Unleashing the potential of combining FGFR inhibitor and immune checkpoint blockade for FGF/FGFR signaling in tumor microenvironment

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Abstract

Background Fibroblast growth factors (FGFs) and their receptors (FGFRs) play a crucial role in cell fate and angiogenesis, with dysregulation of the signaling axis driving tumorigenesis. Therefore, many studies have targeted FGF/FGFR signaling for cancer therapy and several FGFR inhibitors have promising results in different tumors but treatment efficiency may still be improved. The clinical use of immune checkpoint blockade (ICB) has resulted in sustained remission for patients.

Main Although there is limited data linking FGFR inhibitors and immunotherapy, preclinical research suggest that FGF/FGFR signaling is involved in regulating the tumor microenvironment (TME) including immune cells, vasculogenesis, and epithelial-mesenchymal transition (EMT). This raises the possibility that ICB in combination with FGFR-tyrosine kinase inhibitors (FGFR-TKIs) may be feasible for treatment option for patients with dysregulated FGF/FGFR signaling.

Conclusion Here, we review the role of FGF/FGFR signaling in TME regulation and the potential mechanisms of FGFR-TKI in combination with ICB. In addition, we review clinical data surrounding ICB alone or in combination with FGFR-TKI for the treatment of FGFR-dysregulated tumors, highlighting that FGFR inhibitors may sensitize the response to ICB by impacting various stages of the "cancer-immune cycle".

Keywords Fibroblast growth factor receptor, Immune checkpoint blockade, Tumor microenvironment, Immunotherapy

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Introduction

As a member of the receptor tyrosine kinase (RTK) family, the fibroblast growth factor (FGF) receptor family promotes dimerization and activation of intracellular tyrosine residues upon ligand binding, causing recruitment of bridging proteins and docking of RAS/RAF/ mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (AKT), phospholipase C gamma (PLCγ), and signal transducer and activator of transcription (STAT) activation of four key signaling cascades [1, 2]. Through these signaling cascades, FGF signaling can regulate cell growth, proliferation, and survival, along with other functions [3, 4]. When the highly conserved cascade becomes dysfunctional, a series of intracellular events drive tumorigenesis [5, 6], tumor cell metastasis, angiogenesis, and immune evasion [7]. The results of preclinical experiments targeting FGFR variants are encouraging, and antitumor effects have been observed in mouse models of various tumors (including breast, lung, gastric, and urothelial cancers) [7]. FGFR-tyrosine kinase inhibitors (FGFR-TKIs) are also being progressively applied in the clinic to bring effective disease control to patients [6], but in some early clinical trials only 10% of patients achieved remission [7]. This may be related to the co-expression of different FGFRs, Klothoβ expression, bypass signaling activation, and tumor heterogeneity [7, 8]. Although some benefits have been achieved in certain tumors, FGFR-TKI therapy should be further improved. In an attempt to fully and accurately elucidate the impact of FGFR signaling on tumor progression, preclinical trials pointed towards its involvement in the formation of the tumor microenvironment (TME) and further explored the rationale for the use of FGFR-TKIs in combination with immune agents. Analysis of data from early clinical trials also suggests that the combination of FGFR-TKIs and ICB could enhance therapeutic efficacy [9].

This paper reviews the regulatory role of the FGFR signaling pathway on the TME and the immune landscape. FGFR signaling can form abnormal vascular systems and promote interstitial changes but seems to be more involved in inducing the formation of an immunosuppressive microenvironment [17, 18]. This may be the result of FGFR signaling inhibiting T-cell activation and infiltration through factors such as interferon-γ (IFN-γ), granzyme B (GZMB) and chemokines, promoting macrophage M2-type transformation and recruitment and maintaining the presence of Myeloid-derived suppressor cells (MDSCs) [19–21]. However, in recent years, many studies have explored the effects of FGFR signaling on the microenvironment of different tumors in detail; some reach contradictory conclusions, which we speculate may be related to tumor heterogeneity [22–25]. Subsequently, we analyzed the impact of ICB treatment on dysregulated

FGFR signaling and found inconsistent results from various studies. Preclinical studies have shown improved efficacy of ICI combined with FGFR-TKIs, possibly because FGFR-TKIs boost the cancer-immune cycle. However, more clinical trial data and stronger evidence are needed to support the use of FGFR-TKIs in combination with ICB in the clinical treatment of different tumors.

ICBs, which restore host anti-tumor and immune effects by blocking immune checkpoints (e.g., cytotoxic T-lymphocyte associated protein 4 [CTLA-4], programmed cell death protein 1 [PD-1]/programmed death-ligand 1 [PD-L1]), have achieved breakthroughs in multiple clinical practices and are gradually redefining the treatment paradigm for tumors [10, 11]. However, long-term survival data for ipilimumab (anti-CTLA-4) for melanoma suggest that only approximately 21% of patients achieve long-term (5–10 years) disease control or exhibit evidence of clinical response [12]. Others exhibited non-responsiveness (primary resistance) or early progression (acquired resistance) to immunotherapy [13]. Such differences in treatment efficacy between patients may be due to genetic heterogeneity. Mutations in certain specific loci (e.g. *EGFR* and *ALK*) are associated with innate immune resistance and can act on the TME, leading to poor treatment efficacy [14]. FGFR signaling is also involved in the regulation of the TME, and its mechanisms of action are complex and have been discussed in depth [15]. Previously, some researchers proposed a "cancer-immune cycle" theory [16]. Dendritic cells (DCs) capture and process neoantigens released by tumors and present them to T-cells. This presentation of cancer-specific antigens induces the differentiation and activation of naïve T-cells into effector T-cells. The effector T-cells then traffic to the tumor site and infiltrate it and the surrounding tumor bed through lymph nodes and blood vessels to specifically identify and kill target cancer cells. The dead cancer cells release additional tumor-associated antigens, leading to a deeper and wider immune response. Thus, T-cells need to undergo complex signal transduction to exert anti-tumor effects. FGFR signaling mediates several of these processes, which may be a potential mechanism for the anti-FGFR treatment of sensitized ICB.

FGF/FGFR signaling oncogenic dysregulation and treatment

FGF was originally extracted from the brain and pituitary gland as a mitogen for fibroblasts, and the 22 identified FGFs are divided into two major groups according to their function; secreted signaling proteins that signal to RTK(FGF1-10,16–23), and intracellular non-signaling voltage-gated sodium channel proteins(FGF11-14) [1, 26]. as FGFR ligands, secretory signaling proteins are further subdivided into five paracrine subfamilies (heparin/

heparan sulfate (HS) for cofactor-mediated receptor binding) and one endocrine subfamily (Klotho family of cofactor-mediated receptor binding proteins), in which heparan-sulfate proteoglycans(HPSGs) and Klothoβ, cofactors in the FGFR signaling pathway, play a role in enhancing the efficiency of FGF/FGFR binding [2, 27]. The receptors associated with FGFs include the highly conserved RTK family consisting of FGFR1-4, whose internal structure includes three extracellular immunoglobulin folds, a transmembrane region and an intracellular kinase domain [3, 28]. In addition, there exists a subtype of FGFRL1 (also known as FGFR5) that does not carry an intracellular kinase structural domain [29, 30]. FGFs bind to FGFRs which then dimerize to activate the tyrosine activation domain. This activates four key downstream signaling cascades, namely PI3K/AKT, RAS/MAPK, JAK/STAT and PLCγ pathways, either directly or indirectly dependent on FGFR substrate 2 (FRS2) [3], regulating cell growth, metastasis, immunomodulation, and angiogenesis, among other effects [6, 7] (Fig. 1). Depending on the cellular environment, FGFRs also activate the Jun N-terminal kinase pathway and ribosomal protein S6 kinase 2 signaling (RSK2) [3, 31].

FGFR is highly conserved in organisms and regulates key cellular behaviors such as proliferation, differentiation, and survival [3, 5]. Thus, stable FGFR signaling is important for stable cellular functioning, and multiple intracellular and extracellular signals are cross-linked to maintain this homeostasis. Positive signals downstream of the FGFR pathway, such as FRS2α, can be fine-tuned by the negative feedback regulation of certain regulators [32, 33]. In addition, cell adhesion molecules (CAMs), G protein-coupled receptors (GPCRs), and other members of the RTK family can interact with FGFR signaling to regulate cell fate [2, 34–39]. FGF-FGFR signaling is activated by L1CAM, fibrillin leucine-rich transmembrane protein 3 (FLRT3), and FGF binding protein (FGFBP) [27, 40–42] while the Sprouty protein family, germin, MAPK phosphatase 3 (MKP3), similar expression to FGF(SEF) and other proteins are involved in inhibiting it [43]. Thus, FGFR is highly conserved in organisms and plays key role in driving cell proliferation, migration and survival [43].

Under ligand-dependent or ligand-independent conditions, the function of the FGF/FGFR signaling axis is hijacked by tumor cells, leading to oncogenic behavior [3, 6]. The mechanisms of FGF/FGFR oncogenic dysregulation include genetic alterations (gene amplification, activating mutations, oncogenic fusions), autocrine and paracrine signaling (e.g., FGF signaling), angiogenesis, and epithelial-mesenchymal transition [3, 5, 6]. These dysregulations promote the occurrence of proliferation, survival, migration, invasion, angiogenesis and other
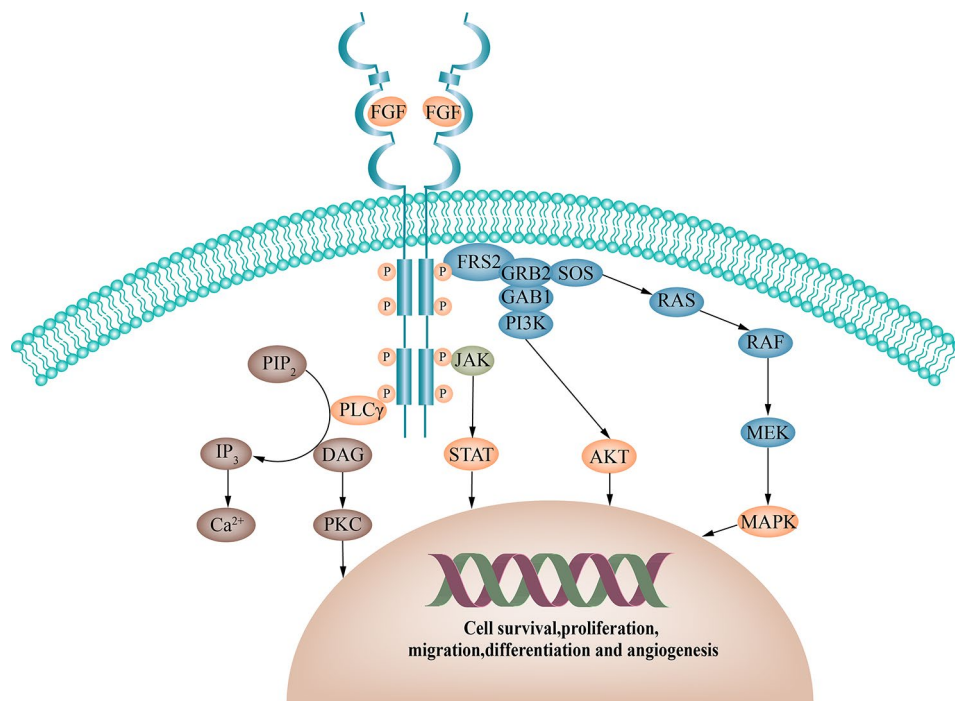
Fig. 1 FGFR signaling network. Upon ligand-receptor binding, activation regions are mutually transphosphorylated, leading to the docking of junctional proteins and activation of four key downstream pathways: RAS/RAF/MAPK, PI3K/AKT, PLCγ, and STAT (orange). PIP$_2$, phosphatidylinositol-4,5-bisphosphate; IP$_3$, inositol triphosphate; PLCγ, phospholipase C gamma; DAG, diacylglycerol; PKC, protein kinase C; FRS2α, FGFR substrate 2α; GRB2, growth factor receptor-bound 2; GAB1, GRB2-associated binder-1; SoS, son of sevenless; P, phosphorylation; JAK, Janus kinase; PI3K, phosphatidylinositol 3-kinase; STAT, signal transducer and activator of transcription; AKT, protein kinase B; MAPK, mitogen-activated protein kinase

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oncogenic behaviors, thus promoting tumorigenesis [3, 6].

Analysis of the molecular profiles of clinical patients revealed a 7.1% incidence of *FGFR* variants in malignant tumors [44]. The mutant forms of *FGFR* may differ in different tumors: *FGFR1* gene amplification is associated with squamous non-small cell lung cancer and breast cancer; *FGFR2* mutation is linked to endometrial cancer and gastric cancer; *FGFR2* gene fusion implicated in hepatocellular carcinoma(HCC); *FGFR3* fusion seen in myeloma; *FGFR3* mutation is associated with identified in bladder cancer; and *FGFR4* amplification/mutation has been identified in patients with rhabdomyosarcoma [44].

In the era of precision medicine, it is of particular significance to explore the relationship between FGFR dysregulation and tumor treatment. More recently, preclinical trials targeting FGFR have yielded promising results. Experiments showed that liver metastases significantly regressed after blocking FGF2 signaling. The liver tumor load of FGF2-deficient mice injected with colon, pancreatic, and lung cancer cell lines were all significantly reduced compared with that of wild-type (WT) mice [45]. However, clinical results are in consistent. In early clinical trials in HCC, the overall effectiveness of FGFR-TKI in tumor treatment was only 7-17%, and most patients exhibited only partial responses [46]. The results of several clinical studies of FGFR inhibitors in the treatment of FGFR2 fusion-positive intrahepatic cholangiocarcinoma (ICC) patients also showed objective remission rates of <50% [47]. In addition, the *FGF/FGFR* genes were only genetically altered in 13–21% of ICC and <20% of HCC cases [8, 47]. This low efficiency of FGFR-TKI may be influenced by co-expression of different FGFRFGFRs, expression of Klothoβ, activation of bypass signaling, and tumor heterogeneity [7]. The literature indicates that inactivation of FGFR4 alone is not sufficient to inhibit the proliferation of FGF19-positive HCC cells and suggests that Klothoβ, FGFR3, and FGFR4 together mediate the survival function of FGF19 [8].

To achieve individualized treatment and enhance therapeutic efficiency, studies in recent years have continued to explore the relationship between FGFR dysregulation and tumorigenesis and treatment. Many studies have focused on the involvement of oncogenic *FGF/FGFR* signaling in the regulation of the TME and contributes to the progression of certain tumors [7, 15, 48–51]. Furthermore, a correlation between FGF/FGFR dysregulation and immunotherapy may be likely. The rationale for FGFR-TKI coupled with ICI therapy is increasingly being explored [9, 52].

FGF/FGFR signaling and TME

During tumor development, individual cancer cells do not act in isolation, but together with immune cells, stromal cells, the extracellular matrix (ECM) and the vascular–lymph node network, forming a complex working network. Together, they constitute the TME, which plays an important role in the dynamic regulation of tumor progression and influences therapeutic outcomes. Recently, increasing research has also focused on treating malignancies by targeting the TME, including ways to ablate the abnormal vascular system, re-educate stromal cells, inhibit tumor-associated macrophage(TAM) recruitment, and restore T-cell depletion [53]. Previous studies have pointed out that mutations in tumor-driven pathways can lead to the activation of immune resistance or dysregulation of immune responses by acting on the TME, thereby promoting immune escape by tumors. Surprisingly, there is growing evidence that activation of the FGF/FGFR pathway is related to the TME (Figs. 2 and 3). In this section, we discuss the role of FGF/FGFR signals in the TME, and the effects of these signals on different cells in the TME are summarized in Table 1.

T-lymphocyte infiltration

Preclinical experiments involving a variety of tumors point to the association of dysregulated FGF/FGFR signaling with the non-T-cell inflammatory phenotype of tumors. This is associated not only with T-cell exhaustion due to increased PD-1 expression, but also with decreased clonality and infiltration. FGFR4 expression is negatively correlated with the number of infiltrating lymphocytes in gastric malignancies [54]. *FGFR3*-mutant urothelial carcinomas have also been noted to possess an immune microenvironment background with increased T-cell exhaustion [55]. Experiments have also shown that bFGF and VEGFA signaling upregulates PD-1, CTLA-4 and TIM-3 expression in T-cells, leading to T-cell exhaustion [22]. Genetically engineered mouse models (GEMMs) of lung cancer and immunohistochemistry of human lung cancer tissues have demonstrated that the TME of *FGFR*-mutant tumors is characterized by low T-cell infiltration and high PD-L1 expression in tumors and immune cells [23]. Consistently, elevated CD4^{+} and CD8^{+} T-cells expression was experimentally detected in FGF2 signaling-deficient mice [45].

The mechanisms of action underlying the T-cell depletion phenotype have been extensively studied, constructing complex regulatory networks that emphasize the role of the IFN-γ and peroxisome proliferator-activated receptor-gamma(PPARG) pathways and Nuclear factor-kappa B(NF-kB) signaling [21, 56, 57]. At the same time, the FGFR pathway has been noted to lead to a non-T-cell infiltrating phenotype, possibly through these networks.
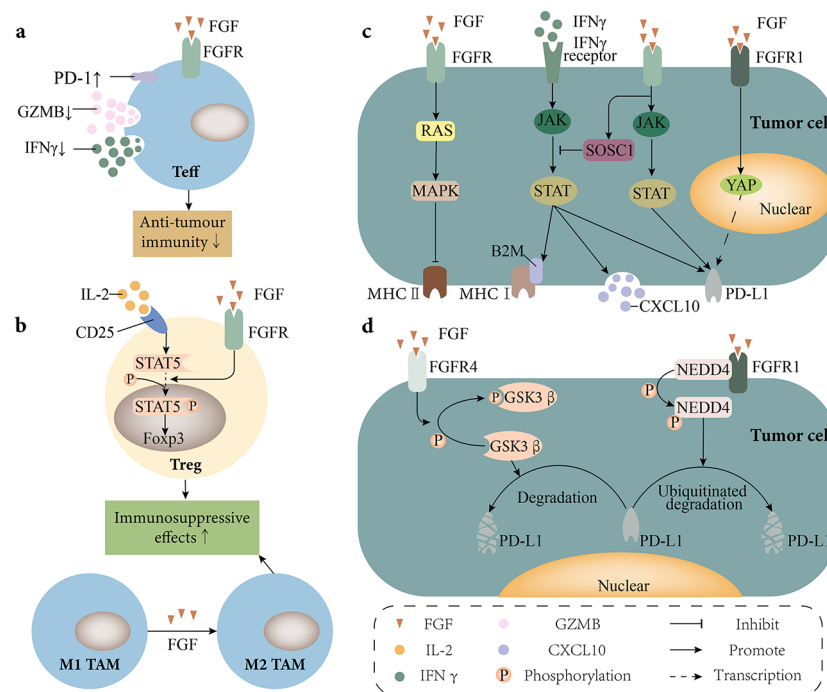
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Fig. 2 Effects of FGFR signaling on the TME. a.| FGF/FGFR promotes PD-1 expression and reduces IFNγ and GZMB secretion by effector T cells, resulting in a decrease in anti-tumor immunity of T-cells. **b.|** FGF/FGFR promotes Treg cell survival by assisting IL-2-mediated STAT5 phosphorylation. FGF also promotes the M2-type polarization of TAMs. These functions of FGF/FGFR enhance immunosuppressive effects. **c.|** FGF/FGFR signaling directly inhibits MHC II expression via the RAS/MAPK pathway. At the same time, FGF/FGFR signaling also inhibited interferon-mediated expression of MHC I and PD-L1 and secretion of CXCL10 via SOSC1. In addition, FGF/FGFR signaling promotes PD-L1 expression through the JAK/STAT pathway and initiates PD-L1 transcription through the upregulation of YAP. **d.|** On the one hand, FGFR4 reduces PD-L1 degradation by promoting GSK3β phosphorylation at the Ser 9 site. On the other hand, FGFR1 promotes the degradation of ubiquitinated PD-L1 by promoting NEDD4 phosphorylation. IFN-γ, interferon-γ; GZMB, granzyme B; TAM, tumor-associated macrophage; MHC, major histocompatibility complex; PD-L1, SOSC1, suppressor of cytokine signaling 1; GSK3β, glycogen synthase kinase 3 beta

FGFR alterations may promote a non-T-cell infiltrative phenotype by inhibiting the production of IFN-γ and GZMB (Fig. 2a). IFN-γ is an important intermediate factor in tumor immunity that exerts its antitumor effects mainly by promoting T-cell differentiation and immune cell recruitment [58]. Inhibition of FGFR signaling in head and neck squamous cell carcinoma(HNSCC) can upregulate IFN-γ [59]. Analysis of data sets from clinical trials revealed that reduced T-cell infiltration is associated with impaired FGFR expression and IFN-γ signaling [20, 60, 61]. Combined stimulation of VEGFA and bFGF inhibits IFN-γ and GZMB secretion by HCC patient-derived T-cells [22]. The use of anti-VEGFR and anti-FGFR monoclonal antibodies increases the percentage of IFN-γ and GZMB secreted by activated CD8+ T-cells [62]. Furthermore, inhibition of FGFR attenuates PD-L1 expression mediated through IFN-γ, as inhibition of FGFR in the absence of IFN-γ has no regulatory effect on PD-L1 expression [24]. Meanwhile, FGFR3 knockdown results in significant upregulation of the IFN-responsive genes *BST2* and *IRF9* [20, 55]. A study on renal cancer further showed that activated FGFR signaling inhibits the IFN-γ-mediated JAK/STAT

signaling pathway and consequently reduces the expression of β2-microglobulin(β2M), PD-L1, and CXCL10 [63] (Fig. 2c). These proteins are directly associated with activation of the antitumor immune system.

In addition, FGFR alterations may also promote an inflammatory phenotype through the upregulation of PPARG signaling. Numerous studies have confirmed that PPARG signaling is associated with non-T-cell infiltration phenotypes of tumors [55, 64, 65], while the β-catenin, PPARG and FGFR3 pathways are simultaneously activated in non-T-cell inflammatory tumors [21]. Genomic analysis of *FGFR3*-mutant tumors compared with WT tumors found that upregulated *PPARG* gene signaling is significantly associated with *FGFR3* mutations [66]. At the same time, PPARG signaling leads to an anti-inflammatory environment through the inhibition of NF-κB [67]. Predictably, *FGFR* alterations may potentially inhibit NF-κB and reduce T-cell infiltration through PPARG pathway activation, but this remains to be corroborated by further studies.

Paradoxically, FGF/FGFR signaling dysregulation in specific tumors may instead lead to T-lymphocyte infiltration. Earlier studies pointed out that chronic
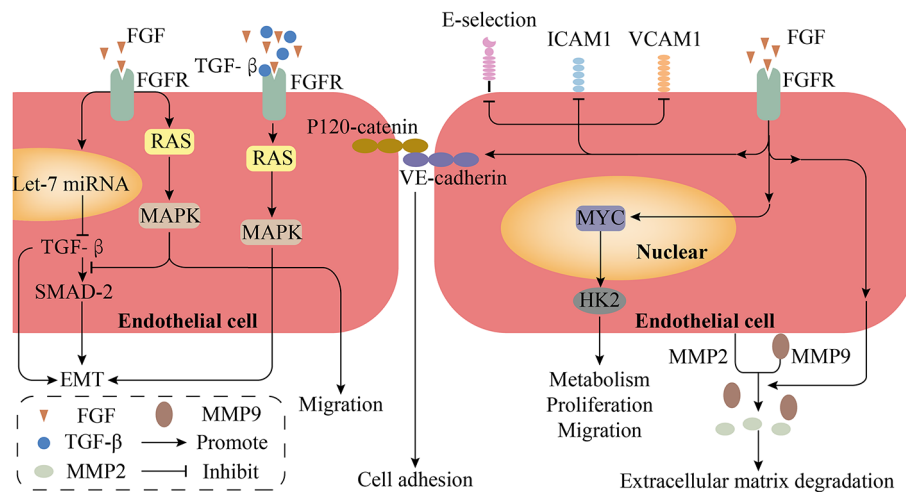
Fig. 3 **Effects of FGFR signaling on the vascular system.** On the one hand, TGF-β facilitates the heterodimeric conversion of FGFR to promote EMT. On the other hand, FGF/FGFR signaling blocks TGF-β activation via let-7 miRNA and Smad2 activation via RAS/MAPK signaling, thus preventing EMT in endothelial cells. FGF promotes endothelial cell adhesion and tight junctions through the coupling of p120-cadherin and VE-cadherin and stimulates matrix metalloproteinase 2 (MMP2) and MMP9 shedding from the cell surface, leading to ECM degradation and promoting angiogenesis. FGF/FGFR also controls the expression of the glycolytic enzyme hexokinase 2 (HK2) via c-MYC, which assists in the metabolism, proliferation and migration of vascular endothelial cells. FGF is involved in the inhibition of expression and secretion of endothelial VCAM1, E-selectin, and ICAM1, which in turn impairs T-cell homing and recruitment. TGF-β, transforming growth factor beta; EMT, epithelial-mesenchymal transition; VCAM1, vascular cell adhesion molecule 1; ICAM1, intercellular cell adhesion molecule 1; ECM, extracellular matrix

Table 1 Effects of FGF/FGFR signaling on cells in tumor microenvironment

Cell of TME	Trigger signal	Mechanism	Effect
T-cell	bFGF+VEGFA [22], FGFR [23]	The expression of PD-1, CTLA-4 and TIM-3 in T-cells was up-regulated	T-cell Exhaustion↑
	bFGF+VEGFA [22], VEGFR+FGFR [62], FGFR [63], FGFR1 [59], FGFR3 [20, 55], FGFR4 [24]	Inhibit the production of IFN-γ and GZMB	T-cell infiltration↓
	FGFR3 [66]	Upward PPARG signal	
	FGFR [115, 121]	Indirectly inhibited the recruitment of CD8+T- cells via CXCL16	
	FGFR1 [54, 71, 72]	Promote IL-2 production by activating NF-κB	T-cell infiltration↑
Tumor-cell	FGFR [23], FGFR4 [24], FGFR2 [89],FGFR1 [88]	The expression of PD-L1 in tumors was up-regulated	Immune escape↑
	FGFR [63],FGFR1 [59],	Inhibit the expression of MHC I and MHC II molecules in tumor cells	
	FGFR3 [25]	Promote PD-L1 degradation in tumor cells	Immune escape↓
Macrophage	FGFR1 [19]	Promote macrophage recruitment through induction of CX3CL1 expression	Immunosuppression↑
	FGF2 [45]	Promote M2-type polarization of macrophages	
Treg-cell	FGFR4 [24]	Promote the differentiation and survival of Treg cells by regulating IL-2	
Epithelial-cell	FGF2-FGFR1/2IIIc [86, 131–133]	The FGF2-FGFR1/2IIIc signaling axis promotes cellular EMT	EMT↑
	FGF2 [134], FGF [135]	FGF signal inhibits EMT by blocking TGF-β	EMT↓
Endothelial-cell	FGF2-FGFR [17]	Enhance endothelial cell chemotaxis by regulating MAPK signaling	Endothelial migration and generation ↑
	FGF [155]	Promote extracellular matrix degradation by stimulating the shedding of MMP2 and MMP9	
	FGF2/FGFR1 [18]	Control endothelial cell energy metabolism by inducing HK2 expression	
	FGF [152]	Involved in inhibiting the expression of endothelial cell adhesion molecules	T-cell homing and recruitment↓

immune injury (e.g. rheumatoid arthritis) drives some CD4+ T-cells to express FGFR1 [68–70]. This FGFR signaling promotes interleukin (IL)-2 production by degrading IκBα and activating NF-κB, which promotes T-lymphocyte proliferation by activating RAS and PI3K with the help of SNT-like proteins [71, 72]. Bioinformatic analysis of tissues from gastric cancer patients also revealed that the degree of infiltration of CD8+ and CD4+

T-cells, macrophages and DCs was positively correlated with the expression of FGFR1 in tumor cells [54]. This suggests that the mechanisms by which different FGFR activating alterations act in tumors may be different and regulated by different factors and require more detailed and comprehensive studies for elucidation.

Major histocompatibility complex (MHC) expression

The MHC system shapes all the components of the presenting peptide and subsequent immune responses [73]. MHC molecules bind to antigenic peptides through their peptide-binding grooves and present them on the cell surface for recognition by T-cells, a process that helps stimulate subsequent anti-tumor responses [74]. However, tumors will act on MHC molecules to evade immune surveillance through several mechanisms, chief among which is altered MHC expression. Of note, FGFR signaling downregulates MHC expression(Fig. 2c). Early experiments have shown that IFN-γ plays a role in inducing the expression of MHC Class II molecules [75, 76]. In the absence of IFN-γ, upregulation of human leukocyte antigen(HLA)-DR and expression of MHC Class II transactivator (CIITA) in HNSCC are still observed after the use of FGFR inhibitors [59]. In addition, Toll-like receptor 2 can inhibit CIITA expression by inducing MAPK signaling [77]. Notably, the MAPK signaling pathway is a common pathway downstream of multiple proteins such as FGFR and EGFR [5, 78]. Combining these results, we speculate that FGFR may be linked to MHC via the MAPK pathway. Recently, a study on HNSCC demonstrated through in vivo and in vitro assays that inhibition of MAPK/EPK signaling promotes CIITA expression while that of STAT3 or PI3K does not affect HLA expression in tumors [59]. Meanwhile, other experiments showed that FGFR signaling leads to a decrease in β2M expression by inhibiting the IFN-γ-mediated JAK/STAT signaling pathway [63]. β2M is an important subunit of MHC Class I molecules and is involved in mediating its antigen presentation [79]. Thus, FGFR signaling indirectly inhibits the expression of MHC Class I molecules by tumor cells through inhibition of the IFN-γ-mediated JAK/STAT signaling pathway and inhibits the expression of MHC Class II molecules in tumor cells on the other, thereby reducing T-cell infiltration and promoting immune escape.

PD-1/PD-L1 regulation

Macrophages, T-lymphocytes, natural killer (NK) cells and dendritic cells (DC) in the TME together construct an antitumor innate immune defense [80]. In addition to this, the adaptive immune response is also critical in the TME and involves the activation of T-lymphocytes and B-lymphocytes, which are capable of recognizing and responding to specific antigens. Together, the innate and adaptive immune responses work to provide a multilayered defense against the tumor threat. DCs, CD4+T helper (Th) cells, and CD8+cytotoxic T-lymphocytes (CTL) play a central role in antitumor immunity and are significantly associated with tumor prognosis [81]. T-cells rely on the combined involvement of antigenic peptide-MHC complexes, co-receptors, and co-stimulatory signals to achieve effective activation [82–84]. Expression of multiple co-inhibitory molecules by T-cells results in a significant reduction in T-cell proliferation and effector function [83]. For example, PD-1 can interfere with T-cell antigen receptor-mediated signaling and thereby inhibiting T-cell responses [85]. Such depleted T-cells expressing co-repressor molecules exhibit limited anti-tumor responses.

Consistent with this immune exhaustion, FGFR signaling can lead to immune resistance through the upregulation of PD-1/PD-L1 [86, 87] (Fig. 2a, c, d). A mouse model of HCC demonstrated that VEGFR and FGFR signaling inhibit the secretion of IFN-γ and GZMB from T-cells, significantly upregulating PD-1 expression in T-cells and PD-L1 in tumor cells [22, 24]. More importantly, such experiments further suggested that PD-L1 expression may be dependent on FGFR4-mediated phosphorylation of glycogen synthase kinase 3 beta (GSK3β) at Ser9, which affects the stability of PD-L1 rather than its transcription [24]. In addition, in lung squamous cell carcinoma, FGFR1 also initiates PD-L1 transcription through YAP upregulation [88]. In vitro colon cancer assays demonstrated that FGFR2 signaling promotes PD-L1 expression through the JAK/STAT signaling pathway and is not affected by mammalian target of rapamycin (mTOR) or MAPK signaling [89]. In contrast, in vitro trials in lung adenocarcinoma cases found no reduction in PD-L1 expression by tumor cells after blockade using inhibitors of mTOR, MEK1/2, JAK1/2, or STAT3/5 alone, suggesting that achieving complete regulation of PD-L1 expression may require simultaneous blockade of several FGFR downstream pathways [23].

However, not all FGFR signaling in all tissues promotes PD-L1/PD-1 upregulation. Positive PD-L1 expression by tumor cells was observed in only one of 58 FGFR2 fusion-positive ICC patients, but was detected in eight of the FGFR2 fusion-negative specimens [47]. Genetic clustering analysis of 489 ICC cases noted that no significant PD-1/PD-L1 alterations were seen in FGFR expression clusters [90]. These studies suggest that FGFR signaling in ICC may not be significantly associated with PD-1 expression. Moreover, in bladder urothelial carcinoma with FGFR-activating mutations, FGFR3 promotes PD-L1 degradation via NEDD4 [25] (Fig. 2d). Analysis of patients with bladder urothelial carcinoma in some early clinical trials and real-world studies also revealed that

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lower PD-L1 expression is observed in *FGFR3*-mutated tumors [91–94].

Thus, the regulation of PD-L1/PD-1 expression by FGFR signaling is a complex process with paradoxical outcomes that may depend on the histological context.

Regulation of immunosuppressive cell infiltration and macrophage polarization

Tumor development is also a process accompanied by the recruitment and activation of immunosuppressive cells (including macrophages, MDSCs, regulatory T [Treg] cells). Cells such as M2-TAMs, Treg cells, and MDSCs in the TME are an important part of tumor evasion from immune cell surveillance and destruction [80]. Macrophages exhibit significant plasticity throughout tumorigenesis [95]. Macrophages in the earliest stages of tumorigenesis are involved in tumor clearance in concert with T-cells [95]. Subsequently, stimulated by various cytokines in the TME, TAMs polarize into the M2 type and promote tumor growth through mechanisms that regulate angiogenesis, tumor cell proliferation, metastatic potential, chemoresistance, and immune escape [45, 96–99]. As a group of immature myeloid cells capable of suppressing immune responses, MDSCs inhibit the immune response mainly by acting on the tumor immune environment (including activation of M2-TAM and Treg cells and suppression of CD8^{+} T-cells and NK cells), blocking lymphocyte homing, and promoting epithelial–mesenchymal transition (EMT) and angiogenesis [100–105]. Th2 subtype CD4^{+} T-cells and Treg cells also have anti-tumor immune responses that suppress CTL and NK cells [98, 106–108].

Activation of FGFR promotes leukocyte recruitment, with macrophages being the most dominant T-cell type [109, 110]. Increased infiltration by TAMs and Treg cells is observed in FGFR-expressing lung malignancies [23]. Analysis of a dataset of triple-negative breast cancers revealed that tumors with high FGFR expression have decreased infiltration of CD8^{+} T-cells and M1 macrophages but increased infiltration of M2 macrophages [111]. Relatedly, activated FGFR1 signaling promotes macrophage recruitment through NF-κB signaling-induced chemokine CX3CL1 expression [19]. However, CX3CL1 can also be involved in the recruitment of CD8^{+} T-cells, NK cells, and DCs [112]. This suggests that macrophage recruitment may not be the only role of CX3CL1.

In addition, FGF/FGFR signaling was involved in regulating the M2 polarization of macrophages and the survival of Treg cells (Fig. 2b). A previous study detected increased expression of FGFR1/2 in bone marrow-derived macrophages (BMDMs) after co-culturing with tumor cells [45]. Further experiments demonstrated that FGF2-deficient BMDMs had higher levels of

pro-inflammatory cytokines (e.g., CXCL1, IL-1β, IL-6, and TNF-α) and reduced expression of M2 markers Ym1 and Ym2 compared to WT BMDMs [45]. In addition, reduced FOXP3 levels were detected after treatment with lenvatinib in a murine model of HCC, suggesting that Treg cells may be activated by FGFR signaling [24]. These results further suggest that Treg infiltration is not the result of cell recruitment but rather a result of pro-cellular differentiation and survival exerted by FGFR signaling through regulation of IL-2 [24].

Although inhibition of FGFR can reduce the infiltration of MDSCs, the mechanism of FGFR signaling on MDSCs remains to be elucidated. FGFR inhibitors have been shown to decrease proliferation and lung metastasis of breast tumors and reduce infiltration of MDSCs [49, 113–115]. The use of FGFR inhibitors decreases granulocyte colony-stimulating factor(G-CSF) levels via mTOR signaling, thereby reducing the mobilization of MDSCs [116]. However, analysis of some experimental pools revealed that FGFR indirectly inhibited the expansion of MDSCs and the recruitment of CD8^{+} T cells via CXCL16. By analyzing the results of experiments in mouse breast cancer model, it was found that inhibition of FGFR led to a significant increase in CXCL16 expression and was consistent with infiltration of CD8^{+} T cells [115, 117]. The same results were also seen in the analysis of the human bladder cancer dataset (GSE52452) [115]. CXCL16 induces MDSC expression of CD38 in vitro, which regulates MDSC amplification [118–120]. On the other hand, an important study pointed out that CXCR6, the receptor for CXCL16, plays a key role in CTL-mediated tumor control, and contributes to the survival and local expansion of effector-like CTL in the TME [121]. Meanwhile, CXCL16 expression promotes the accumulation of tumor-specific CXCR6^{+}CD8^{+} T cells in tumor tissues [117, 121, 122].

Changes within the interstitial space

EMT refers to the process by which epithelial cells acquire mesenchymal features and is associated with tumorigenesis, metastasis, invasion, immune escape, and treatment resistance [123–125]. Mesenchymal breast cancer cell lines with more EMT markers weakly express MHC Class I molecules and promote the recruitment of Treg cells and M2-TAMs [126]. EMT also promotes PD-L1 expression [126–128].

As research on this continues, the potential role of the FGF/FGFR signaling axis in EMT continues is being further revealed. Transforming growth factor β(TGF-β) plays an important role in EMT and FGF/FGFR can be used as a marker of TGF-β1 signaling [129, 130], as TGF-β acts synergistically with FGF-2 to promote EMT and tumorigenesis [131]. Specifically, TGF-β induces EMT while promoting the heterodimeric conversion of

FGFR2IIIb to FGFR1IIIc on normal epithelial cells, which elevates cellular sensitivity to FGF-2 [131]. Subsequently, FGF-2 promotes the formation of phosphorylated δEF1-CtBP1 complexes through the MAPK/ERK pathway to enhance EMT [131]. Following EMT, the expression levels of FGFR1IIIc and β3 integrin increase and utilize focal adhesion kinase (FAK) to aberrantly activate ERK1/2, which also enhances the response to FGF-2 [132]. This suggests that FGFR1IIIc can drive aberrant downstream signaling in concert with other effector molecules of EMT to promote tumor growth and metastasis [132]. Furthermore, the data suggest that FGFR2IIIb expression is not associated with EMT, whereas FGFR2IIIc expression and activation contribute to the response to FGF-2, triggering EMT [133]. Thus, the switch between FGFR2IIIb and FGFR2IIIc induces EMT [133]which may be due to selective splicing facilitated by the AKT3/IWS1 pathway [86]. Notably, bladder cancer expressing FGF-2 has also been identified as a tumor subtype prone to EMT, which may be related to the induction of KDM2B and EZH2 expression by FGF-2 [86]. In conclusion, FGF-2 and FGFR1/2IIIc appear to play an important role in the development of cellular EMT in the TME.

However, the findings of other studies are different. Compared with FGFR3-WT in urothelial carcinoma, FGFR3 alteration results in low expression of TGF-β and EMT signaling [20]. In both in vivo and in vitro experiments, FGF2 signaling blocks SMAD2 activation via RAS/MAPK signaling, which inhibits TGF-β signaling and further blocks EMT in lymphatic endothelial cells(LECs) [134]. In addition, FGF signaling blocks TGF-β activation by promoting let-miRNA, which impedes EMT in vascular endothelial cells [135]. Thus, the conflicting effects of FGF/FGFR signaling on EMT may be related to the crosstalk between different FGF/FGFR signals.

Cancer associated fibroblasts (CAFs) in the TME have been shown to play an important role in tumor progression and regulation of immunity, and can support tumor growth through multiple mechanisms, including ECM deposition and matrix proteases production [136], which can provide a pathway for local invasion and migration by tumor cells and act as a barrier to immune cell infiltration [137–139]. Evidence suggests that FGF contributes to CAFs activation [45, 136]. Additionally, in breast cancer dataset (GSE114727), an increased number of fibroblasts and decreased number of CD8+ T-cells were observed in a high FGFR1 expression group [111]. Experiments also further indicated that blocking FGFR signaling inhibits CAF proliferation and migration by downregulating the MAPK signaling pathway, which would disrupt the physical barrier established by CAF [111]. In addition, blocking FGFR prevents CAF from secreting the vascular cell adhesion molecule 1 (VCAM1), which is closely associated with tumor metastasis and angiogenesis [111]. These alterations promote T-cell infiltration. Furthermore, FGFR signaling in breast cancer induces STAT3 activation, which results in a hyaluronic acid-rich microenvironment that contributes to tumor growth and metastasis [140].

Abnormal vascular network

The abnormal vascular system (both lymphatic and vascular networks) in the TME manifests as elevated interstitial fluid pressure (IFP) and decreased vascular supply efficiency, which affects the supply of oxygen and drugs in the blood and increases tumor aggressiveness [141, 142]. In addition, this abnormal vascular system can prevent immune cell entry through differential expression of integrins and CAMs [143]. Thus, the vascular network system plays an important role in regulating tumor progression and immunotherapeutic efficacy [53].

Tumor vasculogenesis is a complex process driven by the VEGF, PDGF, EGF, FGF, and ANG families, with VEGF-VEGFR and FGF2-FGFR1/2 signaling playing key roles by promoting endothelial cell proliferation and migration, duct formation, and protease production [18, 144–146]. Assays on murine brain capillary endothelial cells (MBEC) point to enhanced chemotaxis of MBEC by FGF2/FGFR, an effect is associated with MAPK signaling [17, 147]. Several studies have also indicated that TAMs can further influence the immune microenvironment by secreting FGF in concert with FGFR signaling to promote angiogenesis [142, 148]. In addition, FGF/FGFR signaling stimulates matrix metalloproteinase 2 (MMP2) and MMP9 shedding from the cell surface, which leads to ECM degradation, promoting angiogenesis [149, 150]. FGF is also involved in suppressing the expression of endothelial VCAM1, E-selectin, and intercellular cell adhesion molecule 1, which in turn impairs T-cell homing and recruitment [151–153].

Interestingly, FGF-FGFR1/2 signaling is noted to play a key role in injury-induced angiogenesis without affecting vascular permeability and reactivity under physiological homeostatic conditions [154]. However, research indicates that FGF signaling also plays an important role in maintaining vascular-lymphoid endothelial cell homeostasis. As described previously, FGF/FGFR blocks EMT in vascular and LECs [134, 135]. Inhibition of FGF also results in the decoupling of p120-catenin from VE-cadherin and further disrupts the subsequent adhesion and tight junctions of arterial and venous endothelial cells, which leads to the loss of endothelial cell-cell contacts [155].

Notably, one study also linked the vascular regulatory role of FGF2/FGFR1 to endocrine metabolism [18]. In FGFR1/3 double-knockout mice, significantly impaired retinal vascular growth and branching reduced anterior

migration of LECs, and reduced numbers of LECs in branches and the skin were observed [18]. Importantly, these effects were not seen with FGFR3 knockout alone, and FGFR1/3 double-knockout produced similar effects to those seen with FGFR1 knockout alone [18]. This suggests that FGFR1 signaling may be a more important component of vasculogenesis. This study further found that FGF2/FGFR1 signaling strongly induced expression of the enzyme hexokinase 2 (HK2) in glycolysis, which is strongly associated with MYC signaling [18]. Thus, FGF regulates the expression of HK2 through control of c-MYC expression, thereby promoting vascular endothelial cell proliferation and migration [18] (Fig. 3).

In summary, FGF/FGFR signaling can accelerate tumor metastasis through the formation of abnormal physical and chemical barriers (Fig. 3).

Immunological effects of FGFR-TKI

Involvement of FGFR-TKI in tumor microenvironment regulation

Immunogenic tumor death (ICD) is the death of tumor cells accompanied by the synthesis and release of large numbers of damage-associated molecular patterns (DAMPs), which can enhance immunogenicity and induce the recruitment and activation of antigen-presenting cells, ultimately activating innate and adaptive immune responses [156–158]. Certain targeted drugs can directly kill tumor cells, further enhancing immunogenicity by driving tumor antigen re-expression and T-cell infiltration [159, 160]. EGFR-TKI has been shown to induce ICD [161]. Recent experimental studies have also suggested that FGFR-TKIs stimulate immunogenic tumor death [23, 59]. In an FGFR-insensitive KRAS-mutant lung cancer GEMM, neither the use of FGFR inhibitors alone nor in combination with anti-PD-1 monoclonal antibodies controlled tumors to improve survival in mice [23]. Further experiments also failed to observe increased tumor T-cell infiltration, decreased Treg cells, and down-regulation of PD-L1 in tumor cells in KRAS-mutant GEMM [23]. In contrast, reduced tumor clonality and an increased T-cell fraction were detected in FGFR-mutant tumors treated with FGFR inhibitors compared to those subjected to anti-PD-1 treatment therapy [23]. These results indirectly suggest that treatment with FGFR inhibitors induces tumor cell death, thus further stimulating ICD and promoting immune activation. However, this still needs to be corroborated by in-depth and direct experiments.

FGFR-TKI induces normalization of the tumor vascular system, which is a prerequisite for the extravasation of immune cells and T-lymphocyte infiltration [144, 145, 162]. Anti-angiogenic therapy including anti-FGF signaling has been well-documented in numerous studies to enhance the efficacy of immunotherapy [163–166].

Anti-VEGFR and anti-FGFR treatment significantly reduce tumor microvessel density and perfusion [22, 167]. Additionally, anti-VEGFR treatment reduces IFP, enhances osmotic pressure gradients and boosts perivascular cell coverage, promoting normalization of the vascular wall [168]. Inhibition of FGF/FGFR signaling disrupts endothelial cell adhesion and tight junctions, leading to vascular system breakdown [145], causing tumor cell death and promoting immune cell infiltration. In addition, immune cell activity is regulated by microenvironmental hypoxia and low pH, and vascular normalization helps to reverse this effect [96, 151].

FGFR-TKI has been reported to be involved in regulating T-cell activation, enhancing T-cell infiltration, and decreasing PD-1/PD-L1 expression in a variety of tumors, including lung, breast, and liver cancers. In vitro trials in both lung and breast cancers indicated that FGFR-TKI enhances infiltration of CD4^{+} helper T-cells and CD8^{+} effector T-cells and inhibits the generation of Treg cells and end-depleted T-cells [23, 114, 115]. Importantly, erdafitinib (an FGFR inhibitor) does not affect the expression of single depletion marker-positive CD4^{+} and CD8^{+} T-cells in lung cancer. Targeting FGFR also reduces IFN-γ-induced PD-L1 expression [23]. In a mouse model of liver cancer, lenvatinib (a dual inhibitor of VEGFR and FGFR) reduced the expression of PD-1 on T cells, and PD-L1 on tumor and umbilical vascular endothelial cells. Lenvatinib also promotes the secretion of IFN-γ and GZMB by CD8^{+} T-cells, which contributes to effective immune activation [22, 24, 62]. Notably, after lenvatinib treatment of HCC cells, knockdown of the *FGFR4* gene, and FGF19 stimulation, the mRNA levels of *FGFR* but not *PD-L1* were affected [24]. This suggests that FGFR signaling does not affect PD-L1 expression at the gene level. Further experiments delved deeper and indicated that lenvatinib targeting of FGFR4 in liver malignancies leads to β-phosphorylation of GSK3Ser9, which contributes to the ubiquitination and degradation of PD-L1 in HCC cells [24]. However, in a mouse bladder cancer model with *FGFR3*-activating mutations, inhibition of FGFR rescinded the ubiquitination and degradation of PD-L1 by NEDD4 and significantly reduced the ratio of Ki67, TNF-α, GZMB and perforin positivity released from activated CD8^{+} T-cells, which severely inhibits the tumor-killing effect of CD8^{+} T-cells [25]. Meanwhile, CD8^{+} T-cell depletion markers, including TIM-3, LAG-3 and PD-1, were not regulated by Erdafitinib targeting [25]. These contradicting results suggest tumor heterogeneity in terms of FGFR signaling and modulation by more intrinsic molecules.

Lenvatinib rescues IFN-γ-induced T-cell sensitivity, which helps reduce the development of acquired immune resistance [24]. Nevertheless, how such effects are produced, possibly related to MHC expression, require more

comprehensive studies. FGFR-TKI possibly promotes MHC expression in tumor cells, which also affects T-cell activation [59], and also modulates TAMs programming, reduces MDSCs mobilization, and inhibits Treg cell generation, which can further prevent the immune escape of tumors [113, 114]. In contrast to acting on chemokine-mediated recruitment of TAMs and survival of MDSCs, lenvatinib blocks Treg differentiation rather than acting on chemokine-induced cell recruitment, and this effect is associated with IL-2-mediated phosphorylation of STAT5 [24].

FGFR-TKI and cancer-immune cycle theory
The tumor immune cycle theory states that the whole process of anti-cancer immune responses consists of seven steps: production and release of tumor neoantigens, capture of antigen-presenting cells, activation of effector T-cells, transport by the vascular system, tumor bed infiltration, MHC-mediated recognition of homologous peptides, and killing of tumor cells [16, 169]. Dead tumor cells again release additional tumor-associated antigens, once again promoting circulating reactivity [16]. Furthermore, the anti-tumor effects of T-cells are influenced by a combination of intrinsic tumor properties (epigenetic alterations) and extrinsic factors (e.g., TME) [13, 170]. Combined with the theory of immune circulation, the onset of T-cell antitumor action is not a single process.

We hypothesized that FGFR-TKI could act as an adjuvant to target T-cell activation in certain tumors in a cancer immune cycle-dependent manner (Fig. 4). First, FGFR-TKI directly causes epigenetic alterations in T-cells, promotes T-cell lineage diversification, reduces T-cell PD-1 expression, intrinsically restores T-cell antitumor activity and prevents active T-cell death. Second, FGFR-TKI also promotes IFN-γ and GZMB secretion and inhibits PPARG signaling, which contributes to T-cell activation and infiltration. In addition, FGFR-TKI relieves the immunosuppressive effect on T-cell activation by correcting incorrect immunosuppressive cells in the TME. FGFR-TKI remodels the tumor immune microenvironment by reducing the infiltration and survival of Treg cells and MDSCs and reversing the M2-type polarization of TAMs, which partially relieves the drug resistance response to ICB treatment via an extrinsic mechanism. In addition to this, FGFR-TKI interferes with the infiltrative migration of immune cells and promotes tumor bed infiltration of T-cells. FGFR-TKI can promote the normalization of abnormal blood vessels in tumors and exert anti-tumor effects while reducing the shunting of T-lymphocytes and drugs. They can derepress the inhibitory effect of FGFR on chemokine expression and drive T-cell homing and tumor bed infiltration. Finally, FGFR-TKI can also directly target tumor cells, resulting in increased TME tumorigenic antigen exposure, which further enhances immune responses. This tumorigenic death allows amplification of the tumor signal, contributing to activation of the immune system in vivo and promoting T-cell infiltration.

Overall, FGFR-TKI acts at various steps of the cancer-immune cycle, further assisting in the activation of T-cells.

Combination of FGFR-TKI and immune checkpoint therapy
Immune checkpoint therapy and oncogenic mutations
Immune checkpoints play an important role in promoting immune escape, such as CTLA-4 that blocks co-stimulatory signals thereby attenuating and terminating T-cell responses, as well as mediating the generation of immune escape [171]. By blocking immune checkpoints, ICBs can reactivate T-cell function and kill cancer cells by
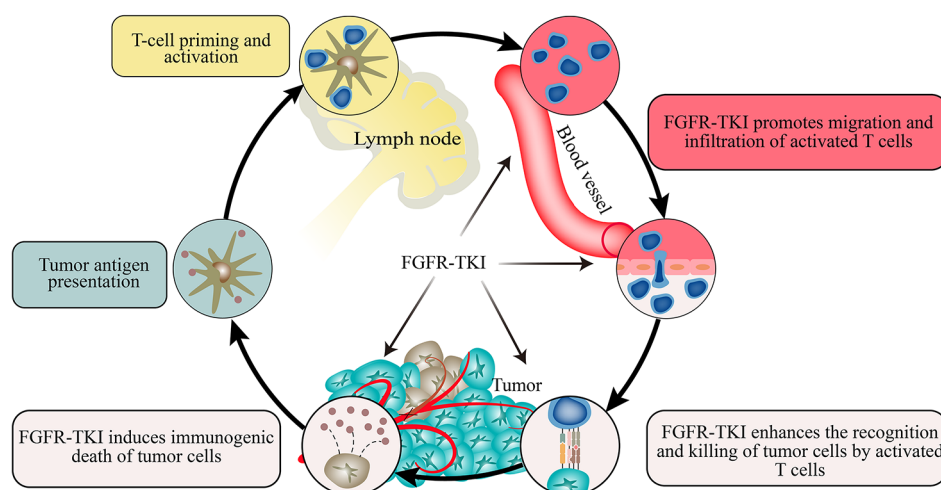

Fig. 4 Targeting FGF/FGFR signaling to regulate the cancer-immunity cycle in multiple steps

restoring autoimmune function [10, 11]. ICBs can reactivate T-cell function by blocking the immune checkpoint, relying on the restoration of autoimmune function to kill cancer cells. In many preclinical studies and clinical trials, ICBs, including CTLA-4 and PD-1/PD-L1 inhibitors, have achieved impressive results [171].

Although the clinical use of ICB has significantly improved the prognosis of patients with certain advanced tumors, the low positive rate of immunotherapy and the development of drug resistance are clinical problems that remain unresolved [144, 172, 173]. The anti-tumor immune response is regulated by tumor cell mutations, epigenetic alterations, and environmental factors [85]. Recent studies have pointed out that the components in TME doubly influence the efficacy of ICB [174]. In addition, the TME plays a more important role than immune checkpoints in immune escape and surveillance of tumors [151, 175, 176]. Experiments have also indicated that certain site-specific mutations may lead to innate immune resistance by acting on the TME and are associated with ICB treatment resistance. For example, patients with tumors carrying *EGFR* or *ALK* mutations have reduced levels of tumor-infiltrating lymphocytes, elevated PD-L1 expression, and benefit poorly from ICB therapy [14, 177–181]. Granulocyte-macrophage colony-stimulating factor produced by KRAS^{G12D} mutant pancreatic cancer also leads to suppression of CD8$^+$ T-cells and depletion and recruitment of MDSCs, thereby reducing the efficacy of immunotherapy [182]. FGFR is also involved in the formation of TME and seems to be targeted as a potential immune resistance-related molecular site.

Role of FGFR dysregulation in determining tumor response to PD-1/PD-L1 inhibitors

As mentioned previously, oncogenic *FGFR* mutations are closely associated with a non-inflammatory environment in certain malignancies, which may lead to poor responses to ICB treatment [9]. It has been demonstrated that overexpression of FGFR4 impairs the immunotherapeutic effect in gastric malignancies [54]. Consistently, a mathematical model of bladder cancer has shown that FGFR WT tumors are more susceptible to anti-PD-L1 therapy than *FGFR*-mutated tumors [183]. An analysis of melanoma patients treated with immunotherapy revealed relatively higher *FGFR1* mRNA expression in pretreatment tumors in non-responders compared to responders [111]. Furthermore, compared with low FGFR-expressing patients, high FGFR1-expressing patients receiving anti-PD-1 therapy had shorter overall survival(OS) and high FGFR3-expressing patients had shorter progression-free survival (PFS) [111]. Meanwhile, the results of anti-PD-L1 therapy in patients with advanced urothelial carcinoma showed that the median OS was lower in

FGFR-positive patients than in FGFR-negative patients (3.1 months vs. 6.1 months; hazard ratio [HR], 1.33; 95% confidence interval[CI], 0.78–2.26, P=0.30) [184, 185]. Patients with FGFR-positive urothelial carcinoma also had a lower response rate to PD-(L)1 therapy compared to FGFR-negative patients [186]. In addition, sequencing of samples from patients with hepatocellular carcinoma treated with immunotherapy combined with anti-angiogenic therapy revealed that FGF3/4/19 amplification may also lead to a high rate of disease progression [187].

In fact, a proportion of patients experience rapid cancer progression during immunotherapy, namely hyperprogressive disease (HPD) [188]. Patients with FGF3, FGF4 and FGF19 amplification tumors were reportedly more prone to HPD after immunotherapy [189]. A recent study has elucidated the molecular basis of HPD in ICI patients and indicated the key role of FGF-2 [190]. It unexpectedly found that patients with complete response and HPD exhibited similar levels of IFN-γ and Interferon Regulatory Factor 1(IRF1), as well as similar T-cell infiltration during immunotherapy, suggesting that patients with HPD are not exclusively associated with immune exclusion [190]. IFN-γ is known to play a dual role in antitumor immunity and immune escape [58, 191, 192]. The data also indicate that ICI can promote tumor growth in a CD8$^+$ T-cell-dependent manner [190]. Thus, ICI may contribute to HPD by activating oncogenic pathways through IFN-γ signaling from T-cells [190]. Further experiments indicated that IFN-γ activated β-catenin signaling in HPD tumor cells as a result of it reducing NAD$^+$ levels to enhance β-catenin acetylation [190]. Moreover, IFN-γ phosphorylates M2 pyruvate kinase(PKM2) to an inactive form [190]. PKM2 activation blocks IFN-γ-mediated β-catenin activation and subsequent HPD [190]. Thus, IFN-γ targets PKM2 to diminish sirtuin-mediated β-catenin deacetylation via NAD$^+$ reduction, causing β-catenin acetylation and activation [190]. Subsequent experiments indicated that FGF2 signaling contributes to ICI-triggered HPD and the expression of IFN-γ/FGF-2/β-catenin was consistent [190]. In conclusion, mechanistically, IFN-γ secreted by T-cells promotes HPD by acting on FGF-2-PKM2-β-catenin signal transduction in tumor cells [190].

Paradoxically, murine models of gastric cancer point to an improved immunotherapeutic effect of FGFR1 expression [54]. Analysis of clinical data noted that melanoma patients with FGFR mutations treated with ICI had better survival than those without mutations (median OS: 60.00 months vs. 31.00 months; HR: 0.58, 95% CI: 0.42–0.80; *P*=0.0051) [193]. Meanwhile, a retrospective analysis noted that patients with non-small cell lung cancer carrying FGFR4 alterations had better objective remission rates (ORR) (50.0% vs. 19.4%; *P*=0.057) and longer median PFS to immunotherapy (13.17 vs. 3.17

months; HR 0.37; 95% CI 0.14–1; *P*=0.04) [194]. However, in urothelial carcinoma, some evidence indicate that the remission and survival rates after ICB monotherapy are independent of whether *FGFR* is mutated or not [20, 66, 195–197]. Real-world retrospective studies evaluating the effect of ICB therapy in patients with mutated *FGFR3* and WT *FGFR3* tumors observed no significant difference in OS or PFS between the two [66]. Analysis of two phase 2 clinical trials, Checkmate 275 and IMVigor 210, revealed no statistically significant differences in ICB treatment response rates or OS in patients with or without *FGFR3* mutations [20]. This may be due to the fact that *FGFR* mutations reduce mesenchymal-mediated immunosuppression, which counteracts the immunosuppression caused by low levels of T-cell infiltration in *FGFR*-mutated tumors [20, 198].

In conclusion, multiple outcomes exist for FGFR dysregulation on immune monotherapy. We summarized the different immunotherapy outcomes caused by FGF/FGFR signaling in Table 2. At present, there is a lack of sufficient evidence to indicate that FGFR signaling can be used as a specific marker for the effectiveness of ICB therapy.

Effectiveness of FGFR inhibitors in combination with ICB therapy

Despite controversial findings surrounding ICB monotherapy in *FGFR*-mutated tumors, most preclinical trial results indicate that FGFR-TKI combined with ICB therapy can effectively enhance the antitumor effect in *FGFR*-mutated tumors compared with any monotherapy

[22, 23, 55, 144]. Evidence suggests that inadequate T-cell activation and inappropriate TME will impede the normal tumor-killing function of T-cells and thus diminish ICB efficacy [170]. Successful antitumor immune responses accompanied by immune checkpoint blockade require reactivation and clonal proliferation of antigen-experienced T-cells in the TME [170, 173, 199]. FGFR-TKI may assist ICB treatment through tumor immune circulation compared with anti-PD-1 treatment alone and CD8+ T-cells secrete more IFN-γ and GZMB after combination treatment with lenvatinib, which induces a more intense anti-tumor response [24, 62]. Lenvatinib co-treatment with anti-PD-1 therapy also leads to long-term immune memory formation while synergistically regulating the TME and tumor vascular normalization and enhancing the cytotoxic effects of T-cells, promoting therapeutic efficacy in HCC [22]. In a mouse model of lung cancer, FGFR-TKI enhanced the antitumor effects of PD-1/PD-L1 inhibitors by increasing T-cell infiltration and inducing ICD [23]. Analysis of multiple mouse models of bladder cancer showed that combination treatment with erdafitinib and anti-PD-1 antibodies increased the proportion and activation of CD8+ T-cells [25]. Moreover, the combination treatment group achieved the best results in both prolonging survival and inhibiting tumor growth compared to the control group [25].

Given the remarkable results achieved in preclinical studies of the combination of FGFR-TKI and ICI, relevant clinical trials are in full swing. In Table 3, we summarize the clinical trials of ICB in combination with FGFR-TKI, the majority of which are still in phase 1/2

Table 2 Relationship between FGF/FGFR dysregulation and immunotherapy

	Tumor	Data sources	Mutation information	Results of immune monotherapy	Refs
FGFR dysregulation reduces immuno-therapy efficacy	Locally advanced and unresectable or metastatic UC	NCT02365597	FGFR Mutations / Fusions	1 of 22 patients (5%) responded to previous immunotherapy	[9]
	Melanoma	GSE78220	FGFR1/FGFR3 +	High FGFR1+pts have Shorter OS; FGFR3+pts have poorer PFS	[111, 204]
	Advanced UC	Real world	FGFR+	OS: FGFR+/FGFR- (3.1 mo vs. 6.1 mo, HR 1.33, 95% CI 0.78–2.26, p=0.30)	[184]
	Advanced UC	NCT03390504	FGFR+	FGFR+pts have shorter OS and lower ORR and DCR	[186]
	NSCLC, Esophageal carcinoma etc.	Real world	FGF3/4/19 amplification	Tumor hyperprogression	[189]
FGFR dysregulation enhances immuno-therapy efficacy	Melanoma	Real world	FGFR Mutations	FGFR+pts have better mOS and higher ORR	[193]
	Nonsmall cell lung cancer	Real world	FGFR4-altered	FGFR4-altered pts have better ORR and longer mPFS	[194]
FGFR dysregulation not associated with immunotherapy efficacy	Metastatic Advanced UC	IMvigor 210+Check-Mate 275	FGFR3 Mutations	There was no statistically significant difference in response rate or OS	[20]
	Muscle-invasive Urothelial Bladder Carcinoma	NCT02736266.	FGFR3-altered	No correlation was found between FGFR3 activity or mutations/fusions and CR	[195]
	UC	Real Worldv	FGFR3-altered	ORR:FGFR3-altered/FGFR-wild(12% vs. 19%, p=0.73)	[66]

UC, urothelial carcinoma; +, positive; -, negative; pts, patients; OS, overall survival; mOS, median overall survival; PFS, progression-free survival; mPFS, median progression-free survival; mo, month; HR, hazard ratio; CI, confidence interval; ORR, objective response rate; DCR, disease control rate; CR, complete response

Table 3 Clinical trials of FGFR-TKI combination immunotherapy

NCT Number	Phases	Status	Tumor	Intervention1	Intervention 2	Intervention 3	Intervention 4	Treatment line	Gene state
NCT05614739	Phase 1	Recruiting	Urinary Bladder Neoplasms Neoplasm Metastasis Ureteral Neoplasms	LOXO-435	LOXO-435 +Pembrolizumab			After standard therapies	FGFR3-altered
NCT04601857	Phase 2	Recruiting	Advanced and Metastatic Urothelial Cancer	Futibatinib +Pembrolizumab				First-line	FGFR3 Mutation; FGFR1-4 Fusion/Rearrangement
NCT02401542	Phase 1/2	Terminated	Locally Advanced or Metastatic Urothelial Cell Carcinoma Urinary Bladder Disease Urological Diseases	Vofatamab +Docetaxel	Docetaxel +Placebo	Vofatamab		Second or subsequent	FGFR3 Mutant/Fusion
NCT05267470	Phase 1	Recruiting	Squamous-Cell Non-Small-Cell Lung Cancer	Bemarituzumab +Docetaxel	Bemarituzumab	Bemarituzumab +Pembrolizumab +Carboplatin +Paclitaxel		Intervention 1: Second or subsequent Intervention2: Third or subsequent Intervention3: First or subsequent	FGFR2b Overexpression
NCT05564416	Phase 2	Recruiting	Localized Bladder Cancer	Erdafitinib	Erdafitinib +Atezolizumab			Neoadjuvant	FGFR2/3 Alterations
NCT04604132	Phase 1/2	Completed	Gastric Adenocarcinoma	Derazantinib	Derazantinib +Paclitaxel +Ramucirumab	Derazantinib +Atezolizumab	Paclitaxel +Ramucirumab	Second or subsequent	FGFR2 Fusions/Rearrangements/ Amplifications; FGFR1-3 Mutations/Short variants
NCT05174650	Phase 2	Recruiting	Intrahepatic Cholangiocarcinoma	Atezolizumab +Derazantinib				First or Second line	FGFR2 Fusions/Rearrangements
NCT05510427	Phase 1	Not yet recruiting	Cholangiocarcinoma Liver Cancer	Infigratinib +Atezolizumab +Bevacizumab				Second or subsequent	FGFR2 Fusion/Amplification
NCT04045613	Phase 1/2	Completed	Urothelial Carcinoma	Derazantinib	Derazantinib +Atezolizumab	Derazantinib +/-Atezolizumab		Intervention 1: Second or subsequent Intervention2: First-line Intervention3: Second-line	FGFR1-3 Mutations/Short variants and Rearrangements/fusions
NCT05004974	Phase 2	Not yet recruiting	Advanced Non Small Cell Lung Cancer	Sintilimab +Pemigatinib				First-line	FGFR Mutation

Table 3 (continued)

NCT Number	Phases	Status	Tumor	Intervention1	Intervention 2	Intervention 3	Intervention 4	Treatment line	Gene state
NCT03473743	Phase 1/2	Active, not recruiting	Urothelial Carcinoma	Erdafitinib +Cetrelimab	Erdafitinib +Cetrelimab +Cisplatin/ Carboplatin	Erdafitinib		Intervention 1: Any line Intervention2/3: First-line	FGFR Alterations
NCT04828486	Phase 2	Recruiting	Advanced Hepato-cellular Carcinoma	Futibatinib +Pembrolizumab				Second-line	FGF-19 Positive
NCT03473756	Phase 1b/2	Active, not recruiting	Locally Advanced or Metastatic Urothelial Carcinoma	Rogaratinib+Atezolizumab				First-line	FGFR1/3 mRNA expression
NCT02325739	Phase 1/2	Completed	Solid Malignancies	FGF401	FGF401 +PDR001			Intervention 1: After standard therapies Intervention2: Third or subsequent	
NCT02925533	Phase 1	Terminated	Bladder Cancer	Vofatamab +Pembrolizumab				Second or subsequent	
NCT03123055	Phase 1/2	Terminated	Locally Advanced or Metastatic Urothelial Cell Carcinoma	Vofatamab	Vofatamab +Pembrolizumab			First-line	
NCT04003610	Phase 2	Terminated	Metastatic Urothelial Carcinoma Unresectable Urothelial Carcinoma	Pemigatinib +Pembrolizumab	Pembrolizumab	Gemcitabine +Carboplatin		First-line	
NCT04699643	Phase 1/2	Recruiting	Advanced Solid Tumors	EVER4010001 +Pembrolizumab				After standard therapies	
NCT05111626	Phase 3	Recruiting	Gastric Cancer Gastroesophageal Junction Adenocarcinoma	Bemarituzumab +Nivolumab +mFOLFOX6	Nivolumab +mFOLFOX6 +Placebo			First-line	
NCT05173142	Phase 1/2	Recruiting	Solid Tumor	HMPL-453 monotherapy	HMPL-453 + chemo-therapy /anti-PD-1 mAb			After standard therapies	
NCT05253053	Phase 1/2	Recruiting	Advanced Solid Tumor	TT-00420	TT-00420 +Atezolizumab	TT-00420 +nab-paclitaxel		After standard therapies	
NCT05322577	Phase 1	Recruiting	Gastric Cancer Gastroesophageal Junction Cancer	Bemarituzumab +CAPOX	Bemarituzumab +CAPOX +Nivolumab	Bemarituzumab +SOX +Nivolumab		First-line	
NCT05369286	Phase 1	Recruiting	Solid Tumor	MAX-40279-01 +Toripalimab					

of clinical trials. The only phase 3 trial (ClinicalTrials. gov number, NCT05111626) will also undergo a phase 1b safety evaluation prior before the trial. This phase 3 trial was designed to compare the efficacy of chemotherapy plus immunotherapy with that of FGFR-TKI plus immune plus chemotherapy in advanced gastric and gastroesophageal junction cancer with FGFR2b overexpression. Regardless of the results, it will have specific implications for guiding clinical treatment. In addition, an early phase clinical trial (ClinicalTrials.gov number, NCT02325739), for which results are available, evaluated the safety of the combination therapy ICB [52]. The results indicated the safety of biologically active doses of FGF401 (an FGFR4 inhibitor) alone or in combination with spartalizumab (an anti-PD-1 antibody) in the treatment of FGFR4/KLB-positive tumors. In addition, other studies have noted that the combination was generally well tolerated with acceptable side effects [200–202]. Notably, in a pivotal trial of erdafitinib(ClinicalTrials.gov number, NCT02365597), response rates were higher in patients with prior ICB treatment compared to the entire cohort (59% vs. 40%) [9]. Other clinical trials (ClinicalTrials.gov numbers, NCT04604132, NCT04045613, and NCT04003610) have been completed and await publication of the final results. In the real world, the efficacy of combination therapy has also been supported. In breast cancer patients, complete remission in 60% of the combination treatment group in breast cancer patients and there was a significant increase in CD4$^+$ and CD8$^+$ T-cell infiltration and a decrease in MDSCs, M1-type macrophages, and Treg cell infiltration were observed [111]. However, some clinical study data suggest that FGFR-ICB combination therapy does not achieve a significant benefit [144, 203]. This contradictory finding of FGFR-ICB therapy in combination with ICB in terms of efficacy has been suggested to be related to different tumor staging and certain biomarkers [144].

In conclusion, although certain preclinical studies suggest that the combination of FGFR-TKI and ICB treatment may promote antitumor effects, this finding has only been demonstrated in a small number of malignancies treated in clinical trials, and direct results have not been observed in other tumors. Related clinical trials are also advancing in a variety of malignancies, and more clinical results are expected to conclude the efficacy of the combination therapy.

Conclusion and perspective

Aberrant regulation of FGFR signaling assists in tumor generation and further promotes tumor cell proliferation and survival. In this review, we summarize the specific roles of the FGFR signaling pathway in the TME, noting that FGFR signaling shapes immunosuppressive TME by promoting non-T-cell immune infiltration, recruitment

and survival of MDSCs and TAMs, EMT, and angiogenesis, leading to immune escape and tumor metastasis. In contrast, FGFR-TKI therapy can reverse the immunosuppressive microenvironment by promoting IFN-γ and GZMB secretion, inhibiting PD-1/PD-L1 and MHC expression, suppressing chemokine production, and promoting normalization of the vascular system. We further discussed the relationship between *FGFR* alteration and ICB treatment, drawing contradictory conclusions. In addition, we highlight that FGFR-TKI may aid ICB therapy with the help of cancer immune circulation (e.g., assisting immune cell transport and infiltration, promoting T-cell initiation, reducing immunosuppressive cells, and elevating tumor antigenicity). Although the findings of certain clinical trials do not seem to support the effectiveness of FGFR-TKI in combination therapy with ICB, further analysis of additional studies and data is required.

Of course, there are still some questions worth thinking about and exploring. First, the emergence of drug resistance during the treatment of oncology patients is an unavoidable topic. Analyzing the mechanism of FGFR-TKI resistance will bring benefits to clinical treatment. Previous studies have also pointed out that the coexpression of different FGFRs, the expression of Klothoβ, and the activation of bypass signaling are associated with FGFR-TKI resistance. In TME, stromal or tumor cells can induce the development of drug resistance by secreting soluble factors [204]. However, the state of the microenvironment in FGFR-TKI-resistant patients has not been clearly demonstrated, and the exploration of the correlation between the development of FGFR-TKI resistance and the microenvironment is also promising. For FGFR-TKI-resistant patients, whether the therapeutic effect after combination immunotherapy can be restored or improved is also a topic worth discussing. Currently, the mechanism of FGFR-TKI and immunotherapy combination in tumors has not been clearly explored and more relevant explorations should be performed, such as single-cell sequencing, Organoid-immune cell co-culture model, more relevant clinical trials, etc. Secondly, in our article and existing clinical trials, the combination of FGFR-TKI with ICI therapy is basically anti-PD-(L)1 therapy. There is no evidence to support the combination therapy of other immune checkpoints (e.g., anti-CTLA4, LAG3, etc.).

In the past decade, immunotherapy has made significant breakthroughs in improving the prognosis of cancer patients, and we believe that FGFR inhibitors have great potential in the treatment of tumors in the future. To expand and prolong the benefits of FGFR inhibitors for patients, we need a better understanding of primary and secondary resistance. The development of combination protocols and next-generation inhibitors that can delay or overcome drug resistance may improve the efficacy of

current FGFR-signaling pathway-based tumor treatment regimens.

Abbreviations

APCs	Antigen-presenting cells
BMDMs	Bone marrow-derived macrophage
CAFs	Cancer associated fibroblasts
CAMs	Cell adhesion molecules
CIITA	MHC Class II transactivator
CTL	Cytotoxic T-lymphocytes
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
DAMPs	Damage-associated molecular patterns
DC	Dendritic cells
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
FGF	Fibroblast growth factor
FGFBP	FGF binding protein
FGFR	Fibroblast growth factor receptor
FGFR-TKI	FGFR-tyrosine kinase inhibitors
FLRT3	Fibrillin leucine-rich transmembrane protein 3
FRS2	FGFR substrate 2
G-CSF	Decreases granulocyte colony-stimulating factor
GEMM	Genetically engineered mouse models
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCRs	G protein-coupled receptors
GZMB	Granzyme B
HCC	Hepatocellular carcinoma
HK2	Hexokinase 2
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma
HPSG	Heparan-sulfate proteoglycans
HS	Heparan sulfate
ICAM1	Intercellular cell adhesion molecule 1
ICC	Intrahepatic cholangiocarcinoma
ICD	Immunogenic tumor death
ICB	Immune checkpoint blockade
IFN-γ	Interferon-γ
IFP	Interstitial fluid pressure
L1CAM	L1 cell adhesion molecule
LECs	Lymphatic endothelial cells
MHC	Major histocompatibility complex
MKP3	MAPK phosphatase 3
MMP2	Matrix metalloproteinase 2
mTOR	Mammalian target of rapamycin
MDSCs	Myeloid-derived suppressor cells
NK	Natural killer
OS	Overall survival
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PLCγ	Phospholipase C
RSK2	Ribosomal protein S6 kinase 2
RTK	Receptor tyrosine kinase
SEF	Similar expression to FGF
SOSC1	Suppressor of cytokine signaling 1
STAT	Signal transducer and activator of transcription
TAM	Tumor-associated macrophage
TGF-β1	Transforming growth factor β1
Th	T helper
TILs	Tumor-infiltrating lymphocytes
TLR2	Toll-like receptor 2
TME	Tumor microenvironment
Treg	Regulatory T
VCAM1	Vascular cell adhesion molecule 1
WT	Wildtype

Availability of data and materials
Not applicable.

Declarations

Ethical approval
Not applicable.

Competing interests
The authors have no conflict of interest to disclose.

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