFR2 have also been synthesised—not for blocking isoform-specific ligand binding, but rather for attaching cytotoxic moieties and thus targeting FGFR2-overexpressing tumors [256]. Although such an approach could prove effective in some contexts, e.g., FGFR2 amplification [257], it does not address the issue of differential FGFR2 isoform coexpression in tumors lacking such amplification.

Ligand-specific antibodies—to FGF8 and FGF2, though not yet to more specific FGFR2 growth factors such as FGF7 or FGF10—have also been tested. Another strategy is to use

| Table 1: Key findings from this analysis. |
|-----------------------------------------|
| 1 | The FGFR2 gene undergoes differential splicing in normal epithelial and mesenchymal tissues, resulting in respective FGFR2b and FGFR2c receptor splice isoforms that differ in the affinity of their extracellular domains for specific ligands. |
| 2 | The FGFR2b receptor isoform often exerts prodifferentiation and proapoptotic effects, whereas the FGFR2c isoform is promitogenic. Pathological tumor splice switching from FGFR2b to FGFR2b is causally implicated in the mechanism of tumor progression via epithelial-mesenchymal transition (EMT). |
| 3 | Small-molecule kinase-inhibitory drugs that simultaneously cross-inhibit FGFR2b and FGFR2c could have unintended and/or conflicting effects in tumor or stromal compartments. |
| 4 | Clinically effective tumor-specific FGFR2 drug targeting will depend in part on greater use of nuanced diagnostic assays that clarify which receptor isoform is driving tumor behavior within any unique epistatic context of genetic changes. |
| 5 | New FGFR2 isoform-specific drugs are now available for trial use. Their long-term success is likely to be determined in part by the molecular sophistication of patient/cancer selection and by their rational use in combination with other targeted drugs. |
FGFR isoform-specific extracellular domains as low-toxicity decoys or “ligand traps” for growth factors [258, 259], re-capitulating the physiological inhibition of FGFR2c by FGFR2-binding (but kinase-inactive) FGFR5 [8]. The prospect of FGFR2c-specific antibodies selectively blocking extracellular ligand binding would seem likely to have wide-scale therapeutic applications [166]. One concern about such high-precision signal-inhibitory treatments is whether they will yield sufficient benefit when used as monotherapies in early-phase clinical trials—which outcome might not be rationally expected, given the network-based signaling involved—to justify subsequent inclusion in the combination protocols that seem most likely to transform patient outcomes.

3. Conclusions

FGFR2 differs from its homologs FGFR1 and FGFR3 in terms of epigenetic repressibility, structural predisposition to splicing-dependent variants, and androgen-dependent inducibility of its high-specificity ligands. The FGFR2b isoform also differs markedly from its splice partner FGFR2c in terms of its prodifferentiation and proapoptotic functions, which can be abrogated by heterologous suppressor gene aberrations. These differences underline a growing need for today’s oncologists and trialists to understand the biological spectrum of FGFRs and hence to factor in more sophisticated predictive data for stratifying patients and tumors.

These concerns are relevant to future anticancer drug development (see Table 1). Pan-FGFR druggability strategies remain in vogue as a way of circumventing the association of FGFR gene aberrations with resistance, but this approach faces limitations which now look likely to defy empirical research. The adaptive complexity of FGFR signaling has created a moving target of unprecedented difficulty for the young science of precision oncology, but biomarker-informed targeting using isoform-specific large molecules that block either FGFR2c or FGFR2b/FGF7 could prove a useful starting point for the next phase of this key therapeutic challenge.

Abbreviations

CRC: Colorectal cancer  
EGF(R): Epidermal growth factor (receptor)  
EMT: Epithelial-mesenchymal transition  
FGF(R): Fibroblast growth factor (receptor)  
HSPG: Heparan sulfate proteoglycan  
IBD: Inflammatory bowel disease  
IL-1: Interleukin-1  
KGF(R): Keratinocyte growth factor (receptor)  
PI3K: Phosphatidylinositol-3-kinase  
SAHA: Seborrhea-acne-hirsutism-alopecia (syndrome)  
TA: Transactivating  
TGFα: Transforming growth factor-alpha  
VEGF: Vasoactive endothelial growth factor.

Conflicts of Interest

The authors declare no conflicts of interest relating to this work.

Authors’ Contributions

RJE conceived and wrote the first draft of the article; TLJ and GYF reviewed and revised the manuscript. All authors participated in approval of the final draft.

References

[1] M. Katoh, “Therapeutics targeting FGF signaling network in human diseases,” Trends in Pharmacological Sciences, vol. 37, no. 12, pp. 1081–1096, 2016.
[2] S. J. Coleman, C. Bruce, A.-M. Chioni, H. M. Kocher, and R. P. Grose, “The ins and outs of fibroblast growth factor receptor signalling,” Clinical Science, vol. 127, no. 4, pp. 217–231, 2014.
[3] J. S. Rubin, D. P. Bottaro, M. Chedid et al., “Keratinocyte growth factor as a cytokine that mediates mesenchymal-epithelial interaction,” Experientia Supplementum, vol. 74, pp. 191–214, 1995.
[4] D. M. Ornitz and N. Itoh, “The fibroblast growth factor signaling pathway,” Wiley Interdisciplinary Reviews: Developmental Biology, vol. 4, no. 3, pp. 215–266, 2015.
[5] N. Turner and R. Grose, “Fibroblast growth factor signalling: from development to cancer,” Nature Reviews Cancer, vol. 10, no. 2, pp. 116–129, 2010.
[6] I. McIntosh, G. A. Bellus, and E. Wang Labs, “The pleiotropic effects of fibroblast growth factor receptors in mammalian development,” Cell Structure and Function, vol. 25, no. 2, pp. 85–96, 2000.
[7] V. P. Eswarakumar, I. Lax, and J. Schlessinger, “Cellular signaling by fibroblast growth factor receptors,” Cytokine & Growth Factor Reviews, vol. 16, no. 2, pp. 139–149, 2005.
[8] M. Sleeman, J. Fraser, M. McDonald et al., “Identification of a new fibroblast growth factor receptor, FGFR5,” Gene, vol. 271, no. 2, pp. 171–182, 2001.
[9] M. Mohammadi, J. Schlessinger, and S. R. Hubbard, “Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism,” Cell, vol. 86, no. 4, pp. 577–587, 1996.
[10] U. M. Polanska, D. G. Fernig, and T. Kinnunen, “Extra-cellular interactome of the FGF receptor-ligand system: complexities and the relative simplicity of the worm,” Developmental Dynamics, vol. 238, no. 2, pp. 277–293, 2009.
[11] C. Lanzi and G. Cassinelli, “Receptor tyrosine kinases and heparan sulfate proteoglycans: interplay providing anti-cancer targeting strategies and new therapeutic opportunities,” Biochemical Pharmacology, vol. 178, p. 114084, 2020.
[12] A. Winterpacht, K. Hilbert, C. Stelzer et al., “A novel mutation in FGFR-3 disrupts a putative N-glycosylation site and results in hypochondroplasia,” Physiological Genomics, vol. 2, no. 1, pp. 9–12, 2000.
[13] N. Itoh and D. M. Ornitz, “Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease,” Journal of Biochemistry, vol. 149, no. 2, pp. 121–130, 2011.
[14] Y. Xie, “FGF/FGFR signaling in health and disease,” Signal Transduct Target Therapy, vol. 5, no. 1, p. 181, 2020.
[15] T. Helsten, S. Elkin, E. Arthur, B. N. Tomson, J. Carter, and R. Kurzrock, “The FGFR landscape in cancer: analysis of 4,853 tumors by next-generation sequencing,” Clinical Cancer Research, vol. 22, no. 1, pp. 259–267, 2016.
[16] M. A. Krook, “Fibroblast growth factor receptors in cancer: genetic alterations, diagnostics, therapeutic targets and mechanisms of resistance,” Cancer, vol. 23, 2020.

[17] V. D. Acevedo, M. Ittmann, and D. M. Spencer, “Paths of FGFR-driven tumorigenesis,” Cell Cycle, vol. 8, no. 4, pp. 580–588, 2009.

[18] S. R. Chandana, H. M. Babiker, and D. Mahadevan, “Clinical complexity of utilizing FGFR inhibitors in cancer therapeutics,” Expert Opinion on Investigational Drugs, vol. 29, no. 12, pp. 1413–1429, 2020.

[19] I. S. Bahina and N. C. Turner, “Advances and challenges in targeting FGFR signalling in cancer,” Nature Reviews Cancer, vol. 17, no. 5, pp. 318–332, 2017.

[20] P. Tetu, “FGF2 induces resistance to nilotinib through MAPK pathway activation in KIT mutated melanoma,” Cancers (Basel), vol. 12, no. 5, 2020.

[21] S. Boichuk, “Inhibition of FGF2-mediated signaling in GIST: promising approach for overcoming resistance to imatinib,” Cancers (Basel), vol. 12, no. 6, 2020.

[22] F. Harbinski, V. J. Craig, S. Sanghavi et al., “Rescue screens with secreted proteins reveal compensatory potential of receptor tyrosine kinases in driving cancer growth,” Cancer Discovery, vol. 2, no. 10, pp. 948–959, 2012.

[23] H. Kotani, H. Ebi, H. Kitai et al., “Co-active receptor tyrosine kinases mitigate the effect of FGFR inhibitors in FGFR1-amplified lung cancers with low FGFR1 protein expression,” Oncogene, vol. 35, no. 27, pp. 3587–3597, 2016.

[24] B. Kwabi-Addo, F. Ropiquet, D. Giri, and M. Ittmann, “Alternative splicing of fibroblast growth factor receptor 1 in African-American prostate cancer drives aggressive phenotypes and docetaxel resistance,” Molecular Cancer Research, vol. 17, no. 10, pp. 2115–2125, 2019.

[25] J. Olender, B.-D. Wang, T. Ching et al., “A novel FGFR3 splice variant preferentially expressed in African American prostate cancer drives aggressive phenotypes and docetaxel resistance,” Molecular Cancer Research, vol. 16, no. 2, pp. 163–172, 2001.

[26] H. R. Burgar, H. D. Burns, J. L. Elsdon, M. D. Lalioti, and J. K. Heath, “Association of the signaling adaptor FRS2 with fibroblast growth factor receptor 1 (Fgfr1) is mediated by alternative splicing of the juxtamembrane domain,” Journal of Biological Chemistry, vol. 277, no. 6, pp. 4018–4023, 2002.

[27] A. B. Moffa and S. P. Ethier, “Differential signal transduction of alternatively spliced FGFR2 variants expressed in human mammary epithelial cells,” Journal of Cellular Physiology, vol. 210, no. 3, pp. 720–731, 2007.

[28] M. Kato, “Fibroblast growth factor receptors as treatment targets in clinical oncology,” Nature Reviews Clinical Oncology, vol. 16, no. 2, pp. 105–122, 2019.

[29] O. Elakad, A. M. Lois, K. Schmitz et al., “Fibroblast growth factor receptor 1 gene amplification and protein expression in human lung cancer,” Cancer Medicine, vol. 9, no. 10, pp. 3574–3583, 2020.

[30] D. Morgensztern, N. Karaseva, E. Felip et al., “An open-label phase II study to evaluate GS9823220 in combination with paclitaxel and carboplatin, or docetaxel, in FGFR1-amplified non-small cell lung cancer,” Lung Cancer, vol. 136, pp. 74–79, 2019.

[31] Y. Loriot, A. Necchi, S. H. Park et al., “Erdafitinib in locally advanced or metastatic urothelial carcinoma,” New England Journal of Medicine, vol. 381, no. 4, pp. 338–348, 2019.

[32] C. Aggarwal, M. W. Redman, P. N. Lara et al., “SWOG S1400D (NCT02965378), a phase II study of the fibroblast growth factor receptor inhibitor AZD4547 in previously treated patients with fibroblast growth factor pathway-activated stage IV squamous cell lung cancer (Lung-MAP substudy),” Journal of Thoracic Oncology, vol. 14, no. 10, pp. 1847–1852, 2019.

[33] A. D’Angelo, “Overview of the clinical use of erdafitinib as a treatment option for the metastatic urothelial carcinoma: where do we stand,” Expert Review Clinical Pharmacology, vol. 23, pp. 1–8, 2020.

[34] G. K. Abou-Alfa, V. Sahai, A. Hollebeque et al., “Pembrolimus for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study,” The Lancet Oncology, vol. 21, no. 5, pp. 671–684, 2020.

[35] L. Goyal, S. K. Saha, L. Y. Liu et al., “Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma,” Cancer Discovery, vol. 7, no. 3, pp. 252–263, 2017.

[36] M. A. Krook, A. Lenyo, M. Wilberding et al., “Efficacy of FGFR inhibitors and combination therapies for acquired resistance in FGFR2-fusion cholangiocarcinoma,” Molecular Cancer Therapeutics, vol. 19, no. 3, pp. 847–857, 2020.

[37] H. Dianat-Moghadam and L. Teimoori-Toolabi, “Implications of fibroblast growth factor (FGF) receptors in cancer: from prognostic to therapeutic applications,” Current Drug Targets, vol. 20, no. 8, pp. 852–870, 2019.

[38] R. Roskoski, “The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder,” Pharmacological Research, vol. 151, p. 104567, 2020.

[39] L. Formisano, “Ablant FGF2 signals mediates resistance to CDK4/6 inhibitors in ER+ breast cancer,” Nat Commun, vol. 10, no. 1, p. 1373, 2019.

[40] J. Z. Drago, L. Formisano, D. Juric et al., “FGFR1 amplification mediates endocrine resistance but retains TORC sensitivity in metastatic hormone receptor-positive (HR+) breast cancer,” Clinical Cancer Research, vol. 25, no. 21, pp. 6443–6451, 2019.

[41] D. Carene, A. Tran-Dien, J. Lemonnier et al., “Association between FGFR1 copy numbers, MAP3K1 mutations, and survival in axillary node-positive, hormone receptor-positive, and HER2-negative early breast cancer in the PACS04 and METABRIC studies,” Breast Cancer Research and Treatment, vol. 179, no. 2, pp. 387–401, 2020.

[42] S. Navid, C. Fan, P. O Flores-Villanueva, D. Generali, and Y Li, “The fibroblast growth factor receptors in breast cancer: from oncogenesis to better treatments,” International Journal of Molecular Sciences, vol. 21, no. 6, 2020.

[43] B. Farrell and A. L. Breeze, “Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting,” Biochemical Society Transactions, vol. 46, no. 6, pp. 1753–1770, 2018.

[44] M. J. Donovan and C. Cordon-Cardo, “Implementation of a precision pathology program focused on oncology-based diagnostic and therapeutic targets in clinical oncology,” JCO Clinical Cancer Informatics, vol. 4, no. 1, pp. 71–88, 2020.

[45] A. Mahipal, S. H. Tella, A. Kommalapati, J. Yu, and R. Kim, “Prevention and treatment of FGFR inhibitor-associated toxicities,” Critical Reviews in Oncology/Hematology, vol. 155, p. 103091, 2020.

[46] Y. Zhang, M. C. Gorry, J. C. Post, and G. D. Ehrlich, “Genomic organization of the human fibroblast growth
factor receptor 2 (FGFR2) gene and comparative analysis of the human FGFR gene family,” *Gene*, vol. 230, no. 1, pp. 69–79, 1999.

[48] Y. Lee and D. C. Rio, “Mechanisms and regulation of alternative pre-mRNA splicing,” *Annual Review of Biochemistry*, vol. 84, no. 1, pp. 291–323, 2015.

[49] R. G. Ingersoll, “Fibroblast growth factor receptor 2 (FGFR2): genomic sequence and variations,” *Cyto遗传 Cell Genet.*, vol. 94, no. 3-4, pp. 121–126, 2001.

[50] D.-L. Shi, C. Laynay, V. Fromentoux, I.-J. Feige, and J.-C. Boucaut, “Expression of fibroblast growth factor receptor-2 splice variants is developmentally and tissue-specifically regulated in the amphibian embryo,” *Developmental Biology*, vol. 164, no. 1, pp. 173–182, 1994.

[51] M. Guo, W. Liu, S. Serra, S. L. Asa, and S. Ezzat, “FGFR2 isoforms support epithelial-stromal interactions in thyroid cancer progression,” *Cancer Research*, vol. 72, no. 8, pp. 2017–2027, 2012.

[52] D. Ranieri, B. Rosato, M. Nanni, F. Belleudi, and M. R. Torrisi, “Expression of the FGFR2c mesenchymal splicing variant in human keratinocytes inhibits differentiation and promotes invasion,” *Molecular Carcinogenesis*, vol. 57, no. 2, pp. 272–283, 2018.

[53] C. L. Mummery, M. Vanrooyen, M. Bracke, J. VandenEijndenvanraaij, E. J. Vanzoelen, and K. Alitalo, “Fibroblast growth factor-mediated growth regulation and receptor expression in embryonal carcinoma and embryonic stem cells and human germ cell tumors,” *Biochemical and Biophysical Research Communications*, vol. 191, no. 1, pp. 188–195, 1993.

[54] F. Belleudi, V. Purpura, and M. R. Torrisi, “The receptor tyrosine kinase FGFR2b/KGFR controls early differentiation of human keratinocytes,” *PLoS One*, vol. 6, no. 9, 2011.

[55] P. W. Finch and J. S. Rubin, “Keratinocyte growth Factor/Fibroblast growth factor 7, a homeostatic factor with therapeutic potential for epithelial protection and repair,” *Advances in Cancer Research*, vol. 91, pp. 69–136, 2004.

[56] S. Takizawa-Shirasawa, S. Yoshide, F. Yue et al., “FGF7 and cell density are required for final differentiation of pancreatic amylase-positive cells from human ES cells,” *Cell and Tissue Research*, vol. 354, no. 3, pp. 751–759, 2013.

[57] L. Albardi, “Immunolocalization of FGF7 (KGF) in the regenerating tail of lizard suggests it is involved in the differentiation of the epidermis,” *Acta Histochemica*, vol. 117, no. 8, pp. 718–724, 2015.

[58] A. Petiot, “Development of the mammalian urethra is controlled by Fgfr2-IIIB,” *Development*, vol. 132, no. 10, pp. 2441–2450, 2005.

[59] J.-T. Jiang, H.-L. Xu, Y.-P. Zhu et al., “Reduced Fgf10/Fgfr2 and androgen receptor (AR) in anorectal malformations male rats induced by di-n-butyl phthalate (DBP): a study on the local and systemic toxicology of DBP,” *Toxicology*, vol. 338, pp. 77–85, 2015.

[60] T. J. Fairbanks, F. G. Sala, R. Kanard et al., “The fibroblast growth factor pathway serves a regulatory role in proliferation and apoptosis in the pathogenesis of intestinal atresia,” *Journal of Pediatric Surgery*, vol. 41, no. 1, 2006.

[61] K. Yu, “Conditional inactivation of FGFR receptor 2 reveals an essential role for FGF signaling in the regulation of osteoblast function and bone growth,” *Development*, vol. 130, no. 13, pp. 3063–3074, 2003.

[62] A. Mansukhani, P. Bellotta, M. Sahni, and C. Basilio, “Signaling by fibroblast growth factors (FGF) and fibroblast growth factor receptor 2 (FGF2)-activating mutations blocks mineralization and induces apoptosis in osteoblasts,” *Journal of Cell Biology*, vol. 149, no. 6, pp. 1297–1308, 2000.

[63] M. Kunova Bosakova, M. Varecha, M. Hampi et al., “Regulation of ciliary function by fibroblast growth factor signaling identifies FGFR3-related disorders achondroplasia and thanatophoric dysplasia as ciliopathies,” *Human Molecular Genetics*, vol. 27, no. 6, pp. 1093–1105, 2018.

[64] M. J. Pfaff, K. Xue, M. C. Horowitz, D. M. Steinbacher, and J. V. P. Eswarakumar, “FGFR2c-mediated ERK-MAPK activity regulates coronal suture development,” *Developmental Biology*, vol. 415, no. 2, pp. 242–250, 2016.

[65] J. Anderson, “Apert syndrome mutations in fibroblast growth factor receptor 2 exhibit increased affinity for FGF ligand,” *Human Molecular Genetics*, vol. 7, no. 9, pp. 1475–1483, 1998.

[66] M. K. Hajhosseini, R. Duarte, J. Pegrum et al., “Evidence that Fgf10 contributes to the skeletal and visceral defects of an Apert syndrome mouse model,” *Developmental Dynamics*, vol. 238, no. 2, pp. 376–385, 2009.

[67] K. Yu and D. M. Ornitz, “Uncoupling fibroblast growth factor receptor 2 ligand binding specificity leads to Apert syndrome-like phenotypes,” *Proceedings of the National Academy of Sciences*, vol. 98, no. 7, pp. 3641–3643, 2001.

[68] Y. Tanimoto, M. Yokozeki, K. Hiura et al., “A soluble form of fibroblast growth factor receptor 2 (FGF2) with S252W mutation acts as an efficient inhibitor for the enhanced osteoblastic differentiation caused by FGF2 activation in Apert syndrome,” *Journal of Biological Chemistry*, vol. 279, no. 44, pp. 45926–45934, 2004.

[69] O. A. Ibrahimii, E. S. Chiu, J. G. McCarthy, and M. Mohammadi, “Understanding the molecular basis of Apert syndrome,” *Plastic and Reconstructive Surgery*, vol. 115, no. 1, pp. 264–270, 2005.

[70] Y. Wang, M. Sun, V. L. UhIhorn et al., “Activation of p38 MAPK pathway in the skull abnormalities of Apert syndrome Fgfr2+P253R mice,” *BMC Developmental Biology*, vol. 10, no. 1, p. 22, 2010.

[71] B. Melnik, “Role of FGF2-signaling in the pathogenesis of acne,” *Dermato-Endocrinology*, vol. 1, no. 3, pp. 141–156, 2009.

[72] A. Lomri, J. Lemmonnier, P. Delannoy, and P. J. Marie, “Increased expression of protein kinase ca, interleukin-1α, and RhoA guanosine 5’-triphosphatase in osteoblasts expressing the Ser252Trp fibroblast growth factor 2 Apert mutation: identification by analysis of complementary DNA microarray,” *Journal of Bone and Mineral Research*, vol. 16, no. 4, pp. 705–712, 2001.

[73] C. S. Munro and A. O. Wilkie, “Epidermal mosaicism producing localised acne: somatic mutation in FGFR2,” *The Lancet*, vol. 352, no. 9129, pp. 704–705, 1998.

[74] B. C. Melnik, F. Vakilzadeh, C. Aslanidis, and G. Schmitz, “Unilateral segmental aceniform naevas: a model disorder towards understanding fibroblast growth factor receptor 2 function in acne?” *British Journal of Dermatology*, vol. 158, no. 6, pp. 1397–1399, 2008.

[75] D. Kiritsi, A. I. Lorente, R. Happle, J. Bernabeu Wittel, and C. Has, “Blaschko line acne on pre-existent hypomelanosis function in acne?” *British Journal of Dermatology*, vol. 130, no. 6, pp. 1397–1399, 2008.

[76] Z. Wang, P. Dollé, W. V. Cardoso, and K. Niederreither, “Retinoic acid regulates morphogenesis and patterning of posterior foregut derivatives,” *Developmental Biology*, vol. 297, no. 2, pp. 433–445, 2006.
[77] T. J. Desai, S. Malpel, G. R. Flentke, S. M. Smith, and W. V. Cardoso, "Retinoic acid selectively regulates Fgfr10 expression and maintains cell identity in the prospective lung field of the developing foregut," Developmental Biology, vol. 273, no. 2, pp. 402–415, 2004.

[78] L. Pertovaara, J. Tienari, S. Vainikka et al., "Modulation of fibroblast growth factor receptor expression and signaling during retinoic acid induced differentiation of tera 2 teratocarcinoma cells," Biochemical and Biophysical Research Communications, vol. 191, no. 1, pp. 149–156, 1993.

[79] B. C. Melnik, G. Schmitz, and C. C. Zouboulis, "Anti-acne agents attenuate FGFR2 signal transduction in acne," Journal of Investigative Dermatology, vol. 129, no. 8, pp. 1868–1877, 2009.

[80] M. Gilaberte, L. Puig, and A. Alomar, "Isotretinoin treatment of acne in a patient with Apert syndrome," Pediatric Dermatology, vol. 20, no. 5, pp. 443–446, 2003.

[81] L. Sundaresan, P. Kumar, J. Manivannan et al., "Thalidomide and its analogs differentially target fibroblast growth factor receptors: thalidomide suppresses FGFR gene expression while pomalidomide dampens FGFR2 activity," Chemical Research in Toxicology, vol. 32, no. 4, pp. 589–602, 2019.

[82] L. A. Hansen, N. Alexander, M. E. Hogan et al., "Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development," The American Journal of Pathology, vol. 150, no. 6, pp. 1959–1975, 1997.

[83] S. Segaert and E. Van Cutsem, "Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors: thalidomide suppresses FGFR gene expression while pomalidomide dampens FGFR2 activity," Journal of Clinical Pathology, vol. 129, no. 8, pp. 1868–1877, 2009.

[84] M. Gilaberte, L. Puig, and A. Alomar, "Isotretinoin treatment of acne in a patient with Apert syndrome," Pediatric Dermatology, vol. 20, no. 5, pp. 443–446, 2003.

[85] L. Sundaresan, P. Kumar, J. Manivannan et al., "Thalidomide and its analogs differentially target fibroblast growth factor receptors: thalidomide suppresses FGFR gene expression while pomalidomide dampens FGFR2 activity," Chemical Research in Toxicology, vol. 32, no. 4, pp. 589–602, 2019.

[86] L. A. Hansen, N. Alexander, M. E. Hogan et al., "Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development," The American Journal of Pathology, vol. 150, no. 6, pp. 1959–1975, 1997.

[87] S. Segaert and E. Van Cutsem, "Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors: thalidomide suppresses FGFR gene expression while pomalidomide dampens FGFR2 activity," Journal of Clinical Pathology, vol. 129, no. 8, pp. 1868–1877, 2009.
[165] T. Ishiwata, Y. Matsuda, T. Yamamoto, E. Uchida, M. Korc, and Z. Naito, “Enhanced expression of fibroblast growth factor receptor 2 IIIc promotes human pancreatic cancer cell proliferation,” The American Journal of Pathology, vol. 180, no. 5, pp. 1928–1941, 2012.

[166] Y. Matsuda, M. Hagi, T. Seya, and T. Ishiwata, “Fibroblast growth factor receptor 2 IIIc as a therapeutic target for colorectal cancer cells,” Molecular Cancer Therapeutics, vol. 11, no. 9, pp. 2010–2020, 2012.

[167] K. Cho, T. Ishiwata, E. Uchida et al., “Enhanced expression of keratinocyte growth factor and its receptor correlates with venous invasion in pancreatic cancer,” The American Journal of Pathology, vol. 170, no. 6, pp. 1964–1974, 2007.

[168] H. Lei and C.-X. Deng, “Fibroblast growth factor receptor 2 signaling in breast cancer,” International Journal of Biological Sciences, vol. 13, no. 9, pp. 1163–1171, 2017.

[169] S. Rivetti, “Fgfr10/Fgfr2b signaling in mammary gland development, homeostasis, and cancer,” Frontiers Cell Development Biology, vol. 8, p. 415, 2020.

[170] J. H. Tchaicha, E. A. Akbay, A. Altabef et al., “Kinase domain activation of FGFR2 yields high-grade lung adenocarcinoma sensitive to a Pan-FGFR inhibitor in a mouse model of NSCLC,” Cancer Research, vol. 74, no. 17, pp. 4676–4684, 2014.

[171] E. Hollenbach, M. Neumann, M. Vieth, A. Roessner, P. Mallertheiner, and M. Naumann, “Inhibition of p38 MAP kinase and RICK/NF-κB-signaling suppresses inflammatory bowel disease,” The FASEB Journal, vol. 18, no. 13, pp. 1550–1555, 2004.

[172] G. Docena, L. Rovedatti, L. Kruidenier et al., “Down-regulation of p38 MAP kinase and RICK/NF-κB-signaling suppresses inflammatory bowel disease,” Clinical & Experimental Immunology, vol. 162, no. 1, pp. 108–115, 2010.

[173] R. Yaeger, M. A. Shah, V. A. Miller et al., “Genomic alterations observed in colitis-associated cancers are distinct from those found in sporadic colorectal cancers and vary by type of inflammatory bowel disease,” Gastroenterology, vol. 151, no. 2, pp. 278–287, 2016.

[174] M. Jauhari, “Targeted molecular profiling of rare genetic alterations in colorectal cancer using next-generation sequencing,” Medical Oncology, vol. 33, no. 10, p. 106, 2016.

[175] T. Tanaka, T Kobunai, Y Yamamoto et al., “Colitic cancer develops through mutational alteration distinct from that in sporadic colorectal cancer: a comparative analysis of mutational rates at each step,” Cancer Genomics & Proteomics, vol. 14, no. 5, pp. 341–348, 2017.

[176] N. Erez, E. Zamir, B. J. Gour, O. W. Blaschuk, and B. Geiger, “Induction of apoptosis in cultured endothelial cells by a cadherin antagonist peptide: involvement of fibroblast growth factor receptor-mediated signalling,” Experimental Cell Research, vol. 294, no. 2, pp. 366–378, 2004.

[177] S. G.-D. De Medina, Z. Popov, D. K. Chapin et al., “Relationship between E-cadherin and fibroblast growth factor receptor 2b expression in bladder carcinomas,” Oncogene, vol. 18, no. 41, pp. 5722–5726, 1999.

[178] Y. Katoh and M. Katoh, “FGFR2-related pathogenesis and FGFR2-targeted therapeutics (Review),” Oncogene, vol. 23, no. 3, pp. 307–311, 2009.

[179] N. Han, M. A. Kim, H. S. Lee, and W. H. Kim, “Evaluation of fibroblast growth factor receptor 2 expression, heterogeneity and clinical significance in gastric cancer,” Pathobiology, vol. 82, no. 6, pp. 269–279, 2015.

[180] S. Ahn, J. Lee, M. Hong et al., “FGFR2 in gastric cancer: protein overexpression predicts gene amplification and high H-index predicts poor survival,” Modern Pathology, vol. 29, no. 9, pp. 1095–1103, 2016.

[181] L. Hong, Y. Han, J. Liu, and L. Brain, “Fibroblast growth factor receptor 2: a therapeutic target in gastric cancer,” Expert Review of Gastroenterology & Hepatology, vol. 7, no. 8, pp. 759–765, 2013.

[182] T. Huang, L. Wang, D. Liu et al., “FGF7/FGF2 signal promotes invasion and migration in human gastric cancer through upregulation of thrombospondin-1,” International Journal of Oncology, vol. 50, no. 5, pp. 1501–1512, 2017.

[183] K. Kunii, L. Davis, J. Gorenstein et al., “FGFR2-amplified gastric cancer cell lines require FGFR2 and ErbB3 signaling for growth and survival,” Cancer Research, vol. 67, no. 7, pp. 2340–2348, 2008.

[184] P. Grygielewicz, B. Dymek, A. Bujak et al., “Epithelial-mesenchymal transition confers resistance to selective FGFR inhibitors in SNU-16 gastric cancer cells,” Gastric Cancer, vol. 19, no. 1, pp. 53–62, 2016.

[185] J. A. Galván, M. Helbling, V. H. Koele et al., “TWIST1 and TWIST2 promoter methylation and protein expression in tumor stroma influence the epithelial-mesenchymal transition-like tumor budding phenotype in colorectal cancer,” Oncotarget, vol. 6, no. 2, pp. 874–885, 2015.

[186] D.-Y. Zhu, “Twist1 correlates with poor differentiation and progression in gastric adenocarcinomavaccineavation of FGFR2 expression,” World Journal of Gastroenterology, vol. 20, no. 48, pp. 18306–18315, 2014.

[187] J. Li, “PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer,” Science, vol. 275, no. 5308, pp. 1943–1947, 1997.

[188] A. M. Martelli, I. Faenza, A. M. Billi et al., “Intracellular 3'- phosphoryositide metabolism and Akt signaling: new mechanisms for tumorigenesis and protection against apoptosis?” Cellular Signalling, vol. 18, no. 8, pp. 1101–1107, 2006.

[189] P. M. Pollock and M. G. Gartside, “Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes,” Oncogene, vol. 26, no. 50, pp. 7158–7162, 2007.

[190] W. X. Peng, M Kudo, T Fujii, K Teduka, and Z Naito, “Altered expression of fibroblast growth factor receptor 2 isoform IIc: relevance to endometrioid adenocarcinoma carcinogenesis and histological differentiation,” International Journal of Clinical and Experimental Pathology, vol. 7, no. 3, pp. 1069–1076, 2014.

[191] S. A. Byron, M. G. Gartside, C. L. Wellens et al., “Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation,” Cancer Research, vol. 68, no. 17, pp. 6902–6907, 2008.
[119] L. M. Packer, X. Geng, V. F. Bonazzi et al., “PI3K inhibitors synergize with FGFR inhibitors to enhance antitumor responses in FGFR2mutant endometrial cancers,” Molecular Cancer Therapeutics, vol. 16, no. 4, pp. 637–648, 2017.

[120] A. T. Sengal, A.-M. Patch, C. E. Snell et al., “FGFR2c mesenchymal isoform expression is associated with poor prognosis and further refines risk stratification within endometrial cancer molecular subtypes,” Clinical Cancer Research, vol. 26, no. 17, pp. 4569–4580, 2020.

[121] N. Bansal, V. Yenduri, and R. M. Wenham, “The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies,” Cancer Control, vol. 16, no. 1, pp. 8–13, 2009.

[122] M. Katoh and M. Katoh, “FGFR2 and WDR11 are neighboring oncogene and tumor suppressor gene on human chromosome 10q26,” International Journal of Oncology, vol. 22, no. 5, pp. 1155–1159, 2003.

[123] E. A. Alekseeva, E. B. Kuznetsova, A. S. Tanas et al., “Loss of heterozygosity and uniparental disomy of chromosome region 10q23.3–26.3 in glioblastoma,” Genes, Chromosomes and Cancer, vol. 57, no. 1, pp. 42–47, 2018.

[124] M. E. Hegi, L. Liu, J. G. Herman et al., “Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity,” Journal of Clinical Oncology, vol. 26, no. 25, pp. 4189–4199, 2008.

[125] S. Wemmert, R. Ketter, J. Rahnenfuhrer et al., “Patients with high-grade gliomas harboring deletions of chromosomes 9p and 10q benefit from temozolomide treatment,” Neoplasia, vol. 7, no. 10, pp. 883–893, 2005.

[126] A. L. Rivera, C. E. Pelloski, M. R. Gilbert et al., “MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma,” Neuro-Oncology, vol. 12, no. 2, pp. 116–121, 2010.

[127] K. Hertzler-Schafer, G. Mathew, A.-K. Somani et al., “Pten loss induces autocrine FGF signaling to promote skin tumorigenesis,” Cell Reports, vol. 6, no. 5, pp. 818–826, 2014.

[128] A. R. Guntur, M. I. Reinhold, J. Cuellar, and M. C. Naski, “Conditional ablation ofPtenin osteoprogenitors stimulates FGF signaling,” Development, vol. 138, no. 7, pp. 1433–1444, 2011.

[129] Y. Otsuki, K. Ueda, C. Satoh, K.-i. Yoshiura, and S. Iseki, “Intermediate phenotype between ADULT syndrome and EE syndrome caused by R243Q mutation in TP63,” Plastic and Reconstructive Surgery-Global Open, vol. 4, no. 12, p. e1185, 2016.

[130] A. Yang, M. Kaghad, Y. Wang et al., “p63, a p53 homolog at 3q27–29, encodes multiple products with transactivating, death-inducing, and dominant-negative activities,” Molecular Cell, vol. 2, no. 3, pp. 305–316, 1998.

[131] E. Candi, R. Cipollone, P. Rivetti di Val Cervo, S. Gonfloni, G. Melino, and R. Knight, “p63 in epithelial development,” Cellular and Molecular Life Sciences, vol. 65, no. 20, pp. 3126–3133, 2008.

[132] G. P. Dotto, “p63 and FGFR: when development meets proliferation,” EMBO Molecular Medicine, vol. 4, no. 3, pp. 165–167, 2012.

[133] A. Fomenkov, Y.-P. Huang, O. Topaloglu et al., “p63α mutations lead to aberrant splicing of keratinocyte growth factor receptor in the hay-wells syndrome,” Journal of Biological Chemistry, vol. 278, no. 26, pp. 23906–23914, 2003.

[134] K. Nylander, B. Vojetesek, R. Nenutil et al., “Differential expression of p63 isoforms in normal tissues and neoplastic cells,” The Journal of Pathology, vol. 198, no. 4, pp. 417–427, 2002.

[135] Q. Luo, H Liu, Z Zhang et al., “A dual-regulated oncolytic adenovirus carrying λp63 gene exerts potent antitumor effect on colorectal cancer cells,” American Journal of Translational Research, vol. 9, no. 6, pp. 2966–2974, 2017.

[136] K. E. King, R. M. Ponnamperuma, T. Yamashita et al., “ΔNp63α function as both a positive and a negative transcriptional regulator and blocks in vitro differentiation of murine keratinocytes,” Oncogene, vol. 22, no. 23, pp. 3635–3644, 2003.

[137] S. A. Byron, “FGFR2 point mutations in 466 endometrioid endometrial tumors: relationship with MSI, KRAS, PIK3CA, CTNNB1 mutations and clinicopathological features,” PLoS One, vol. 7, no. 2, 2012.

[138] C. A. Flannery, A. G. Fleming, G. H. Choe et al., “Endometrial cancer-associated FGFR18 expression is reduced by bazedoxifene in human endometrial stromal cells in vitro and in murine endometrium,” Endocrinology, vol. 157, no. 10, pp. 3699–3708, 2016.

[139] E. Candi, A. Rufini, A. Terrinoni et al., “Np63 regulates thymic development through enhanced expression of FGFR2 and Jag2,” Proceedings of the National Academy of Sciences, vol. 104, no. 29, pp. 11999–12004, 2007.

[140] M. R. Ramsey, C. Wilson, B. Ory et al., “FGFR2 signaling underlies p63 oncogenic function in squamous cell carcinoma,” Journal of Clinical Investigation, vol. 123, no. 8, pp. 3525–3538, 2013.

[141] J. Hildesheim, G. I. Belova, S. D. Tyner, X. Zhou, L. Vardanian, and A. J. Fornace, “Gadd45α regulates matrix metalloproteinasises by suppressing ΔNp63α and β-catenin via p38 MAP kinase and APC complex activation,” Oncogene, vol. 23, no. 10, pp. 1829–1837, 2004.

[142] E. Ogawa, R. Okuyama, T. Egawa et al., “p63/p53-induced onset of keratinocyte differentiation via the c-Jun N-terminal kinase pathway is counteracted by keratinocyte growth factor,” Journal of Biological Chemistry, vol. 283, no. 49, pp. 34241–34249, 2008.

[143] O. Karni-Schmidt, M. Castillo-Martin, T. HuaShen et al., “Distinct expression profiles of p63 variants during urothelial development and bladder cancer progression,” The Journal of American Pathology, vol. 178, no. 3, pp. 1350–1360, 2011.

[144] C. A. Franzén, R. H. Blackwell, V. Todorovic et al., “Urothelial cells undergo epithelial-to-mesenchymal transition after exposure to muscle invasive bladder cancer exosomes,” Oncogenesis, vol. 4, no. 8, p. e163, 2015.

[145] H. Nishi, M. Seno, K. H. Nishi et al., “p53 Homologue p63 represses epidermal growth factor receptor expression,” Journal of Biological Chemistry, vol. 276, no. 45, pp. 41717–41724, 2001.

[146] C. Heinzel, Z. Erdem, J. Paur et al., “Is fibroblast growth factor receptor 4 a suitable target of cancer therapy?” Current Pharmaceutical Design, vol. 20, no. 17, pp. 2881–2898, 2014.

[147] L. Lang and Y. Teng, “Fibroblast growth factor receptor 4 targeting in cancer: new insights into mechanisms and therapeutic strategies,” Cells, vol. 8, no. 1, 2019.

[148] M. Weinstein, X Xu, K Ohyama, and C. X Deng, “FGFR-3 and FGFR-4 function cooperatively to direct alveogenesis in the murine lung,” Development (Cambridge, England), vol. 125, no. 18, pp. 3615–3623, 1998.

[149] Y. Zhao and R. J. Epstein, “Programmed genetic instability: a tumor-permissive mechanism for maintaining the evolvability of higher species through methylation-dependent..."
mutation of DNA repair genes in the male germ line,” *Molecular Biology and Evolution*, vol. 25, no. 8, pp. 1737–1749, 2008.

[226] L. Goyal, L. Shi, L. Y. Liu et al., “TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma,” *Cancer Discovery*, vol. 9, no. 8, pp. 1064–1079, 2019.

[227] A. Yamani, D. Dzdzalk-Bielecka, J. Lipner et al., “Discovery and optimization of novel pyrazole-benzimidazole CPL304110, as a potent and selective inhibitor of fibroblast growth factor receptors FGFR (1-3),” *European Journal of Medicinal Chemistry*, vol. 23, 2020.

[228] M. Javle, M. Lowery, R. T. Shroff et al., “Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma,” *Journal of Clinical Oncology*, vol. 36, no. 3, pp. 276–282, 2018.

[229] D. Wang, L. Yang, Y. Yu, and Y. Zhang, "Investigational fibroblast growth factor receptor 2 antagonists in early phase clinical trials to treat solid tumors," *Expert Opinion on Investigational Drugs*, vol. 28, no. 10, pp. 903–916, 2019.

[230] S. De Keukeleire, D. De Maeseneer, C. Jacobs, and S. Rottey, “Erdafitinib: a clinical trials to treat solid tumors,” *Annals of Oncology*, vol. 23, 2020.

[231] O. Bednova and J. V. Leyton, “Targeted molecular therapies for bladder cancer: ready for clinical practice?” *Acta Clinica Belgica*, vol. 75, no. 1, pp. 49–56, 2020.

[232] K. Roubal, Z. W. Myint, and J. M. Kolesar, “Erdafitinib: a clinical trial in the treatment of FGFR-altered advanced colorectal cancer,” *Molecular Biology and Evolution*, vol. 25, no. 8, pp. 1064–1079, 2018.

[233] R. Garje, J. An, M. Obeidat, K. Kumar, H. A. Yasin, and Y. Zakharia, “Fibroblast growth factor receptor (FGFR) inhibitors in urothelial cancer,” *The Oncologist*, vol. 25, no. 11, pp. e1711–e1719, 2020.

[234] K. Montazeri and G. Sonpavde, “Salvage systemic therapy for metastatic urothelial carcinoma: an unmet clinical need,” *Expert Review of Anticancer Therapy*, vol. 23, pp. 1–15, 2018.

[235] P. Grivas and E. Y. Yu, “Role of targeted therapies in the management of metastatic urothelial cancer,” *Expert Review of Anticancer Therapy*, vol. 20, no. 6, pp. 503–512, 2020.

[236] X.-f. Jiang, Y. Dai, X. Peng et al., “SOMCL-085, a novel multi-targeted FGFR inhibitor, displays potent anticancer activity in FGFR-addicted human cancer models,” *Acta Pharmacologica Sinica*, vol. 39, no. 2, pp. 243–250, 2018.

[237] A. Yamani, D. Zdžalik-Bielecka, J. Lipner et al., “Discovery and optimization of novel pyrazole-benzimidazole CPL304110, as a potent and selective inhibitor of fibroblast growth factor receptors FGFR (1-3),” *European Journal of Medicinal Chemistry*, vol. 23, 2020.

[238] N. S. Clayton, A. S. Wilson, E. P. Laurent, R. P. Grose, and E. P. Carter, “Fibroblast growth factor-mediated crosstalk in cancer etiology and treatment,” *Developmental Dynamics*, vol. 246, no. 7, pp. 493–501, 2017.

[239] S. Rotolo, S. Ceccarelli, F. Romano, L. Frati, C. Marchese, and A. Angeloni, “Silencing of keratinocyte growth factor receptor restores 5-fluorouracil and tamoxifen efficacy on responsive cancer cells,” *PloS One*, vol. 3, no. 6, p. e2528, 2008.

[240] B. D. Wang and N. H. Lee, “Aberrant RNA splicing in cancer and drug resistance,” *Cancers (Basel)*, vol. 10, no. 11, 2018.

[241] B. Rosato, “Role of FGFR2b expression and signaling in keratinocyte differentiation: sequential involvement of PKCdelta and PKCalpha,” *Cell Death Disease*, vol. 9, no. 5, p. 565, 2018.

[242] S. Fukumoto, “Targeting fibroblast growth factor 23 signaling with antibodies and inhibitors, is there a rationale?” *Front Endocrinol (Lausanne)*, vol. 9, p. 48, 2018.

[243] Q. Qin, V. Patel, and M. D. Galsky, “Urothelial carcinoma: the development of FGFR inhibitors in combination with immune checkpoint inhibitors,” *Expert Review of Anticancer Therapy*, vol. 20, no. 6, pp. 503–512, 2020.

[244] A. Saborowski, U. Lehmann, and A. Vogel, “FGFR inhibitors in cholangiocarcinoma: what’s now and what’s next?” *Expert Review of Anticancer Therapy*, vol. 12, 2020.

[245] N. Hallinan, S. Finn, S. Cuffe, S. Rafee, K. O’Byrne, and K. Gately, “Targeting the fibroblast growth factor receptor family in cancer,” *Cancer Treatment Reviews*, vol. 46, pp. 51–62, 2016.

[246] H. Luo, T. Zhang, P. Cheng et al., “Therapeutic implications of fibroblast growth factor receptor inhibitors in a combination regimen for solid tumors (Review),” *Oncology Letters*, vol. 20, no. 3, pp. 2525–2536, 2020.

[247] S. Dai, “Fibroblast growth factor receptors (FGFRs): structures and small molecule inhibitors,” *Cells*, vol. 8, no. 6, 2019.

[248] G. Marseglia, A. Lodola, M. Mor, and R. Castelli, “Fibroblast growth factor receptor inhibitors: patent review (2015–2019),” *Expert Opinion on Therapeutic Patents*, vol. 29, no. 12, pp. 965–977, 2019.

[249] Y. Matsuda, J. Ueda, and T. Ishiwata, “Fibroblast growth factor receptor 2: expression, roles, and potential as a novel molecular target for colorectal cancer,” *Pathology Research and Practice*, vol. 202, no. 11, pp. 930–939, 2020.

[250] I. M. Silverman, A. Hollebecque, L. Friboulet et al., “Clinicogenic analysis of FGFR2-rearranged cholangiocarcinoma identifies correlates of response and mechanisms of resistance to pemigatinib,” *Cancer Discovery*, vol. 11, no. 2, pp. 326–339, 2021.

[251] P. M. Kasi, “Favorable outcomes in FGFR fusion-positive cholangiocarcinomas and evolution on treatment noted on circulating tumor DNA liquid biopsies,” *Case Reports in Oncology*, vol. 13, no. 2, pp. 941–947, 2020.

[252] A. Mahipal, S. H. Tell, A. Kommalapati, D. Anaya, and R. Kim, “FGFR2 genomic aberrations: achilles heel in the management of advanced cholangiocarcinoma,” *Cancer Treatment Reviews*, vol. 78, pp. 1–7, 2019.

[253] F. Li, M. N. Peiris, and D. J. Donoghue, “Functions of FGFR2 corrupted by translocations in intrahepatic cholangiocarcinoma,” *Cytokine & Growth Factor Reviews*, vol. 52, pp. 56–67, 2020.

[254] J. H. Carter, “FGFR2 amplification in colorectal adenocarcinoma,” *Future Oncology*, vol. 23, 2017.
[258] M. Presta, P. Chiodelli, A. Giacomini, M. Rusnati, and R. Ronca, “Fibroblast growth factors (FGFs) in cancer: FGF traps as a new therapeutic approach,” *Pharmacology & Thera uetics*, vol. 179, pp. 171–187, 2017.

[259] G. C. Ghedini, R. Ronca, M. Presta, and A. Giacomini, “Future applications of FGF/FGFR inhibitors in cancer,” *Expert Review of Anticancer Therapy*, vol. 18, no. 9, pp. 861–872, 2018.