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Chapter 1

Oncogenic FGFR4 Signaling in Cancer: New Functions and Therapeutic Opportunities

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Abstract

FGFR4, a member of the FGFR family, is highly activated by the amplification of its ligand FGF19 in several solid tumors and hematologic malignancies, especially for hepatocellular carcinoma. Elevated FGFR4 and FGF19, participate in multiple processes of tumorigenesis and cancer progression, including cell proliferation, metastasis, and chemotherapy resistance. The structure of FGFR4 is distinct from the other three family members, allowing potential to develop specific targeting inhibitors. This review aims to summarize the recent advances of the FGF19-FGFR4 axis in cancer biology and specific FGFR4 inhibitors on cancer treatments.

Keywords: FGFR4; FGF19; Cancer; Specific inhibitor; Signaling pathways; Chemotherapy resistance

Introduction

Fibroblast Growth Factors (FGFs) participate in diverse cellular processes, such as cell differentiation, migration, proliferation, and survival. Twenty two members of FGF family have been identified in vertebrates, designated FGF1 through FGF23 (except FGF15) [1]. Most of FGFs' cellular functions conduit through binding with four FGF receptors (FGFR), with the exception of the intracellular FGF11 subfamily [2]. The FGFR family has five members, including FGFR1, FGFR2, FGFR3, and FGFR4, with a Tyrosine Kinase (TK) domain. Recently, another member, FGFR5 (FGFBP1), has been found a lack of a TK domain [3].

1.1 Molecular features of FGFR4

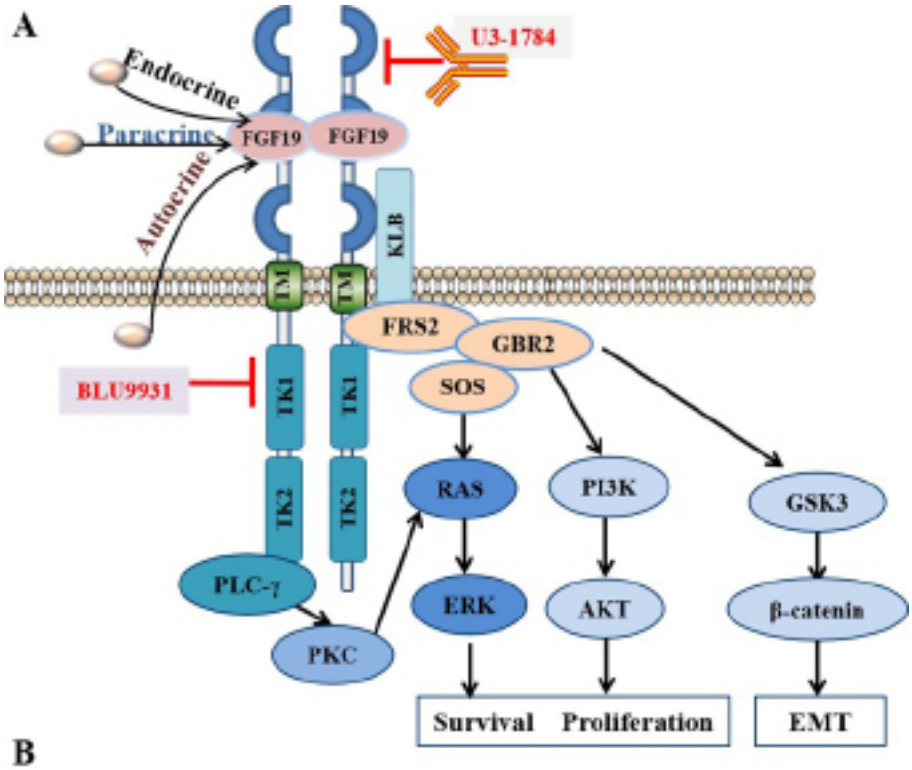
1.1.1. FGFR4 and its isoforms

The human *FGFR4* gene is located on chromosome 5 (5q 35.1) with four transcript variants, three of which encode isoform 1. Compared with isoform 1, isoform 2 lacks the transmembrane region, suggesting isoform 2 is a soluble rather than membrane-bound receptor [4]. *FGFR4* expression can be found during fetal human and mouse embryonic development. When compared against alterations in cholesterol metabolism and elevated bile acids, deletion of *FGFR4* does not lead to developmental abnormalities in mice [5,6]. The liver has the highest *FGFR4* expression levels among adult organs and it is the major site of essential physiological responses to FGFR4 [4].

1.1.2. Molecular structure of FGFR4

Similar to the other three members, FGFR4 contains several vital domains, including three extracellular immunoglobulin-like domains (I, II, and III), which are essential for specific ligand-binding. Moreover, FGFR4 has a single transmembrane domain (TM) and two cytoplasmic TK domains (TK1 and TK2) (**Figure 1**). In contrast to the other family members though, FGFR4 does not contain a splice variant on the immunoglobulin-like domain III [7].

Almost every FGF subfamily can bind FGFR4 Ig domains with different affinities. The FGF1, FGF4, and FGF8 subfamily members have a higher affinity in comparison to other canonical and intracellular FGF subfamilies that bind FGFR4. With the co-receptor β-klotho, the FGF19 endocrine subfamily has a strong and specific binding with FGFR4 [8,9]. Elevated *FGFR4* with amplification of the *FGF19* gene is always found in hepatocellular carcinoma (HCC) and other types of cancer. Therefore, targeting the FGF19-FGFR4 axis becomes an attractive strategy for this deadly disease.



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Drug	Target	Ref
Ponatinib	FGFRs	40
BLU9931	FGFR4	47
H3B-6527	FGFR4	50
U3-1784	FGFR4	38

Figure 1: Summary of the FGF19-FGFR4 signaling cascades with specific targeting drugs. (A) The main signaling pathways downstream of the FGF19-FGFR4 axis, including ERK1/2, AKT, PKC and GSK3β signaling cascades. (B) Representative drugs targeting FGFR4.

1.1.3. Gene alteration and expression in cancer

Gene alterations of FGFRs contribute to carcinogenesis and cancer progression, including gene amplification, fusion, and mutation of gain-of-function. Previous reviews have summarized the effects of FGFRs' gene alterations in different kinds of solid tumors and blood malignancies [2,10]. FGFR4 exhibits similar phenomena with other FGFR members on gene alterations. Amplification of FGFR members can be found in several kinds of tumors. In breast cancers, *FGFR4* amplification was observed in 10% of patients [11]. Translocation of FGFR1-3 genes are common, but this kind of mutation is rare for *FGFR4* in cancers. The *FGFR4* harbors two kinase mutations, K535 and E550, in rhabdomyosarcoma [12]. More research observations indicate that the FGF19-FGFR4 axis is essential for cancers expressing these two genes. However, unlike other family members, the functions and mechanisms of FGFR4 involved in cancer progression are still poorly understood. Here, the review focuses on the recent advances about novel functions of FGFR4 in cancer progression and therapy development to target FGFR4.

1.2. New functions of FGFR4 in cancer progression and chemotherapy resistance

1.2.1. Cell proliferation and survival rely on the FGF19-FGFR4-AKT signaling cascade in breast cancer

FGF19, secreted from autocrine, paracrine, or endocrine pathways, binds to FGFR4 with co-receptor β-Koloth [13]. Stimulated FGFR4 directly phosphorylates substrates to activate several downstream pathways, including MAPK, PI3K-AKT, PLC-γ/PKC, and GSK3β, in order to regulate cell processing, such as increased cell proliferation, survival, and metastasis (Figure 1A) [14-16]. Upregulating AKT signaling enhances cancer cell proliferation and survival, which can be triggered by FGFR4 in HCC [1,17]. Recently, FGFR4 overexpression has been detected in primary breast tumors, as a potential contributor to poor survival rates [18]. Over 28% of primary breast tumors harbor *FGF19* and *FGFR4* co-expression. It has been found that *FGF19/FGFR4* co-expression is strongly associated with AKT phosphorylation. Moreover, AKT phosphorylation is blocked by FGF19 antibody (1A6) or siRNA-mediated silencing of *FGF19* in MDA-MB-468 cells [15]. However, the function of FGFR4-AKT signaling in breast cancer is still not fully elucidated. Our recent findings show the expression of FGF19 is significantly higher in tumor tissues than in adjacent normal tissues [19]. From the GEO database analysis, higher *FGF19* expression levels are strongly associated with lower overall survival and recurrence-free survival rates in breast cancer patients, suggesting the involvement of the FGF19-FGFR4 axis in breast cancer progression. Overexpression of *FGFR4* increased AKT phosphorylation and promoted cancer cell growth and invasion. In contrast, these effects of FGFR4 were significantly attenuated by *FGF19* knockout in MDA-MB-468 cells [19]. AKT phosphorylation accompanied with cell proliferation and invasion was inhibited by BLU9931, a novel irreversible kinase inhibitor specifically targeting FGFR4, in FGF19-stimulating breast cancer cells. These findings indicate that FGFR4-AKT signaling particularly contributes to FGF19 oncogenic functions in breast cancer cells.

1.2.2. Increasing cancer metastasis through promoting epithelial-mesenchymal transition (EMT)

HCC is the third leading cause of cancer mortality in the world due to its highly metastatic properties [20,21]. EMT has been considered the key event in cancer cell metastasis and plays a critical role in the progression of HCC [22]. The EMT process is regulated by several main molecular mechanisms, including the loss of E-cadherin function and the activation of Wnt/β-catenin signaling [23-26]. *FGFR4* is mainly expressed in the liver, while elevated protein is found in over one-third of HCC patients, suggesting *FGFR4* overexpression is associated with HCC development and progression [27]. Moreover, FGF19, the main ligand of FGFR4 in the liver, has a focal amplification on chromosome 11q13.3 in 12–14% of HCC clinical samples, which positively correlates with tumor size, pathological stage, and poor prognosis [28,29].

The functional regulation between the FGF19-FGFR4 signaling pathway and HCC metastasis has been elucidated in our recent study [16]. Exogenous FGF19 altered cell morphology and increased metastasis in HCC cell lines MHCC97L and HepG2. Knockout *FGFR4* gene eliminated morphology changes and EMT in *FGF19* overexpressing MHCC97L, indicating that FGFR4 largely contributes to FGF19-induced EMT. Different pathway inhibitors were recruited to define the mechanism of EMT induced by the FGF19-FGFR4 axis. Only GSK3β inhibitors (TWS119 and Tideglusib) can prevent EMT following FGF19 stimulation in epithelial-like HCC cells [16]. When cell were stimulated by FGF19, FGFR4 phosphorylated GSK3β and then subsequently activated β-catenin to facilitate its nuclear transloation. Then, activated β-catenin initiated expression of the *Snail1* and *Twist* genes, which in turn repressed *E-cadherin* expression to promote EMT in HCC cells [16]. These observations support the critical role of FGFR4 in FGF19-induced EMT, which is accomplished through the activation of the GSK3β/β-catenin/E-cadherin axis. Therefore, suppression of EMT by targeting FGFR4 appears to be an attractive and efficient therapeutic strategy against HCC.

Recently, the FGF19/FGFR4/GSK3β/β-catenin axis has also been linked to the effect of Forkhead box C1 (FOXC1) on metastasis in colorectal cancer (CRC) [30]. Elevated expression of *FOXC1* is tightly correlated with metastasis of CRC. *FGFR4* was identified as one of the target genes for FOXC1 that enhanced CRC metastasis through activating GSK3β/β-catenin signaling [30]. GSK3β/β-catenin signaling induced by *FOXC1* overexpression can be reversed by BLU9931 [30]. The incidence of metastatic colonization and the number of metastatic lung nodules of CRC was also reduced by BLU9931 *in vivo* [30]. These findings demonstrate an essential function of FGFR4 in FOXC1-mediated CRC metastasis on EMT processes.

1.2.3. Induction of chemotherapy resistance in HCC cells

The FGF19-FGFR4 axis participates in chemotherapy resistance in several cancers, including breast cancer, CRC, and HCC, which can be blocked by anti-FGF19 antibody or siRNA-mediated *FGF19* gene silencing, leading to increased sensitivity of FGFR4-positive breast cancer cells to doxorubicin [15]. A synergistic interaction is also observed between *FGFR4* silencing with 5-fluorouracil (5-FU) or oxaliplatin treatment in CRC cells [31].

Sorafenib, a multiple TKs inhibitor (TKI), leads to a survival benefit for patients as a first line anticancer drug in HCC [32]. However, drug resistance with unknown mechanisms occurs in the sorafinib treatment of cancer [33,34]. Currently, our data reveals that activation of the FGF19-FGFR4 axis is one of the main mechanisms for sorafenib resistance in the treatment of HCC [35]. Reactive oxygen species (ROS) and the resulting oxidative stress play a pivotal role in apoptosis [36,37]. Mechanistically, sorafenib induces ROS-associated apoptosis, but this can be suppressed by *FGF19* overexpression in MHCC97L cells. *FGFR4* knockout by CRISPR/Cas9 system decreased cell survival of MHCC97H in response to sorafenib, leading to enhanced

cell apoptosis in sorafenib treatment [35]. Moreover, Silencing *FGF19* or inactivating FGFR4 by the pan-FGFR inhibitor ponatinib can effectively increase the sensitivity to drug treatment in sorafenib-resistant HCC cells, with induced apoptosis and ROS generation [37].

1.3. Targeting FGFR4 to develop novel cancer treatments

Accumulating evidence reveals that upregulated FGF19-FGFR4 pathway plays a vital role in tumorigenesis and cancer progression. Thus, FGFR4 becomes an attractive and promising target to develop novel therapeutic strategies against FGF19-FGFR4 dependent cancers. Recently, monoclonal antibodies and small molecule inhibitors specifically targeting FGFR4 are being quickly developed and intensively tested in clinical trials. Moreover, neutralizing antibodies of FGFR4 by binding extracellular Ig domains have been obtained, including LD-1 and U3-1784. Until now, U3-1784 is the only FGFR4 antibody in clinical trial to treat HCC and advanced solid tumors [38].

FGFR4 has a TK domain that binds ATP, which can be inhibited by multiple TKI (mTKI) and pan-FGFR inhibitors. There are several different mTKIs tested in clinical trials on the FGFR-driven malignancies. For example, ponatinib is a pan-FGFR inhibitor (NCT02272998), which has the potent efficacy toward FGFR4, although its inhibitory effect is much lower compared to that on other three FGFR isoforms (Figure 1B) [39,40]. Several other pan-FGFR inhibitors are being evaluated in clinical trials to treat different types of FGFR driven solid tumors and hematologic malignancies, especially for HCC. Inhibitors of pan-FGFR mainly target TK domains or specific binding pockets through reversible or covalent bonds. NVP-BGJ398 [41] and AZD4547 [42] are selective ATP-competitive inhibitors of FGFRs tested in clinical trials. JNJ-42756493 and LY2874455 target the TK domain showing acceptable toxicity profiles in phase I clinical trials [43,44]. The covalent FGFR irreversible inhibitors (FIIN), includes FIIN-1, 2, and 3, which target a cysteine residue conserved in all four FGFR kinases [45]. However, the overall issue with the pan-FGFR inhibitors is they have moderate to weak potency against FGFR4. Some of these inhibitors, their preferential inhibitory activity is observed against FGFR1-3 over FGFR4. For example, the IC_{50} of AZD4547 on FGFR4 is over 100 fold higher than other FGFR members [46]. Another disadvantage of most pan-FGFR inhibitors is their promiscuous kinome activity [47]. FGFR1, FGFR2 and FGFR3 also play key in physiological processes. Hyperphosphatasemia is a common FGFR-inhibition specific side effect for pan-FGFR inhibitors. In contrast, selective FGFR4 inhibitors have more potential antitumor activity with less side effects on FGF19-FGFR4 driven cancers. Therefore, specific FGFR4 inhibitors have been quickly developed and evaluated in clinical trials to target subgroup cancers driven by the FGF19-FGFR4 axis.

BLU9931 is a specific FGFR4 inhibitor created by forming a covalent bond with Cysteine 552, which is only present in FGFR4 near the ATP-binding site (Figure 1B) [19, 47].

BLU9931 has been wildly used as the specific FGFR4 inhibitor in cancer research. BLU-554 is optimized via BLU9931 and clinically evaluated with enhanced pharmaceutical properties (NCT02508467) [48]. Another FGFR4 inhibitor, FGF401, is also under investigation in a phase I/II study to treat HCC (NCT02325739) [49]. H3B-6527 (H3 biomedicine) is one of many highly selective FGFR4 inhibitors with potential anticancer activity in FGF19 amplified cancer cells *in vitro* and *in vivo* [50]. As the liver has the highest FGFR4 expression in adult humans and therefore, altered FGF19-FGFR4 is common in HCC. Therefore, there is no surprise that HCC is the major indication for FGFR4 inhibitors/antibodies in clinical trials. Novel FGFR4 targeting therapies would provide a promising treatment for the subgroup cancers, which are heavily dependent on the FGF19-FGFR4 axis, especially for HCC.

2. Conclusion

Currently, more research evidence indicates that overactive FGFR4 with FGF19 play a vital role in tumorigenesis and tumor pathological progression. Therefore, FGFR4-specific inhibitors are being developed and evaluated intensively in clinical trials. With more efforts to identify novel mechanisms of the FGF19-FGFR4 axis in cancer progression and specific inhibitor development, the cancer patient subsets driven by FGF19 has the potential to be cured in future.

3. Competing interests

The authors declare no competing financial interests.

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