

Review

FGF/FGFR signaling pathway involved resistance in various cancer types

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Abstract

Resistance becomes major clinical issue in cancer treatment, which strongly limits patients to benefit from oncotherapy. Growing evidences have been indicative of the critical role of fibroblast growth factor (FGF)/receptor (FGFR) signaling played in resistance to oncotherapy. In this review we discussed the underlying mechanisms of FGF/FGFR signaling mediated resistance to chemotherapy, radiotherapy and target therapy in various cancers. Meanwhile, we summarized the reported mechanism of FGF/FGFR inhibitors resistance in cancers.

Key words: FGF/FGFR, resistance, oncotherapy, FGF/FGFR inhibitors

Introduction

Fibroblast growth factor (FGF) family being part of the receptor tyrosine kinase (RTK) families are comprised of 18 ligands, exerting their functions through four highly conserved tyrosine kinase receptors (including FGFR1, FGFR2, FGFR3 or FGFR4) [1, 2]. FGF/FGFR signaling controlled multiple physiological processes, such as endocrine homeostasis, wound repair, and cellular behaviors (including proliferation, differentiation and survival), via activation of fibroblast growth factor receptor substrate2 (FRS2), mitogen activated protein kinase (MAPK)/extra-cellular signal-regulated kinase 1/2 (ERK1/2), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways, signal transducer and activator of transcription3 (STAT3), phospholipase C γ (PLC γ) and ribosomal protein S6 kinase 2 (RSK2) [1,2]. These characteristics make FGF/FGFR signaling

impressionable to be hijacked by oncocytes. The underlying mechanism driving FGF/FGFR signaling is very cancer special, and can be classified into FGFR amplification [3], FGFR mutation [4], abnormality of FGFR involved ligands [5] and nuclear translocation of FGF/FGFR [6]. Recently, increasing studies indicated the close connection of FGF/FGFR signaling with the resistance to oncotherapy in various cancer types. These studies make FGF/FGFR to be a highly potential therapy target in cancers, and drugs targeting FGF/FGFR have been a meaningful and hopeful field in anti-tumor treatment study. However, as a target therapy, scholars are also starting to pay attention to the resistance to FGF/FGFR inhibitors in cancers. In the paper, we reviewed the FGF/FGFR signaling pathway involved resistance in cancer treatment below.

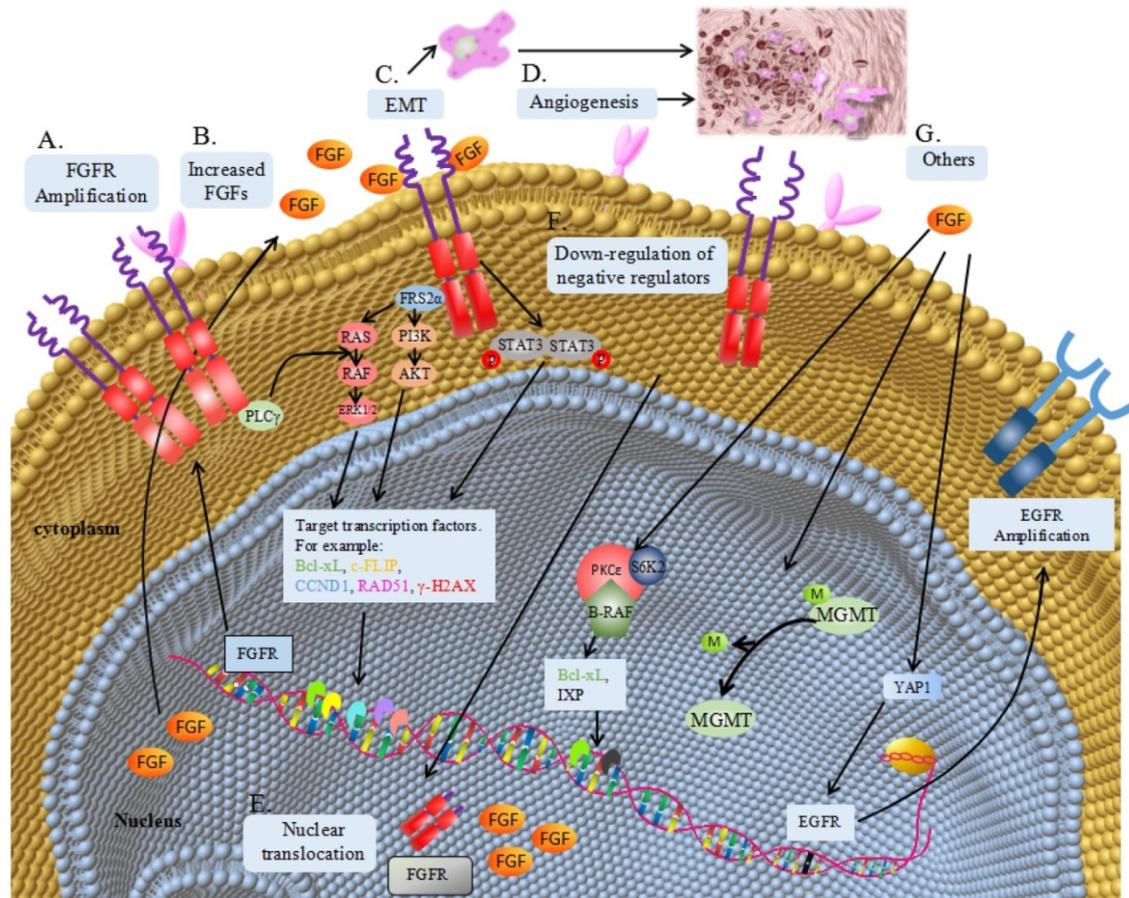


Figure 1. Mechanism of FGF/FGFR signaling pathway involved in resistance to oncotherapy. (A) Gene amplification translates into FGFR overexpression, causing receptor accumulation and continuously activation of the down-stream signaling pathways, including ligands-dependent and independent pathways. (B) Increased FGF from tumor cell or microenvironment can overstimulate FGFR and its down-stream signaling pathways. (C) FGF/FGFR signalling may contribute to epithelial–mesenchymal transition (EMT). (D) FGF/FGFR signalling can promote angiogenesis and further induce resistance to antiangiotherapy. (E) Nuclear translocation of FGF or FGFR can accelerate DNA repairor regulate gene transcription. (F) Downregulation of negative regulated proteins, such as SPRY, can maintain the activation of FGF/FGFR signalling. (G) Activation of other survival signalling. FGF can regulate the expression of Bcl-xL and IXP via a protein complex containing S6K2, PKCε and B-Raf. FGF can promote the demethylation of O⁶-methylguanine-DNA-methyltransferase (MGMT) promoter. FGF can upregulate the expression of EGFR via an intermediate protein YAP1.

FGF/FGFR signaling pathway mediated resistance to treatment in various cancers

The underlying mechanism of FGF/FGFR signaling pathway involved in resistance to oncotherapy can be generally divided into over-expression of ligands or receptors, epithelial-mesenchymal transformation (EMT), angiogenesis, nuclear translocation, downregulation of negative regulator and activation of other survival signaling (Table 1 and Figure 1).

Lung cancer

Lung cancer, including two subclasses, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), is the first leading cause of malignant tumor death around the world [7]. Epidermal growth factor receptor (EGFR) inhibitors, such as erlotinib, gefitinib and afatinib, achieved dramatic response in EGFR addicted NSCLC, while nearly all develop resistance finally [8]. EMT is one confirmed molecular mechanism of resistance to EGFR inhibitors in NSCLC [9]. It has been shown that

mesenchymal NSCLC cells have a distinct reduction in sensitivity to EGFR inhibitors [10]. These cells frequently exhibit aberrant expression of FGFR and related autocrine signaling, which can activate MAPK and PI3K pathways, further leading to the resistance to EGFR inhibitors [10]. In turn, aberrant FGF or FGFR expression also drive EMT in NSCLC and subsequently induce resistance to EGFR inhibitors [11]. Some papers revealed that EGFR inhibitors treatment can upregulate several FGFs/FGFRs, for instance, FGF2, FGF9, FGF13, FGFR1, FGFR2 and FGFR3 [12-15]. FGF/FGFR provide an autocrine receptor tyrosine kinase-driven bypass pathway and induce resistance via their conventional downstream cascades (ERK1/2, AKT and STAT3) in NSCLC, which are initially sensitive to EGFR inhibitors [12-15]. KRAS mutations occur in about 15-30% of NSCLC and often correlate a poor response to EGFR inhibitors [16,17]. Blockade of downstream factors of KRAS-driven pathways, such as MEK, becomes a preferable option for the therapy of this NSCLC

cohort. However, MEK inhibitor, trametinib, induces a compensation referring to FGFR1, leading to signaling rebound and adaptive drug resistance [18]. A combination of trametinib and FGFR inhibitors could be perceived as an effective strategy for treating KRAS mutant NSCLC [19]. Cyclin-dependent kinase 4 (CDK4) has been emerging as another target in KRAS mutant NSCLC. Eric Haines et al indicated that FGFR1 triggered MAPK-mTOR pathway and decreased the sensitivity of NSCLC to CDK4 inhibitor, Palbociclib [20].

SCLC, accounting for 20% of lung cancer, could develop rapidly to chemo-resistance, harbouring a poor overall survival [21]. FGF2 has been reported to be main culprit for this chemo-resistance [21,22]. FGF2 post-transcriptionally modulates inhibitor of apoptosis protein (IAP) levels, decreasing the releasing of second mitochondria-derived activator of caspases (Smac) (progress induced cell apoptosis in response to cell stress), then restraining etoposide-induced cell apoptosis in SCLC cells [21]. Another paper revealed the detailed molecule mechanism underlying how FGF2 upregulates the expression of anti-apoptotic proteins including IAP and Bcl-xL. FGF2 could induce the formation of a protein complex containing S6K2 (ribosomal protein S6 kinase 2), PKC ϵ (protein kinase C epsilon) and B-Raf, which further directly increases the expression of IAP and Bcl-xL [22].

Breast cancer

Estrogen receptor (ER) expresses in approximately 60% of breast cancer (BC). These ER positive BC patients initially respond well to antiestrogens like tamoxifen or Fulvestrant, while they gradually become resistant. Growth of FGF1 or FGF4 transfected ER positive BC cells is not inhibited by treatment of antiestrogen [23]. The autocrine activity in FGF transfected BC cells may bypass the requirement for ER activation in tumor growth [23]. Further study revealed that the antiestrogen resistance may be due to FGF1 induced activation of MAPK and PI3K pathway via FGFRs [24,25]. Nicholas Turner et al found that FGFR1 amplification could drive both ligands dependent and independent signaling pathway, which promoted CCND1 (cyclin D1) expression in ER positive BC, resulting in the resistance to antiestrogen [26]. Another paper demonstrated that FGF2 secreted from tumor microenvironment could also upregulate CCND1 expression and mediate resistance to antiestrogen [27]. Moreover, FGFR1 could also transfer to cell nuclear and regulate the transcription of ER dependent target genes [28]. Taken together, FGF/FGFR can take the place of ER and activate ER associated down-stream signaling in antiestrogen resistant BC cells, which may account for

the resistance to antiestrogen.

Anti-vascular endothelial growth factor (VEGF) therapy has been a promising therapeutic option for cancers, while it failed to improve survival in BC patients [29]. Data from mouse models indicated that diet-induced obesity weakens the effect of anti-VEGF therapy on BC [29]. Upregulation of IL-6 or FGF-2 in obesity may account for the resistance to anti-VEGF therapy [29]. Chemotherapy is also the treatment option for BC patients. It has been reported that FGF2 and FGFR4 were involved in the resistance to chemotherapy in BC [30]. Upregulated FGFR4 reduced apoptosis sensitivity to doxorubicin or cyclophosphamide via decreasing phospho-ERK1/2 levels and Bcl-xL expression in BC[30]. Min Xu et al, however, indicated that FGFR4 caused resistance to doxorubicin through increasing glucose metabolism in BC cells [31]. In Shenduo Li et al's paper, nuclear FGF2 promoted resistance to doxorubicin via increasing DNA-dependent protein kinase (DNA-PK) expression, which could accelerate DNA repair [32].

Table 1. Corresponding FGF/FGFR account for resistance to therapy in cancers

Cancer types	Therapeutic method	Involved FGF/FGFR
Lung cancer	Erlotinib	FGF13, FGFR1/2/3
	Gefitinib	FGF2/9, FGFR1/2/3
	Afatinib	FGFR1
	Trametinib	FGFR1
	Palbociclib	FGFR1
	Cisplatin	FGF2
Breast cancer	Tamoxifen	FGF1/2/4, FGFR1
	Fulvestrant	FGF1/2/4, FGFR1
	Pictilisib	FGF2
	Everolimus	FGF2
	Bevacizumab	FGF2
	Doxorubicin	FGF2, FGFR4
Colorectal cancer	Cyclophosphamide	FGFR4
	radiotherapy	FGFR4
	5-Fu	FGFR4
	Oxaliplatin	FGFR4
Gastrointestinal stromal tumor	5-Fu+radiotherapy	FGFR2
	Imatinib	FGF2, FGFR1/3
Squamous cell carcinoma	Radiotherapy	FGF2, FGFR3
	Bevacizumab	FGF2
	Paclitaxel	FGF2
	Lapatinib	FGF1/7/10
Osteosarcoma	Cisplatin	FGF2
Hepatocellular carcinoma	Gefitinib	FGF8
	Sorafenib	FGFR1
Pancreatic tumors	Antiangiogenic therapy	FGF2
Melanoma	Temozolomide	FGF2
	PLX51107	FGF2
Chronic lymphocytic leukemia	Fludarabine	FGF2
Myeloma	Dexamethasone	FGFR3
Urothelial cancer	Gemcitabine	FGFR3
	Adriamycin	FGFR3
Prostate cancer	Castration	FGF8

CDK4 inhibitor: Palbociclib; Antiestrogens: Tamoxifen, Fulvestrant; PI3K inhibitor: Pictilisib; mTOR inhibitor: Everolimus; BET inhibitor: PLX51107.

Colorectal cancer

Data from 172 rectal carcinoma specimens who underwent neoadjuvant concurrent chemoradiotherapy (CCRT) indicated that high-level expression of FGFR2 is positively associated with advanced stage tumor, poor treatment response and poor prognosis [33]. A systems biology method revealed new genes and pathways involving in drug resistance to oxaliplatin and 5-fluorouracil (5-FU) in colorectal cancer (CRC) and presented FGFR4 as a potential agent of chemo-resistance [34]. Synergistic interaction between FGFR4 silencing and 5-FU or oxaliplatin has been confirmed to have better anti-cancer activity in CRC cell lines [34]. The research pointed out that anomalous expression of FGFR4 increased the activation of pro-survival STAT3 transcription factor and expression of cellular FLICE-like inhibitory protein (c-FLIP, an anti-apoptotic protein), leading to chemo-resistance in CRC [34]. Overexpression of FGFR4 has also been reported in radio-resistant CRC [35]. In CRC cells, enforced expression of FGFR4 stabilizes recombination protein A (RAD51, an important component of DNA double strand fracture repair) levels [36], leading to increasing clearance of γ -H2AX foci (an indication for DNA injury) [37] and cell survival in the mismatch repair-proficient cells [35].

Gastrointestinal stromal tumor

Imatinib, selectively targeting KIT or PDGFRA, has observably improved prognosis in advanced gastrointestinal stromal tumors (GISTs) [38]. However, about half of GISTs cases treated with imatinib gradually develop acquired resistance in the first two years [39]. This event may attribute to secondary KIT mutations [39], while part patients become resistance to imatinib without KIT mutations. Aberrant FGF2 secretion has been detected in imatinib-resistant GISTs cell lines [40]. Addition of FGF2 to GISTs cells reverted KIT phosphorylation during imatinib therapy and reduced the anti-tumor activity of imatinib in GISTs, while RNAi-mediated silencing of FGFR3 could cancel out this phenomenon [40]. Further investigation indicated that FGFR3 crosstalk with KIT stimulated the MAPK pathway to facilitate resistance to imatinib [40]. Another study indicated that continuous activation of KIT in GISTs cells depressed FGFR1 signaling through ERK-dependent feedback mediated by Sprouty (SPRY) proteins [41], a negative regulator of FGFR [42]. Blockage of this feedback loop by imatinib enhanced FGFR1 activation and its down-stream signal pathway, resulting in the poor response of GISTs to imatinib [41]. Indeed, combined treatment with FGFR inhibitors and imatinib can achieve anti-tumor activity in imatinib resistant GISTs [43,44].

Squamous cell carcinoma

Increase of released FGF2 has been reported in the squamous cell carcinoma (SCC) cell lines after irradiation [45]. The increased FGF2 decreased the sensitivity of SCC cells to the subsequent irradiation [45]. Another paper indicated that significant upregulation of FGFR3 has been found in radio-resistant SCC cell lines [46]. FGF2 or FGFR3 inhibition could provide a potent radio-therapeutic strategy for SCC [46]. Data from a SCC xenograft model suggested that upregulation of FGF2 and FGFR3 has also been found in tumor cells with resistance to anti-VEGF therapy [47]. The paper demonstrated that bevacizumab-refractory tumor cells converged on ERK signaling to upregulate FGF2, which mediated aversion of anti-VEGF therapy in turn [47]. Shin Saito et al demonstrated that FGF/FGFR signaling also mediated the lapatinib resistance in esophageal SCC [48].

Osteosarcoma

Previous study on 352 osteosarcoma patients, who received neo-adjuvant chemotherapy, indicated that amplification of FGFR1 gene was found exclusively in the poor response group and represented approximately 18.5% of patients in the group [49]. Due to the comparatively low rate cases with FGFR1 amplification in the study, the essential connection between FGFR1 amplification and poor response to chemotherapy need to be further confirmed. Catarina R et al found that FGF2 promoted the resistance of osteosarcoma cells to cisplatin through a mechanism that involved PKC ϵ , B-RAF and S6K2 protein complexes, which could further control the expression of several anti-apoptotic proteins [50].

Hepatocellular carcinoma

FGF8 upregulated the expression of EGFR in hepatocellular carcinoma (HCC) via increasing the expression of yes-associated protein 1 (YAP1), which then facilitated the resistance to EGFR inhibitors [51]. Victoria Tovar et al uncovered that the FGF/FGFR signaling enriched, including PI3K cascade, in the HCC cells after long-time exposure to sorafenib [52]. Inhibition of FGF/FGFR signaling can also revert resistance in sorafenib-acquired resistant tumors [52,53].

Pancreatic tumors

Antiangiogenic therapy could trigger upregulation of other pro-angiogenic factors in pancreatic tumors. FGF/FGFR signaling made great contribution to escaping anti-angiogenic targeting of VEGF signaling in pancreatic islet tumors and pancreatic neuroendocrine tumors [54,55]. Combined inhibition of FGFR

and VEGFR revert the adaptive resistance to VEGFR targeted therapies in pancreatic tumors [54,55].

Melanoma

Bromodomain and extraterminal (BET) inhibitors could increase the expression of FGFR in uveal melanoma (UM) cells [56]. FGF2 can rescue the UM cells from growth inhibition by BET inhibitors via FGFR [56]. When liver metastasis occurred in UM, BET inhibitors would be ineffective *in vivo*, because hepatic stellate cells (HSCs) secreted FGF2 to promote the resistance to BET inhibitors [56]. Methylation of the O⁶-methylguanine-DNA-methyltransferase (MGMT) promoter decreased the expression of its associated protein O⁶-alkylguanine-DNA-alkyltransferase (AGT) [57]. FGF2 could induce the demethylation of MGMT promoter and further increase the expression of AGT, which then promote the resistance of melanoma to temozolomide [57].

Hematological malignancies

Overexpression of FGFR3 in myeloma confers resistance to dexamethasone, partly via upregulating of Bcl-xL [58]. However, FGFR3 did not alter sensitivity of myeloma to melphalan or doxorubicin [58]. Chronic lymphocytic leukemia (CLL) cells with high intracellular levels of FGF2 appeared to be more resistant to fludarabine treatment, while the underlying mechanism need to be further explored [59].

Urinary tumors

FGF/MAPK signaling detours a requirement for androgens and the androgen receptor in promoting growth of prostate cancer [60]. Cotargeting of FGF/MAPK signaling with capability of providing cell survival and proliferation signals could reverse castration resistance in prostate cancer [60]. In urothelial cancer, FGFR inhibitor ASP5878 can effectively reverse the acquisition of gemcitabine or adriamycin resistance [61].

Molecular mechanism of resistance to FGF/FGFR target therapy in cancers

The contribution of abnormal FGF/FGFR signaling pathway to oncogenesis has given rise to the advancement of a great number of therapies targeting the FGF/FGFR pathways. Though there has been no FGF/FGFR targeted therapies approved good clinical therapeutic effects in cancer treatment yet, the results from plenty of early-phase clinical trials have verified the momentous significance on targeting FGF/FGFR in the clinic. The problem of acquired resistance to targeted tyrosine kinase inhibitors gradually emerges in the clinic, and it may also restrict the clinical appli-

cation of FGF/FGFR inhibitors. Several researches have indicated this phenomenon of resistance to FGF/FGFR inhibitors in cancers and expounded the possible underlying mechanism (Figure 2).

Mutation at the gatekeeper residue of FGFR is the first important mechanism of resistance to FGF/FGFR inhibitors in kinds of cancer types (Table 2). The gatekeeper residue is located deep in the active site, which controls access of the FGFR to the hydrophobic pocket behind the ATP-binding pocket. FGFR1^{V561M} and FGFR1^{N546K} have been reported to be closely associated with the resistance of to FGFR inhibitors [62,63]. The drug-resistance mechanisms are different between these two FGFR1 mutants [63]. FGFR1^{N546K} mutant showed drug resistance by increasing its affinity for ATP, whereas FGFR1^{V561M} mutant showed resistance against PD173074 by reducing its affinity for the drug [63]. V Chell et al revealed that FGFR3^{V555M} gatekeeper mutation is associated with resistance to FGFR inhibitors, AZD4547 and PD173074 [64]. Lipika Goyal et al reported three clinical patients with FGFR2 fusion-positive cholangiocarcinoma and found that FGFR2^{V564F} confers resistance to BGJ398 by causing a steric clash with BGJ398 in its FGFR2 binding pocket [65]. Another research from a RNA sequencing based analysis and mouse models indicated 7 missense mutations, I567S, N568H/T, V581L, E584G, S587L, K660R and K678M, in the kinase domain of FGFR2 [66]. Among them, the residues I567, N568, V581, E584 and S587 are located in the ATP-binding pocket of FGFR2, the residue K660 is adjacent to the ATP-binding site, and the residue K678 is in the FGFR2 kinase activation loop [66]. Further study confirmed these mutations in FGFR2 decreased the sensitivity of AZD4547 in breast cancer [66]. These researches suggested that such FGFR mutations ought to be considered as clinical evaluation proceeds. Previous paper indicated that development of covalent inhibitors may conquer resistance to FGFR inhibitors induced by mutations [67]. In addition, these mutations mainly occurred in the kinase domain of FGFR, and whether the mutations can mediate the resistance to several documented FGFR inhibitors, which achieved their activity via an extracellularly acting and allosteric manner, need to be further explored.

Feedback activation of survival loop caused by FGFR inhibition is another important mechanism for the resistance to FGFR inhibitors (Table 3). High-throughput proteomic approach on DMS114 (SCLC cell line) and RT112 (urothelial carcinoma cell line) cells exposed to BGJ398 indicated that increased activation of AKT and its target GSK3 may account for the acquired resistance to FGFR suppression in cancer cells [68]. Another genetic screen identified that PI3K

pathway could be served as a determinant of resistance to FGFR inhibitors in urothelial carcinoma [69]. Further study uncovered that the elevated PI3K pathway activity may result from EGFR or Erb-B2 receptor tyrosine kinase 3 (ERBB3) reactivation induced by FGFR inhibition [69]. Parallel RNA interference screens on FGFR3 mutant cancer cells also confirmed the crucial roles of EGFR played in resistance to FGFR inhibition [70]. Their deeper data demonstrated that transient downregulation of MAPK signaling induced by FGFR inhibition may result in the continuous activation of EGFR via decreasing ubiquitylation [70]. In endometrial cancer cell lines, loss of PTEN has been suggested as a potential mechanism of resistance to FGFR inhibition [71]. Noticeably, cotreatment of FGFR2 and mTOR has a synergistic effect on the growth of endometrial cancer cell lines bearing an activating FGFR2 mutation, irrespective of PTEN status [71]. In BC, overexpression of MET, inactivation of RASA1 (Ras p21 protein activator 1), and activation of drug efflux transporter ABCG2 (adenosine triphosphate binding protein G2) have been reported to be the resistance mechanism to AZD4547 [66]. In addition, previous research from FGFR inhibitor resistant gastric cancer cell lines indicated that EMT may be also responsible for the resistance to FGFR inhibition [72]. For this

situation, combined therapy may be a better solution for overcoming resistance to FGFR inhibitors.

Table 2. Mutations induce resistance to FGFR inhibitors

FGFR	Mutated site	FGFR inhibitors
FGFR1	V561M	PD173074, dovitinib, ponatinib, BGI-398, E3810
FGFR1	N546K	PD173074, dovitinib, ponatinib, BGI-398
FGFR2	V564F	BGI-398
FGFR2	I567S	AZD4547
FGFR2	N568H/T	AZD4547
FGFR2	V581L	AZD4547
FGFR2	E584G	AZD4547
FGFR2	S587L	AZD4547
FGFR2	K600R	AZD4547
FGFR2	K678M	AZD4547
FGFR3	V555M	AZD4547, PD173074

Table 3. Signaling pathway induces resistance to FGFR inhibitors

Cancer types	FGFR inhibitors	Involved signaling pathway
Lung cancer	BGI398	PI3K/ AKT and GSK signaling pathway
Urothelial cancer	BGI398	PI3K/ AKT and GSK signaling pathway
Urothelial cancer	AZD4547	EGFR/ERBB3-AKT signaling pathway
Bladder cancer	PD173074	EGFR signaling pathway
Endometrial cancer	Ponatinib	Loss of PTEN
Breast cancer	AZD4547	MET, inactivation of RASA1, drug-efflux
Gastric cancer	AZD4547	EMT
Gastric cancer	BGI398	EMT
Gastric cancer	PD173074	EMT

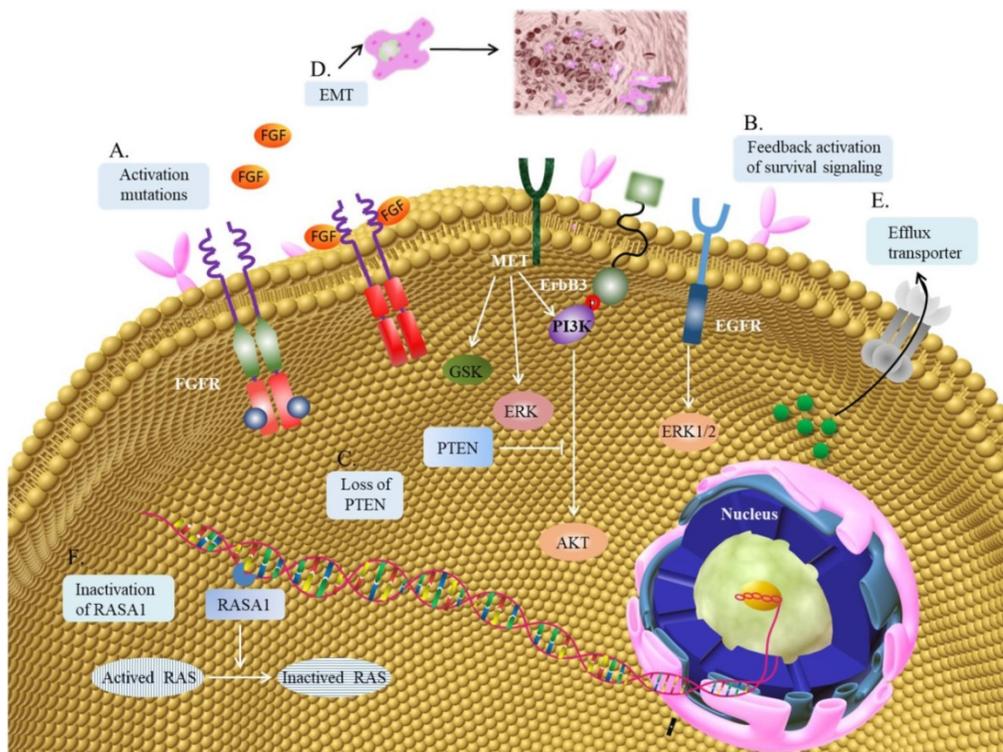


Figure 2. Mechanism of resistance to FGF/FGFR inhibitors. (A) Gatekeeper mutation in the FGFR kinase domain often results in resistance to FGFR inhibitors. (B) FGFR inhibition can activate other membrane receptor signaling pathway in the feedback way, like EGFR, ERBB3 or MET. The downstream cascades may be mediated by MAPK-ERK1/2, PI3K-AKT and GSK signaling pathway. (C) Loss of PTEN can increase the activation of PI3K-AKT signaling pathway. (D) EMT can contribute to the resistance to FGFR inhibitors. (E) ABCG2 regulated drug-efflux can also contribute to the resistance to FGFR inhibitors. (F) RASA1 is a protein activator, which can promote the translation of activated RAS to inactivated RAS. The inactivation of RASA1 may induce the resistance to FGFR inhibitors.

Conclusion

Aberrant activation of ligand dependent or independent FGF/FGFR signaling pathway makes a substantial contribution to oncotherapy resistance via promoting proliferation, survival, angiogenesis or EMT. Other non-canonical signaling mediated by FGF/FGFR, such as nuclear transition of FGFR and FGF [6], FGF/FGFR induced autophagy [73], FGF/FGFR related DNA reparation [74], may also be implicated in the resistance to oncotherapy and should be reinforced in the future study. These researches portend that combined therapy of FGF/FGFR with other oncotherapy may be a potential strategy to conquer resistance in cancers. Unfortunately, none selective FGF/FGFR inhibitors have been applied for clinic, making it difficult to further verify the clinical effectiveness of the combination strategy. Acceleration of FGF/FGFR inhibitors research is necessary and may bring pleasantly surprise for cancer treatment. It is also critical that FGFR mutant or feedback survival pathway may desensitize tumor cells to FGF/FGFR inhibitors. For reducing FGF/FGFR inhibitors resistance, covalent or extracellularly-acting inhibitors even combined therapy may be worthy of further research.

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Competing Interests

The authors have declared that no competing interest exists.

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