Fibroblast growth factor receptor (*FGFR*) gene: pathogenesis and treatment implications in urothelial carcinoma of the bladder

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ABSTRACT

Dysregulation of fibroblast growth factor receptors (*FGFRs*) has been implicated in several human malignancies, including urothelial carcinoma. In urothelial carcinoma, the oncogenic role of mutated *FGFR* is mediated by the RAS-mitogen-activated protein kinase pathway, resembling the effects observed with activated *HRAS*. Activating somatic mutations of *FGFR3* are clustered in three hotspots in exons 7, 10 and 15, and are almost always missense mutations leading to amino acid substitution in the external, transmembrane or intracellular regions of the receptor. A fusion of *FGFR3* to transforming acid coiled-coil containing protein 3, *FGFR3* amplification and alternative splicing leading to aberrant *FGFR3* activation are less common molecular alterations. In April 2020, the Food and Drug Administration (FDA) approved the first targeted *FGFR* therapy, erdafitinib, in patients with locally advanced or metastatic bladder cancer who have progressed on platinum-based chemotherapy. Herein, we reviewed the normal structure and function of *FGFR*. We also explored its role in the development of urothelial carcinoma and major developments in the *FGFR*-targeted therapy.

INTRODUCTION

In the USA, carcinoma of the urinary bladder is the fourth leading cancer diagnosis in men, with an estimated incidence of 81 400 new cases in 2020.[1] Multiple genetic and environmental factors contribute to its development, including hereditary cancer syndromes, exposure to a carcinogenic chemical compound, smoking and infections.[2–6] Histologically, carcinoma of the urinary bladder is heterogeneous, with urothelial carcinoma being the most common.[7] It is known that urothelial carcinoma has a high propensity for divergent differentiation, which may, in part, be reflective of the differences in the underlying molecular pathways.[8–10]

The development and progression of urothelial carcinoma follow at least two major pathways, non-invasive and invasive diseases. The former is usually low grade, papillary and with a high propensity for multiple recurrences; the latter is usually high grade, flat and has the major mortality impact of the disease. Generally, low-grade urothelial carcinoma predominantly follows the fibroblast growth factor receptor 3 (*FGFR3*)/RAF/RAS signalling pathway, while the carcinoma in situ and high-grade invasive disease follows the p53/retinoblastoma pathway, which both are reported to be mutually exclusive by some studies.[3 5 11–13] Although the concept of two different pathways involved in the tumourigenesis exists, the possibility of genetic progression from a low-grade *FGFR3*-mutated to high-grade TP53-mutated tumours have been investigated.[4 5 11 12] In a study by Lott *et al*,[14] 45% of inverted papillomas had *FGFR3* mutations, whereas none had TP53 mutations, supporting the concept that both low-grade and high-grade urothelial neoplasms arise in a background of distinct molecular pathways.

In this review, we summarise the current understanding of the *FGFR* pathway alteration, its relationship to the pathogenesis of urothelial carcinoma and the treatment implications.

FGFR structure and function

The *FGFRs* are a family of tyrosine kinases that constitute four different receptors: *FGFR1–FGFR4*.[15] These receptors are encoded by different genes; however, they all share a high sequencing identity.[16] They are located at the cell membrane and are formed of extracellular, transmembranous and intracellular domains. The diversity between the *FGFRs* is mostly attributed to the alternative splicing of the mRNA sequence that produces the extramembranous domain.[17] This domain is formed of one peptide signalling region, two to three immunoglobulin-like domains (IgL-D) and a hallmark of a serine-rich sequence of the acidic box between IgL-D1 and IGL-D2.[17 18] IgL-D1 and acid box are thought to have a role in receptor autoinhibition, while IgL-D2 and IgL-D3 are important for finding to fibroblast growth factor (FGF) ligands.[19] Additionally, IgL-D3 also has three isoforms (a, b and c), that are formed of alternative splicing of exons 7, 7/8 and 8/9, respectively.[20–22] IgL-D3b and IgL-D3c splice variants are observed in *FGFR1–FGFR3*, while only IgL-D3b variants are observed in *FGFR4*.[17] This alternative splicing also contributes to the receptor specificity, whereby *FGFR1b–FGFR3b* are predominantly epithelial, while *FGFR1c–3c* is mesenchymal.[20]

Like other tyrosine kinases, once bound to the activating FGF ligand through the extracellular domain, the receptor dimerises, enabling transphosphorylation and becomes activated. This, in turn, activates downstream transduction intracellular signalling pathways, including *phospholipase C (PLC)γ*, *phosphatidylinositol 3-kinase (PI3K) -AKT* (also known as protein kinase B (*PKB*), and RAS-mitogen-activated protein kinase (MAPK) pathways.[23 24] The selection of which pathway to be

activated is determined by multiple factors, including the nature of activating FGF ligand and the type of receptor involved; however, no single cause relationship exists between ligand, receptor or pathway activated.[24] For instance, the activation of the (extracellular signal-regulated kinase (ERK)1/2 and p38) MAPK pathways mediates FGF-induced growth arrest of chondrocytes, while promoting endothelial cells in angiogenesis.[25 26]

In recent years, a growing interest has developed toward classifying tumours based on their molecular signature, including urothelial carcinomas. Using gene expression profiling, studies reported luminal, basal and other molecular subtypes of urothelial carcinoma.[27–29] In a meta-analysis by Dadhania *et al*,[27] the superficial papillary urothelial tumours were exclusively luminal, while the invasive ones were almost equally divided into luminal and basal subtypes, concluding that the invasive tumours showing luminal expression signatures most likely represent a progression of superficial papillary urothelial tumours. This tumour subtype is enriched in epithelial markers, including high levels of *FGFR3* and activating *FGFR3* mutations.[28]

Role of *FGFR* in urothelial carcinoma

Dysregulation of *FGFRs* has been implicated in different human malignancies, including urothelial carcinoma. In the urinary bladder, genetic alterations in *FGFR1–FGFR3* have been implicated.[30] *FGFR1* alteration is reported in 7% of urothelial carcinomas, predominantly the *FGFR1β* variant, and switching from *FGFR1α* to *FGFR1β* correlates with increasing stage and grade of the tumour.[31 32]

In urothelial carcinoma, the oncogenic role of the mutated *FGFR3* is mediated by the RAS-MAPK pathway, resembling the effects observed with activated *HRAS*. Activating somatic mutations of *FGFR3* have been detected in 50%–70% of papillary urothelial carcinomas. These mutations are clustered in three hotspots in exons 7, 10 and 15, and are almost always missense mutations leading to amino acid substitution in the external, transmembrane or intracellular regions of the receptor. The most common mutation (up to 70% of tumours harbouring *FGFR3* mutations) occurs in exon 7, codon 249, replacing serine with cysteine, followed by codon 248 (up to 17% of tumours), replacing arginine for cysteine, while mutations in other exons are less common.[30 33–35] These mutations can lead to ligand-independent dimerisation, autophosphorylation and activation of the receptor, or may alternatively decrease the lysosomal degradation pathways.[36] *FGFR3* mutations are common in low-grade tumours but have also been reported in high-grade tumours (figure 1).[37 38] No significant difference between *FGFR* mutational hotspots was identified between low-grade and high-grade tumours, although a higher percentage of high-grade tumours harboured S249C point mutation in a study by Al-Ahmadie *et al*.[37] In another meta-analysis study, the frequency of the *FGFR3* mutations decreased with the increasing stage (65% in pTa to 12% in pT2−pT4, and 70% in grade 1 to 19% in grade 3 tumours).[39] These findings also coincide with subsequent studies where *FGFR3* mutations were found in a subset of high-grade papillary urothelial carcinoma.[37 38]

A fusion of *FGFR3* to transforming acid coiled-coil containing protein 3 (*TACC3*) leads to constitutive tyrosine kinase activation, disruption of mitotic activity and aneuploidy.[40] *FGFR3* amplification and alternative splicing leading to aberrant *FGFR3* activation are less common molecular alterations implicated in the proliferative process of urothelial carcinoma.[41 42]

The frequency of *FGFR3* mutations between upper and lower tract urothelial carcinomas was under investigation by many reports. The upper tract showed a higher rate of *FGFR3* gene mutations when compared with the bladder, although this has not reached a statistically significant level in some reports.[38 43] In a recently published study which included 479 upper tract urothelial carcinomas and 1984 bladder urothelial carcinomas, *FGFR3* mutations were statistically more common in the upper tract versus in the bladder (21% vs 14%, p=0.002). Other *FGFR3* alterations, including amplification and rearrangements, showed no significant difference between both groups.[44] Additionally, Lynch syndrome patients had a significantly higher risk of upper tract urothelial carcinoma development.[45 46] A significant proportion of these patients had *FGFR3* R248C mutation, contrasting with the most common *FGFR3* S249C mutation that was found to be related to APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like)-mediated mutagenesis.

FGFR3-targeted therapy

Most urothelial carcinomas are non-muscle invasive, while up to 25% are muscle invasive. The standard first-line therapy for patients with muscle-invasive urothelial carcinoma is

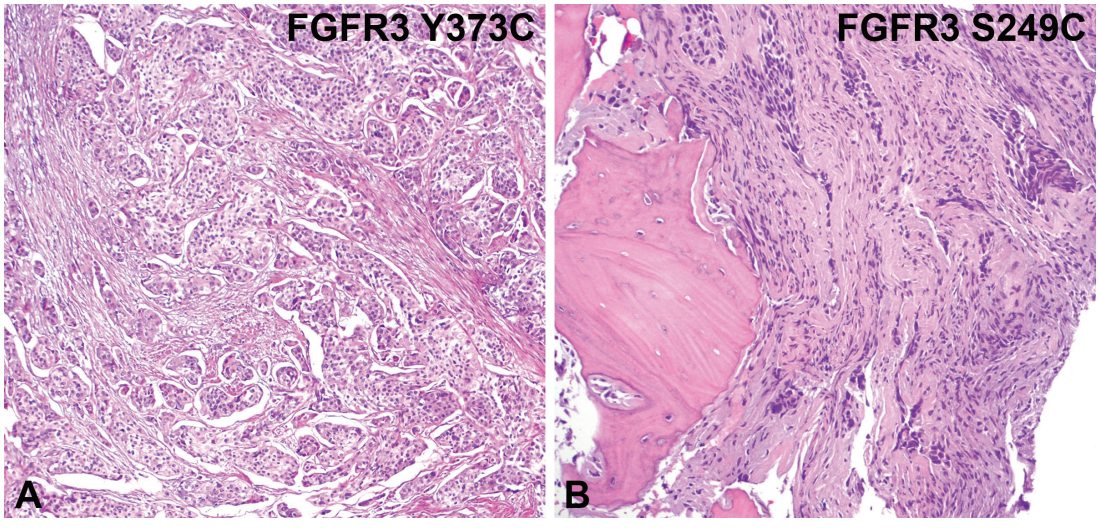

Figure 1 Representative sections of *FGFR3*-mutated urothelial carcinomas. (A) *FGFR3* (Y373C) mutated tumour showing predominantly micropapillary growth pattern. (B) Urothelial carcinoma metastatic to the bone with *FGFR3* (S249C) mutation. *FGFR*, fibroblast growth factor receptor.

Table 1 Fibroblast growth factor receptor inhibitors undergoing clinical trials for treatment of urothelial carcinoma

	NCT number	Phase	Interventions	URL
1	NCT04197986	Phase III	Infigratinib	https://ClinicalTrials.gov/show/NCT04197986
2	NCT02278978	Phase II	BIBF1120	https://ClinicalTrials.gov/show/NCT02278978
3	NCT03390504	Phase III	Erdafitinib	https://ClinicalTrials.gov/show/NCT03390504
4	NCT03410693	Phase II | Phase III	Rogaratinib (BAY1163877)	https://ClinicalTrials.gov/show/NCT03410693
5	NCT02608125	Phase I	PRN1371	https://ClinicalTrials.gov/show/NCT02608125
6	NCT02872714	Phase II	Pemigatinib	https://ClinicalTrials.gov/show/NCT02872714
7	NCT03473756	Phase I | Phase II	Rogaratinib (BAY1163877)	https://ClinicalTrials.gov/show/NCT03473756
8	NCT04045613	Phase I | Phase II	Derazantinib	https://ClinicalTrials.gov/show/NCT04045613
9	NCT04003610	Phase II	Pemigatinib	https://ClinicalTrials.gov/show/NCT04003610
10	NCT00790426	Phase II	Dovitinib (TKI258)	https://ClinicalTrials.gov/show/NCT00790426
11	NCT04228042	Phase I	Infigratinib	https://ClinicalTrials.gov/show/NCT04228042
12	NCT04492293	Phase II	ICP-192	https://ClinicalTrials.gov/show/NCT04492293
13	NCT02365597	Phase II	Erdafitinib	https://ClinicalTrials.gov/show/NCT02365597
14	NCT03123055	Phase I | Phase II	Vofatamab (B-701)	https://ClinicalTrials.gov/show/NCT03123055
15	NCT02052778	Phase I | Phase II	TAS-120	https://ClinicalTrials.gov/show/NCT02052778
16	NCT04294277	Phase II	Pemigatinib	https://ClinicalTrials.gov/show/NCT04294277
17	NCT02401542	Phase I | Phase II	Vofatamab	https://ClinicalTrials.gov/show/NCT02401542
18	NCT03914794	Phase II	Pemigatinib	https://ClinicalTrials.gov/show/NCT03914794
19	NCT02393248	Phase I | Phase II	Pemigatinib	https://ClinicalTrials.gov/show/NCT02393248

cisplatin-containing chemotherapy such as gemcitabine–cisplatin or M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin); however, many patients are not a candidate for cisplatin therapy, requiring an alternative form of treatment, such as carboplatin-based therapies, although the latter correlates with an inferior outcome.[47 48]

To date, multiple clinical trials are ongoing to evaluate the role of *FGFR*-targeted therapy in the treatment of urothelial carcinoma (table 1), including erdafitinib, the first Food and Drug Administration (FDA)-approved targeted therapy. It is approved for the treatment of adult patients diagnosed with locally advanced or metastatic bladder cancer with *FGFR3* or *FGFR2* mutations who have progressed on platinum-based chemotherapy. It is a pan-*FGFR* inhibitor and works by inhibiting the autophosphorylation in the tumour cells and thereby has an antiproliferative property.[49 50] Interestingly, erdafitinib sensitivity is related only to *FGFR* overexpression. In tumour cell lines that harboured *RAS* or *RAF* mutations, erdafitinib lacked its sensitivity indicating that downstream alterations of the *FGFR* pathway can overcome the effects of *FGFR* inhibition.[49] In a multicentre phase I study, erdafitinib response was assessed in patients with different advanced or refractory solid tumours.[49] Only urothelial carcinoma and cholangiocarcinoma responded to erdafitinib. The objective response rate was 46% in urothelial carcinoma and 27% in cholangiocarcinoma in patients with *FGFR* genomic alterations. The response rate was <10% in all other tumour subtypes. Loriot *et al*[51] (ClinicalTrials.gov number: NCT02365597) reported the use of erdafitinib was associated with tumour response in 40% of patients who had locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations, including 59% of patients who had undergone prior immunotherapy. In the same study, a slightly higher response rate was observed in patients with upper tract when compared with lower tract disease (43% vs 39%, respectively), although the difference was not statistically significant. On 12 April 2020, the FDA has approved Qiagen's Therascreen *FGFR* RGQ RT-PCR Kit as a companion diagnostic for erdafitinib. A summary of the *FGFR* point mutations and fusions targets is presented in table 2.

Infigratinib is another *FGFR*-targeted drug. Like erdafitinib, the most observed responses to infigratinib (BGJ398) were in patients with cholangiocarcinoma and urothelial carcinoma. A phase II trial (ClinicalTrials.gov identifier: NCT04233567) assessing the efficacy of infigratinib in treating advanced or metastatic solid tumours in patients with *FGFR* genetic alterations is undergoing.[52] Assessing the efficacy in cases of urothelial carcinoma is currently in phase III trial (ClinicalTrials.gov identifier: NCT04197986) for the adjuvant treatment in patients with invasive urothelial carcinoma with susceptible *FGFR3* genetic alterations. Recently, Necchi and his colleagues found a modest enrichment of *FGFR3* alterations in the upper urothelial tract relative to that of the urinary bladder.[44] Pal *et al*[53] studied the effect of infigratinib on 67 patients with metastatic urothelial

Table 2 Therascreen *FGFR* RGQ RT-PCR Kit assay targets

Point mutations			
Gene	**Amino acid**	**CDS mutation**	**Exons**
FGFR3	p.R248C	c.742C>T	7
FGFR3	p.G370C	c.1108G>T	10
FGFR3	p.S249C	c.746C>G	7
FGFR3	p.Y373C	c.1118A>G	10
Gene fusions			
Fusion ID	**Genes involved**	**Genomic breakpoints**	**Exons**
FGFR3:TACC3v1	*FGFR3*	chr4:1808661 C	17
	TACC3	G(chr4:1 741 428)	11
FGFR3:TACC3v3	*FGFR3*	chr4:1808661 C	17
	TACC3	G chr4:1 739 324	10
FGFR3:BAIAP2L1	*FGFR3*	chr4:1808661 C	17
	BAIAP2L1	A chr7:97 991 744	2
FGFR2:BICC1	*FGFR2*	chr10:123 243 211 G	17
	BICC1	A chr10:60 461 834	3
FGFR2:CASP7	*FGFR2*	chr10:123 243 211 G	17
	CASP7	A chr10:115 457 252	2

FGFR, fibroblast growth factor receptor; *TACC3*, transforming acid coiled-coil containing protein 3.

carcinoma and activating *FGFR3* mutations and/or fusions in the upper tract (n=8) and the urinary bladder (n=59). The authors reported a disease control rate of 100% (n=8/8) and 59.3% (n=35/59) in both groups, respectively. This difference in the response rate was likely attributed to the notable differences in genomic alterations between these upper and lower tract groups of diseases.

Rogaratinib is an *FGFR* selective inhibitor. Its efficacy also correlates strongly with *FGFR* mRNA expression levels.[54] Preliminary data from an ongoing phase II/III clinical trial (ClinicalTrials.gov identifier: NCT03410693) comparing rogaratinib (BAY1163877) and chemotherapy in patients with *FGFR*-positive locally advanced or metastatic urothelial carcinoma reported that in patients with *FGFR1–FGFR3* mRNA-positive urothelial carcinomas, rogaratinib had an efficacy comparable to standard chemotherapy; however, subgroup analysis suggested rogaratinib to be more active in patients with an *FGFR3* DNA alteration (objective response rate of 52% and 27% with rogaratinib and chemotherapy, respectively).[55]

CONCLUSION

FGFR plays an essential role in the normal cellular transduction pathways through the bindings of the FGF. A deeper knowledge of its role in papillary urothelial carcinoma has led to the identification and development of several *FGFR* therapeutic targets, including a recently FDA-approved drug, erdafitinib.

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