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REVIEW ARTICLE

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FGFs: crucial factors that regulate tumour initiation and progression

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Abstract

Fibroblast growth factors (FGFs) are crucial signalling molecules involved in normal cell growth, differentiation and proliferation. Over the past few decades, a large body of research has illustrated effects of individual FGFs on tumour initiation and progression. Tumour development is commonly accompanied with generation of new blood and lymph vessels, which support enhanced cell proliferation. Moreover, acquisition of tumour cells of the epithelial–mesenchymal transition (EMT) phenotype, enhances tumour cell migration and invasion potentials, crucial steps in tumour metastasis. This review summarizes recent findings concerning roles of FGFs in angiogenesis, lymphangiogenesis and EMT.

1 | INTRODUCTION

Fibroblast growth factors (FGFs) are a huge family of polypeptide cytokines displaying multiple functions. FGFs are involved in cell growth, angiogenesis, wound healing, tissue homoeostasis/regeneration and metabolism.[1,2] There are 23 FGF (FGF-1–23) ligands in mammals, which are capable of binding to fibroblast growth factor receptors (FGFRs). Intriguingly, only four human FGFRs were found: FGFR-1 to FGFR-4. The function of FGFRs is triggered by a serial of processes that contribute to multiple isoforms through alternative initiation, alternative splicing and C-terminal truncations.[3] Recently, FGFR-5 has also been found, but the function of this receptor still remains unclear.[4] FGF family exists receptor specificities. On one hand, a part of FGFs only binds to their specific FGFRs. For example, FGF-5 and FGF-7 could only be combined with FGFR-1 and FGFR-2, respectively.[5] FGF-8 would bind to FGFR-3 and FGFR-4 but not bind to FGFR-1 and FGFR-2.[6] By contrast, FGF-10 exists high affinity with FGFR-1/2 but not with FGFR-3/4.[7] On the other hand, there are also some FGFs that could bind with all types of FGFRs, such as FGF-1, FGF-2 and FGF-4.[8]

The mammalian FGF family is classified into five paracrine- or autocrine-acting subfamilies and one endocrine-acting subfamily according to the sequence homology and phylogenetic and structural analysis.[9] The paracrine–autocrine-acting FGF subfamilies comprise FGF-1 subfamily (FGF-1 and FGF-2), FGF-4 subfamily (FGF-4, FGF-5 and FGF-6), FGF-8 subfamily (FGF-8, FGF-17 and FGF-18), FGF-9 subfamily (FGF-9, FGF-16 and FGF-20) and FGF-7 subfamily (FGF-3, FGF-7, FGF-10 and FGF-22). The endocrine-acting FGFs include FGF-15 (mouse)/FGF-19 (human), FGF-21 and FGF-23 [10] (Fig. 1). Different FGF subfamilies modulate a variety of biological functions and associate with various diseases, such as impaired wound healing, metabolic/chronic disease and cancer.[10,11] For instance, some paracrine–autocrine-acting FGFs, such as FGF-1 subfamily, FGF-10 and FGF-18, are involved in tissue repair, and the endocrine-acting FGFs (FGF-15/-19, FGF-21 and FGF-23) regulate metabolism at postnatal stages.[12] FGF-15/-19 and FGF-21, respectively, govern bile acid metabolism in the liver and lipid metabolism in the white adipose tissue, and FGF-23 modulates vitamin D and phosphate homoeostasis.[13,14] FGF-2 is required for angiogenesis. Both FGF-10 and FGF-2 participate in epithelial–mesenchymal transition (EMT), which induces migration and invasion of tumour.[15]

Cells that secrete FGF ligands also produce heparansulphate. The modified domains of heparan sulphate by sulfation and epimerization are the principal binding sites for FGFs. It is worth noting that cofactors are required for the interaction of FGFs with their receptors. Cofactor of paracrine FGF ligands is generally heparan sulphate

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proteoglycans (HSPGs), while Klotho is the co-receptor of endocrine FGF ligands (Fig. 1). Binding of FGF/cofactor to FGFR results in receptor dimerization, receptor activation and finally phosphorylation of downstream molecules.

2 | FGF-MEDIATED INTRACELLULAR SIGNALLING PATHWAYS

Activation of FGFRs by tyrosine residue autophosphorylation transmits extracellular signals into multiple cytoplasmic signal transduction pathways, such as phospholipase Cγ (PLCγ),[16] phosphatidylinositol-3 kinase (PI3K)/AKT, RAS/mitogen-activated protein kinase (MAPK), as well as signal transducer and activator of transcription (STAT) and NFκB pathways (Fig. 2), which are involved in tumour cell proliferation and migration.[17]

2.1 | RAS–MAPK pathway

As a major substrate of FGFR kinase, FGFR substrate 2α (FRS2α) is constitutively associated with the receptor kinase and phospholipase Cγ1 (PLCγ1).[18,19] Activated FRS2α binds with adaptor protein growth factor receptor-bound 2 (GRB2),[20] and then son of sevenless (SOS) and adaptor protein GRB2-associated binding protein 1 (GAB1) are recruited by GRB2. Recruited SOS activates RAS GTPase, which stimulates the activation of the mitogen-activated protein kinase (MAPK) cascade.[20] As a critical signalling pathway in eukaryotic cells, RAS–MAPK enables specific phosphorylation of gene-regulatory proteins on serine and threonine residues, thereby affecting cell proliferation and differentiation by regulating gene expression patterns.[21] FGF–FGFR system could also activate AKT and MAPK pathways in a FRS2α-dependent manner.[22] It has been reported that FGF-1 stimulates the phosphorylation of p38 MAPK (MAPK14) as well as the c-jun N-terminal kinase (JNK)1/2 (MAPK8/9), which is implicated in the regulation of cell apoptosis and growth arrest.[23,24] FGF-2 has a close relationship with PKC and Ca^{2+}[25]. FGF-1-mediated Egr-1 induction is impaired by the inhibition of MEK-1/2.[26] FGF-16 enhances the proliferation of human ovarian adenocarcinoma cells SKOV-3 and OAW-42 through the activation of FGFR-mediated intracellular MAPK pathway.[27] FGF-7 and FGF-10 are also involved in the proliferation of ameloblastoma cells through the MAPK pathway.[28] Overall, these findings suggest that FGF-mediated intracellular signalling pathways may represent the common mechanisms regulating tumour cell proliferation.[29]

2.2 | PI3K–AKT pathway

FGFRs can activate substrate FRS2α, which combines with GRB1/2 and forms a ternary complex to activate class I phosphatidylinositol-3 kinase (PI3K) and AKT.[30] Activated AKT kinase suppresses pro-apoptotic effectors, such as the BCL-2 antagonist of cell death (BAD), forkhead box class O (FOXO) transcription factors and caspases, thereby promoting cell survival.[31,32] In addition, AKT regulates cell cycle, protein synthesis, cell proliferation and differentiation by activating mTOR. A number of studies have indicated the role of FGF-regulated PI3K–AKT signalling pathway in tumorigenesis.[33–35] FGFR-3 plays a causative role in urothelial cancer pathogenesis in PTEN-deficient mice.[36] Similarly, the translational activation of FGF-10 by PTEN

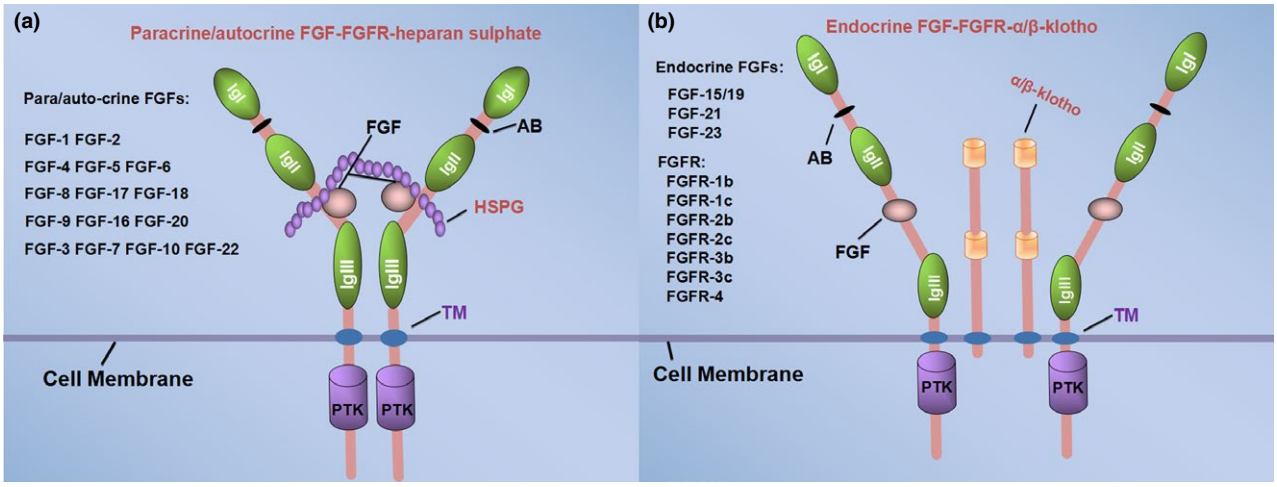

FIGURE 1 The different binding modes of paracrine and endocrine FGF ligands. The FGFs family are grouped into five paracrine–autocrine-acting subfamilies (a) and one endocrine-acting subfamily (b). FGF ligands is required for binding the cofactors to the receptors, and the cofactor of paracrine–autocrine FGF ligands is generally heparan sulphate proteoglycans (HSPGs), while Klotho is the co-receptor of endocrine FGF ligands. The structure of FGFRs comprises three extracellular immunoglobulin-like domains (Ig I to III), a transmembrane domain (TM) and an intracellular protein tyrosine kinase domain (PTK).[118] The binding sites of FGFs and FGFRs located between IgII and Ig III, and the acid box (AB) composed of eight consecutive acidic residues located between Igl and Ig II. The extracellular domain of FGFRs generates the IIIb and IIIc isoforms through the alternative splicing.[119–121] FGFR-1, FGFR-2 and FGFR-3 all have different isoforms except FGFR-4 (b). (These FGFRs in (b) are not endocrine FGF specific receptors, which binding with FGFs regardless of paracrine–autocrine or endocrine.) The binding of receptors with ligands leads to dimerization and activation of the tyrosine kinase domain

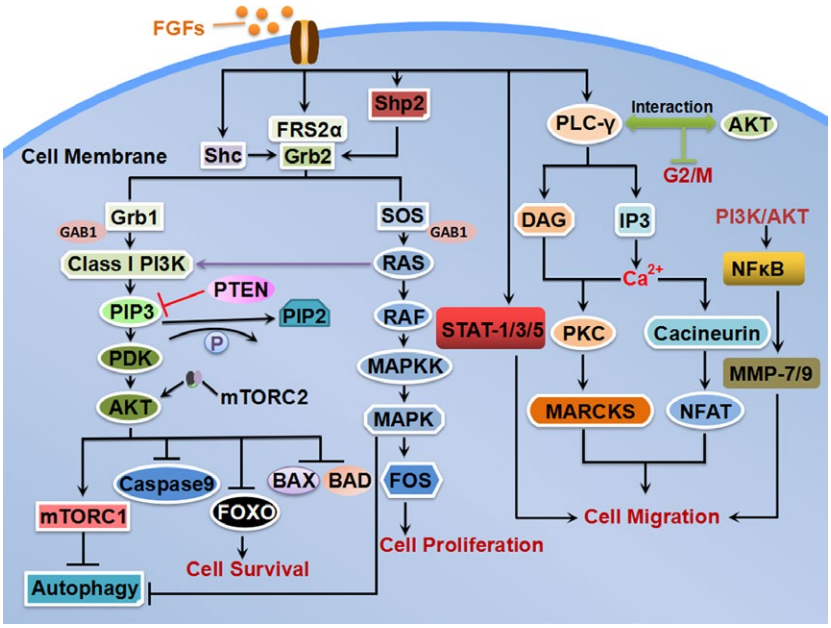

FIGURE 2 Intracellular signal transduction pathways of FGFs. Activation of FGFRs by tyrosine phosphorylation leads to signal transduction through multiple pathways, including phospholipase Cγ (PLCγ), PI3K–AKT pathway, RAS–MAPK pathway and STAT and NFκB pathway. Tumour suppressor Lipid phosphatase (PTEN) negatively regulates the PI3K signalling pathway,[122] which can prevent the signal transduction by promoting dephosphorylation PIP3 into PIP2. Class I PI3K can also be stimulated by RAS, which directly binds to the p110 catalytic subunit of PI3K. Activation of the mTORC2–AKT and ERK signalling pathways promotes cell survival and invasion. AKT promotes cells survival by inhibiting BCL-2 antagonist of cell death (BAD and BAX),forkhead box class O (FOXO) transcription factors and Caspase 9. The PI3K–Akt-regulated mTOR is crucial for the FGFs signalling axis to suppress autophagy. Recruited SOS activates RAS GTPase, which stimulates activation of the mitogen-activated protein kinase (MAPK) cascade and downstream FOS to induce cell proliferation. FGFR substrate 2α (FRS2α) is major substrates of FGFR kinases, which is constitutively associated with the receptor kinase and phospholipase Cγ1 (PLCγ1). Activated PLCγ1 catalyses the hydrolysis of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PtdIns ^{4,5}(P2) into diacylglycerol (DAG) and inositol-1,4,5,-trisphosphate (IP3). Ca^{2+} can activate Cacineurin to regulate transcription factor NFAT and promote cell migration. Whereas Ca^{2+} together with DAG stimulates cytosolic protein kinase C (PKC), which further activates its substrate myristoylatedalanine-rich C-kinase substrate (MARCKS) by phosphorylation. δ-PKC-mediated MARCKS phosphorylation is important for cancer cell migration and adhesion. In addition, PLCγ–AKT interaction regulates the M-phase of cell cycle. The activated FGFR stimulates STAT-1/3/5, which induces cell migration and invasion by regulating STAT pathway target gene expression. NFκB is the downstream molecule of FGFR–PI3K–AKT pathway, which modulates MMP-7/9 expression to increase cancer cell migration

deletion is reversed by genetic disruption of the mTORC1 complex, leading to the prevention of skin tumorigenesis. In another study,[37] it was demonstrated that FGF-2 could regulate G2/M phase of cell cycle by MEK, PI3K and PKC-activated FGFR–RAS–SRC pathway. Based on these results, it can be concluded that FGF–FGFR system is involved in the activation of PI3K pathway and plays critical roles in tumour development and progression.[38]

2.3 | PLCγ–PKC and Ca^{2+} channels

Activated PLCγ1 catalyses the hydrolysis of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PtdIns (4,5) P2) into diacylglycerol (DAG) and inositol-1,4,5,-trisphosphate (IP3).[18] As second messengers, DAG and IP3 regulate different downstream pathway, respectively. IP3 combines with IP3 receptors which locate at endoplasmic reticulum (ER), resulting in opening calcium channels. Then, Ca^{2+} is released from ER and translocates into the cytoplasm, which leads to the accumulation of free Ca^{2+} in cytoplasmic matrix. Ca^{2+} activates a variety of Ca^{2+}-dependent proteins, such as CaM (calmodulin) and Cacineurin. Cacineurin can regulate transcription factor nuclear factor of activated T cells (NFAT) to promote cell migration. Ca^{2+} together with DAG stimulates cytosolic protein kinase C(PKC), which further activates its substrate myristoylated alanine-rich C-kinase substrate (MARCKS). It has been found that δ-PKC-mediated MARCKS phosphorylation is essential for cancer cell migration and adhesion.[39] Activation of the FGFs stimulates PLCγ–PKC pathways, which might be involved in cell proliferation, cell survival and metastasis of tumour cells.[40] Browaeys-Poly et al.[41] found that the disruption of PLCγ–AKT interaction accelerated entry into M-phase of the mitotic cycle. This fact indicated that maintaining PLCγ–AKT interaction triggered by FGFRs might inhibit the cell cycle M-phase entry.[41] Furthermore, FGF-2 increases N-cadherin expression by regulating PLCγ–PKC and Src-kinase pathways, which promotes cell–cell adhesion.[42]

2.4 | STAT and NFκB pathway

The activated FGFRs also stimulate STAT (STAT-1, STAT-3 and STAT-5) and NFκB pathway, two signalling molecules that regulate

the expression of STAT pathway target gene and matrix metalloproteinase (MMP), respectively.[43] FGF–FGFR signalling phosphorylates and activates NFκB through PI3K–AKT pathway, which might induce cancer cell invasion by stimulating MMP. For example, FGF-1/3 is reported to promote tumour progression in colon cancer through ERK and MMP-7 and induce MMP-9 expression through the NFκB pathway.[44] FGF–FGFR pathway also regulates cell migration, invasion and growth arrest by activating STATs.[45]

2.5 | Tendentiousness of intracellular pathways activated by FGFs

Although these signalling pathways mentioned above are commonly activated by FGFs in most cell types, FGFs might have different tendentiousness in regulating these signalling pathways. RAS–MAPK pathway activated by FGFs appears to ubiquitously exist in all cell types, while the various activity of the other three pathways in response to FGFs depends on the cell types.[46,47] In a certain cell type, on one hand, a part of FGFs positively activate a signal transduction pathway, while other FGFs might not be involved in its activation. For instance, FGF-2 has a close relationship with PLCγ–PKC and Ca^{2+}, while FGF-1 has no effect on translocation of PLCγ in ovarian granulosa cells.[25] FGF-2 and FGF-4 rapidly increase AKT and ERK1/2 phosphorylation in bovine granulosa cells, whereas FGF-10 appears not able to trigger typical FGF signalling pathways, such as PI3K–AKT.[47] On the other hand, a FGF may have different correlation with various pathways in a certain cell type. For example, FGF-1-mediated Egr-1 induction in mouse hippocampal neuronal cell is impaired by inhibition of MEK-1/2, but not of PI3K.[26] Another investigation supports that FGF-1 regulates cardiogenesis primarily in a mouse embryonic stem cell through the signalling of PKC, but not MAPK.[48]

3 | ABERRANT EXPRESSION OF FGFS IN TUMOUR

It is a feature that FGFs and their receptors are overexpressed in different types of human cancers. For instance, compared with normal ovarian surface epithelium (OSE), FGF-18 is overexpressed in serous ovarian tumours and modulates ovarian tumour aggressiveness as well as microenvironment by increasing production of oncogenic cytokines and chemokines.[49] Overproduction of FGF-23 from the causative tumours is the main cause of tumour-induced rickets/osteomalacia (TIO), whereas FGF-23 production in normal bone is suppressed.[50] FGF-1 and FGF-6 are undetectable in normal prostate, but their increased expression is observed in prostate cancers.[51] FGF-2 significantly has a higher expression level in cancer tissue when compared with normal prostate.[51]

The ectopic overexpression of FGFs usually correlates with tumorigenesis as well as poor prognosis. For example, the aberrant activation of FGF-1 signalling is not only implicated in tumorigenesis but also associated with tumour invasion and metastasis.[52] FGF-2 in tumour cells is an independent negative prognostic factor. The co-expression of FGF-2/VEGFR-3 and FGFR-1/PDGF-B is strongly associated with poor survival in patients with non–small-cell lung carcinoma (NSCLC).[53] FGF-8b promotes cell cycle progression through the G1 restriction point and regulates key proteins that take part in chromosomal segregation during mitosis and cytokinesis of breast cancer cells.[54] Thus, it is essential to consider the regulation of FGFs in the development of tumour and cancer therapeutics.

4 | FGFS IN THE GENERATION OF NEW BLOOD VESSELS AND LYMPHANGIOGENESIS

Numerous studies show that angiogenesis is one of the early events in the malignant transformation. The balance between endogenous activators and inhibitors of angiogenesis delicately maintains a normal quiescent vasculature to sustain homoeostasis. Disturbance of this balance causes pathogenic angiogenesis. FGF and vascular endothelial growth factor (VEGF) are two angiogenic factors produced by tumours to stimulate angiogenesis, both of them have been reported to be correlated with tumour growth, progression and metastasis[55,56] (Fig. 3). VEGFs which belong to the platelet-derived growth factor super gene family play central roles in the modulation of angiogenesis and lymphangiogenesis.[57,58] In addition, FGFs are commonly reported to modulate angiogenesis through a variety of approaches. FGF-1 and FGF-2 are considered as major angiogenic factors among FGFs, which have been discovered currently.[59] FGF-1 induces angiogenesis in the chicken chorioallantoic membrane (CAM) through AKT–PKB signalling.[60] FGF-1 participating in vascular remodelling in endometriotic angiogenesis contributes to vascular wall formation and migration of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs).[61] FGF-2 could stimulate angiogenesis via a VEGFR-3-independent pathway.[50] FGF-2 priming enhances the angiogenic potential of implanted tissue-engineered constructs through the secretion of both hepatocyte growth factor (HGF) and VEGF.[62] In addition, interleukin-1β (IL-1β) induces the expression of FGF-2 in chondrocytes through ROS–AMPK–p38–NF-κB signalling pathway, which subsequently increases endothelial progenitor cell (EPC) angiogenesis.[63] FGFs also have been justified to play crucial roles in driving angiogenesis so that the formation of new blood vessels could assist in "feeding" cancer.[64] There is a growing body of evidence implicating FGF-1 and FGF-2 in active angiogenesis and rapid tumour growth. For instance, cardiac-specific overexpression of FGF-1 contributes to angiogenesis-independent cardioprotection.[65] Active FGF-2-NDY1/EZH2-miR-101-EZH2 axis is described to induce cell proliferation, migration and angiogenesis in bladder cancer.[66]

Lymphangiogenesis and the remodelling of existing lymphatics accomplish the generation of new lymphatic vessels.[67] Lymphangiogenesis, which is similar to tumour angiogenesis in the molecular control, is distinctly an early step in lymphatic metastasis.[67–69] In addition to the central role of VEGF-C–VEGFR-3 signalling in lymphangiogenesis,[70] FGF-2 may also be responsible for the growth

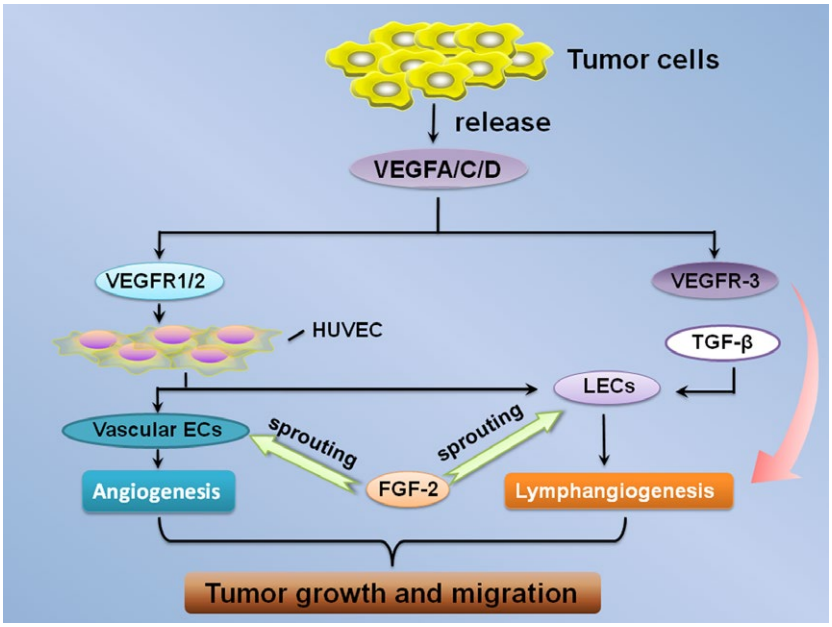

FIGURE 3 FGF-2 in tumour angiogenesis and lymphangiogenesis. VEGF-A/C/D and FGF-2 are commonly expressed in various tumour tissues and their expression levels have been correlated with tumour growth, progression, and metastasis. The receptors of VEGF-A, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1) could induce proliferation, migration and vessel formation of HUVECs.[57,66] Furthermore, the activation of VEGF-C/VEGFR-3 signalling results in lymphangiogenesis, and VEGFR-3-induced tip formation is a prerequisite for FGF-2-stimulated lymphangiogenesis. Moreover, significant new insights such as transforming growth factor β (TGF-β) regulate the growth and remodelling of lymphatic vessels. FGF-2 stimulates the sprouting of vascular ECs and LECs (lymphatic endothelial cells) which are isolated from human umbilical vein ECs (HUVECs). Vascular ECs and LECs independently induces angiogenesis and lymphangiogenesis

and remodelling of lymphatic vasculature.[70] The study by Cao et al.[71] showed that FGF-2 and VEGF-C collaboratively facilitate corneal angiogenesis and lymphangiogenesis and independently stimulate lymphatic vascular endothelial cell (LEC) proliferation and migration. It has been found that FGF-2 may simultaneously provoke lymphangiogenesis in different locations of the cornea through differential expression of VEGF ligands.[72] According to a report, siRNA-mediated FGFR-1 knockdown abolishes FGF-2-mediated LEC proliferation.[73]

Evidence shows that FGFs are involved in tumour development by directly and indirectly regulating tumour angiogenesis.[74] In addition, FGFs can also act in a paracrine manner on tumour lymphatics by facilitating the expression of prolymph angiogenic molecules.[75] In general, FGFs might be the mediator or interact with other signal molecules such as VEGFs in most of cancers to promote angiogenesis and lymphangiogenesis. Thus, targeting FGFs may be a potential strategy to impair tumour progression.

5 | FGFS IN TUMOUR INVASION AND METASTASIS

The development of cancer can be generally divided into two stages: invasion and metastasis of tumour cells.[76] FGFs could mediate PLCγ–PKC and Ca^{2+} pathway to promote cell invasion.[77] FGFs also play a role in tumour invasion and metastasis by interacting with other signalling molecules.[78] For example, FGF-2 participates in melanoma progression and cooperates with Thrombospondin-1 (TSP-1) in determining melanoma invasion and metastasis.[79] Abolished nuclear FGF-2 and FGFR-1 inhibit pancreatic stellate cells (PSCs) invasion.[80] FGF-8 promotes colorectal cancer growth and metastasis by activating YAP1.[81] FGF-10 has also been reported to promote migration and invasion in pancreatic cancer cells.[15] Thus, it can be concluded that FGFs could be the inducer of tumour invasion and metastasis.

Acquisition of the EMT phenotype of tumour cells not only enhances their invasion potentials but also promotes their capacity of metastasis.[82] It is suggested that FGFs might induce EMT through downstream signalling pathways including RAS–MAPK–AKT–PI3K–mTOR and PLCγ–PKC, thus enhancing tumour cell metastasis.[83] For instance, FGF-10 may induce EMT through RAS–MAPK and AKT–PI3K–mTOR pathways.[84] Additionally, TGF-β and FGF-2 may cooperate with each other and regulate EMT in various kinds of cells. TGF-β1 induces EMT through Smad pathway[85] and stimulates the isoform switching of FGF receptors, leading to the epithelial–myofibroblastic transition (EMyoT) by inactivating the MEK-ERK pathway, thus causing the cells to be sensitive to FGF-2.[86] FGF-2 disturbs EMyoT by reactivating the MEK-ERK pathway and subsequently enhances EMT through the formation of MEK-ERK-dependent complexes[87] (Fig. 4). TGF-β1 and FGF-2 can stimulate the EMT of HERS cells which is reversed by the MEK1/2 inhibitor U0126, suggesting that TGF-β1 and FGF-2 induce the EMT of HERS cells through a MAPK/ERK-dependent signalling pathway.[88] In addition, FGF-2 alone could induce EMT in colon cancer cells.[89] However, FGFs may facilitate EMT by increasing the expression of various mesenchymal factors and reducing the expression of epithelial markers.[20] FGF-16 has been reported to regulate the expression of MMP-2, MMP-9, SNAI1 and CDH1, which facilitates cell migration.[27] FGF-9 can be associated with EMT and metastasis by increasing the expression of N-cadherin and VEGF-A in prostate cancer cells.[90] All these investigations demonstrate that FGFs could induce EMT to promote tumour invasion and metastasis.

6 | TARGETING FGF–FGFR SYSTEM FOR CANCER THERAPY

Previous studies have reported that FGFs and FGFRs are significantly overexpressed in various kinds of cancers,[91–93] and it is demonstrated

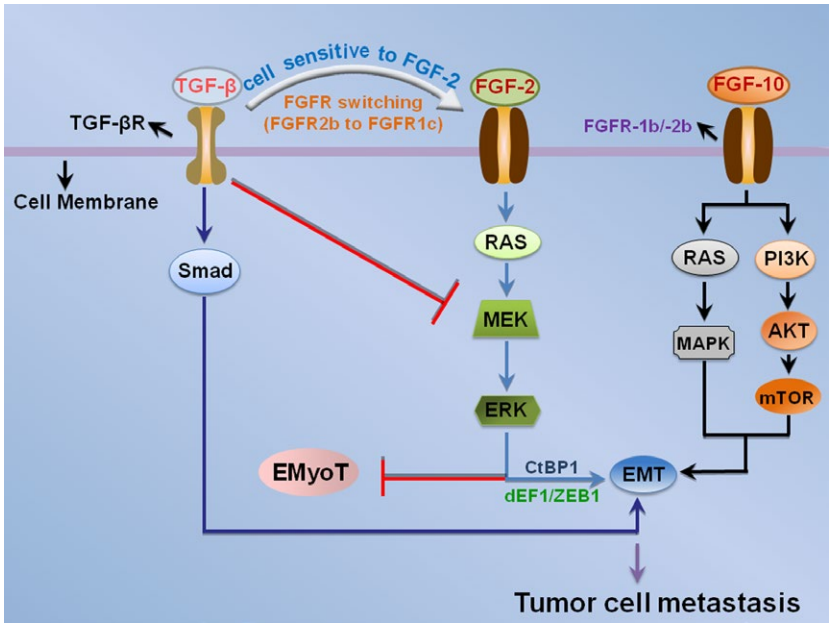

FIGURE 4 The interaction between FGF and TGF-β acts on EMT. TGF-β induces EMT and the isoform switching of FGF receptors (FGFR2b to FGFR1c), causing the cells to be sensitive to FGF-2. In this context, epithelial–myofibroblastic transition (EMyoT) is induced through the inactivation of MEK-ERK pathway. In the presence of FGF-2, FGF-2 perturbed EMyoT by reactivating MEK–ERK pathway and subsequently enhanced EMT through the formation of dEF1–ZEB1–CtBP1 complexes. FGF-10 may also induce EMT by activating RAS–MAPK and AKT–PI3K–mTOR pathways

that FGFs are involved in the regulation of cancer cell proliferation, survival and migration.[94] Inhibitors and antibodies directly targeting different FGF ligands have shown therapeutic promise in different tumours.[95,96] Recently, several studies *in vivo* and *in vitro* have suggested that blocking FGF pathways could reduce the proliferation of tumour cells and inhibit metastasis.[97] FGF-19 is significantly overexpressed in hepatocellular carcinoma (HCC), and the introduction of FGF-19 siRNA is able to reduce proliferation and increase apoptosis in HCC.[98] In addition, the neutralizing antibody of FGF-19 treatment significantly suppresses the growth of established colon cancer tumours *in vivo*.[99] According to Schulze's study,[100] RNAi-mediated FGF-binding protein (FGF-BP) knockdown is integrated in the inhibition of colon carcinoma cell proliferation and induction of apoptosis alterations in redox status. FGF-Trap distinctly abolishes FGF-2-stimulated activation of FGFs signalling and potently inhibits tumour growth and angiogenesis.[101]

Since mutations and amplifications of FGFRs are found in a range of cancers with some of the most striking clinical findings relating to their contribution to pathogenesis and progression of cancers,[102,103] FGFR-targeted agents are currently being investigated in clinical studies for the treatment of cancer.[104–106] For instance, cediranib, which is a multi-tyrosine kinase inhibitor targeting FGFR and is in phase II evaluation, has proved as a monotherapy for recurrent or persistent endometrial cancer well tolerated.[107] There are other inhibitors of FGFR, such as TKI258 and lucitanib. Phase I study shows that TKI258 is tolerable and has antitumour activity in renal cell carcinoma (RCC).[108] Lucitanib is a confirmed and promising drug of treating advanced solid tumours in phase I/IIa study.[109] In addition, the activity of AZD-4547, a novel and potent FGFR kinase inhibitor in CRC cells, is correlated with the FGFR-1/2 expression levels and inhibits CRC cell growth *in vitro*.[110] The new non-ATP competitive FGFR-1 inhibitors A114 and A117 reveal significant anti-tumour activity both *in vitro* and *in vivo* via targeting FGFR-1.[111] Although FGFR-targeted inhibitors efficiently suppress tumour, there are still challenges. For example, TKI-mediated durable clinical responses may be impacted by intrinsic tumour resistance.[112] Furthermore, the median duration response of nintedanib (a inhibitor of FGFR) is only 4 months, and its function might be resisted by tumour through up-regulating FGF signalling.[113]

A research shows that specific FGFR-4-targeted antibodies decreases the tumorigenic and invasive capabilities of colorectal cancer cells by reducing the expressions of Snail, Twist and TGF-β and increasing the expression of E-cadherin.[114] Ablation of FGFR-4 results in a net inhibitory effect on mammary tumour progression.[115] However, FGFR-4 deletion does not lead to an embryonic lethal phenotype, suggesting the possibility that its inhibition in cancer therapy might not cause grave adverse effects.[116,117] FGFR-4-mediated hormonal effects of several FGF ligands may also constitute a tissue-protective tumour suppressor activity in liver.[117] These results suggest that blocking FGF receptors might act different roles compared with FGF ligands in various carcinomas. Therefore, a systemic therapy that targets FGFs and FGFRs may be a potential strategy to inhibit tumour progression and metastatic spread.

7 | CONCLUSION

Previous studies have provided plenty of evidence to support the fact that FGFs linked with FGFRs can activate their downstream crucial signalling pathways, including phospholipase Cγ (PLCγ), PI3K–AKT pathway, RAS–MAPK pathway, and STAT and NFκB pathway. We have described the signal transduction mechanism of these four pathways clearly in this review. In fact, these signalling pathways mentioned above are classic pathways of a majority of FGFs. However, FGFs might have different tendentiousness in regulating these signalling pathways between various cell types. Close link exists between FGF–FGFR system and tumour progression. With further comprehension

of the molecular mechanisms of FGFs signalling and the development of more specific agents targeting FGFs and FGFRs, it is anticipated that an improved understanding of FGFs family and better anti-cancer therapies that modulate FGF–FGFR signalling will emerge.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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