FGFR2-related pathogenesis and FGFR2-targeted therapeutics (Review)

YURIKO KATOH[1] and MASARU KATOH[2]

[1]M&M Medical BioInformatics, Hongo 113-0033; [2]Genetics and Cell Biology Section,
National Cancer Center, Tokyo 104-0045, Japan

Abstract. *FGFR2* gene at human chromosome 10q26 encodes FGFR2b and FGFR2c isoforms functioning as FGF receptors with distinct expression domain and ligand specificity. FGFR2 plays oncogenic and anti-oncogenic roles in a context-dependent manner. Single nucleotide polymorphisms (SNPs) within intron 2 of *FGFR2* gene are associated with breast cancer through allelic *FGFR2* upregulation. Missense mutations or copy number gains of *FGFR2* gene occur in breast cancer and gastric cancer to activate FGFR2 signaling. Aberrant FGFR2 signaling activation induces proliferation and survival of tumor cells. The class switch from FGFR2b to FGFR2c occurs during progression of prostate cancer and bladder cancer because of spliceosome dysregulation. In addition, epidermal *Fgfr2b* knockout mice show increased sensitivity to chemical carcinogenesis partly due to the failure of Nfe2l2 (Nrf2)-mediated detoxification of reactive oxygen species (ROS). Loss of FGFR2b signaling induces epithelial-to-mesenchymal transition (EMT) and unruly ROS. FGFR2 signaling dysregulation due to the accumulation of epigenetic modifications and genetic alterations during chronic inflammation, smoking, increased caloric uptake, and decreased exercise leads to carcinogenesis. PD173074, SU5402, AZD2171, and Ki23057 are small-molecule FGFR inhibitors. Human antibody, peptide mimetic, RNA aptamer, siRNA, and synthetic microRNA (miRNA) are emerging technologies to be applied for cancer therapeutics targeted to FGFR2. Because novel sequence technology and peta-scale supercomputer are opening up the sequence era following the genome era, personalized medicine prescribing targeted drugs based on germline and/or somatic genomic information is coming reality. Application of FGFR2 inhibitors for cancer treatment in patients with *FGFR2* mutation or gene amplification is beneficial; however, that for cancer prevention in people with *FGFR2* risk allele might be disadvantageous due to the impediment of a cytoprotective mechanism against oxidative stress.

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1. Introduction

FGFR2 gene at human chromosome 10q26 encodes FGFR2b and FGFR2c isoforms due to alternative splicing (1-4). FGFR2b and FGFR2c function as fibroblast growth factor (FGF) receptors transducing FGF signals to RAS-ERK and PI3K-AKT signaling cascades through FRS2, and also to DAG-PKC and IP3-Calmodulin signaling cascades through PLCγ (5,6). FGFR2b and FGFR2c with extracellular immunoglobulin-like domains and cytoplasmic tyrosine kinase domain are almost identical except the latter half of the third immunoglobulin-like domain.

Epithelial cells moving as a sheet en block are tightly held together with uniform neighboring cells, while mesenchymal cells moving individually are loosely connected with diverse neighboring cells (7-9). FGFR2b on epithelial cells is a high affinity receptor for FGF1, FGF3, FGF7, FGF10 and FGF22 (10,11). FGFR2c on mesenchymal cells is a high affinity receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16 and FGF20 (10,11). FGFR2b and FGFR2c show distinct expression domain and ligand specificity.

FGF7, FGF10, and FGF22 constitute a subfamily among the FGF family (12-15). FGF7, induced by PDGF, IL-1, IL-1ß or TNF-α, is secreted from fibroblast, smooth muscle cells, endothelial cells, skin dermis, and γδT cells to promote tissue repair (16-18). FGF10 is secreted from mesenchymal cells to orchestrate morphogenesis of gastrointestinal tract, respiratory tract, limb, and other organs or tissues (19,20). FGF22 is

Correspondence to: Dr Masaru Katoh, Genetics and Cell Biology Section, National Cancer Center, 5-1-1 Tsukiji, Chuo Ward, Tokyo 104-0045, Japan
E-mail: mkatoh-kkr@umin.ac.jp

secreted from cerebellar granule cells to regulate synapse formation (21). FGF7, FGF10 and FGF22 transduce signals through FGFR2b on epithelial cells to regulate embryo-genesis and adult tissue homeostasis (18).

FGF signaling cascades interact with WNT, Notch, Hedgehog and BMP signaling cascades to constitute the stem cell signaling network (22,23). Dysregulation of the stem cell signaling network caused by the accumulation of epigenetic modifications and genetic alterations due to single nucleotide polymorphism (SNP), chronic inflammation, smoking, increased caloric uptake and decreased exercise leads to carcinogenesis (24). Because dysregulation of FGFR2 signaling is involved in cancer and congenital disorders (25,26), pathogenesis related to FGFR2 will be reviewed at first, and then therapeutics targeted to FGFR will be described with the emphasis on future clinical application.

2. Oncogenic FGFR2 in human cancer

Missense mutations of *FGFR2* gene occur in endometrial uterus cancer, ovarian cancer, breast cancer, lung cancer and gastric cancer (27-29). FGFR2 mutations around the third immunoglobulin-like domain result in FGFR2 signaling activation due to the creation of autocrine FGF signaling loop, while those within tyrosine kinase domain results in FGFR2 signaling activation due to the release of FGFR2 from auto-inhibition as previously reviewed (25). Copy number gains of *FGFR2* gene in breast cancer and gastric cancer result in FGFR2 signaling activation due to overexpression of FGFR2 (30,31). In addition, C-terminal deletion of FGFR2 occurs during gene amplification process due to the exclusion of the last exon from *FGFR2* amplicon, which results in FGFR2 signaling activation based on the constitutive phosphorylation of FRS2 adaptor molecule (32). Point mutation or gene amplification of *FGFR2*, inducing aberrant FGFR2 signaling activation, is involved in human carcinogenesis (Fig. 1).

Recently, a variety of cancer-associated SNPs have been identified based on genome-wide association study (GWAS). Eight SNPs (rs35054928, rs2981578, rs2912778, rs2912781, rs35393331, rs10736303, rs7895676, and rs33971856) within intron 2 of *FGFR2* gene are associated with increased risk of breast cancer (33-36). Perfect POU (Oct)-binding site is located adjacent to rs35054928 and rs2981578, and putative RUNX-binding site is created on risk allele of rs2981578. Putative estrogen receptor (ER)-binding site is created on risk allele of rs10736303. Putative C/EBPß-binding site is lost from risk allele of rs7895676. Breast cancer-associated allele of rs2981578 is associated with *FGFR2* upregulation in the reporter assay (36); however, precise mechanism how *FGFR2* upregulation is induced by *FGFR2* risk allele spanning the putative enhancer region within intron 2 remains unclear.

Breast cancer-associated allele rs2981578 mentioned above is associated with decreased risk of endometrial uterus cancer (37), and is not associated with risk of epithelial ovarian cancer (38). Because of the diversity of genetic back-ground and carcinogenic scenario, association between *FGFR2* SNPs and risks of several types of cancer should be further investigated among several populations in the world (25).
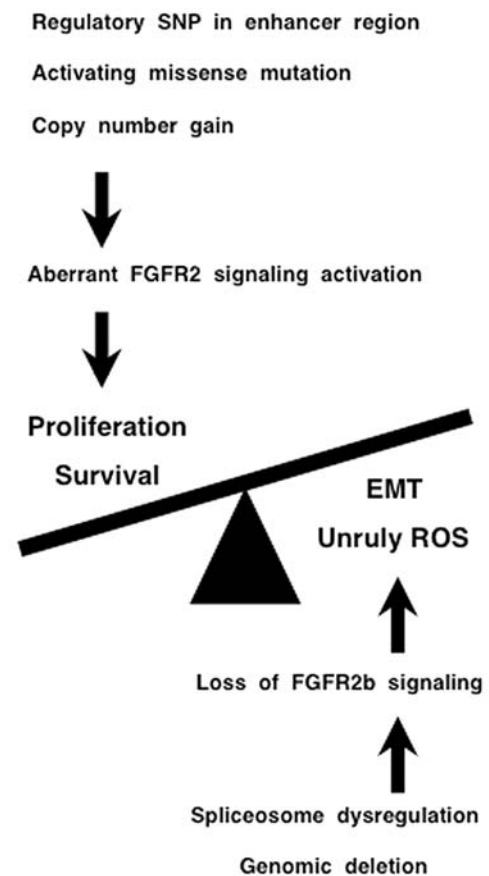

Figure 1. Oncogenic and anti-oncogenic FGFR2.

3. Anti-oncogenic FGFR2b

Class switch from FGFR2b to FGFR2c occurs during pro-gression process of prostate cancer and bladder cancer (39), which is accompanied by epithelial-to-mesenchymal transition (EMT) with increased potential for invasion and metastasis (7-9,40,41). Proliferation and tumorigenicity of prostate or bladder cancer cells with decreased FGFR2b expression are significantly suppressed by the transfection of FGFR2b expression construct (42,43). FGFR2b is anti-oncogenic in prostate cancer and bladder cancer.

Fgf7, Fgf10, and Fgf22 transduce signals through Fgfr2b in skin epidermis (18). Mice with conditional Fgfr2b knockout in skin epidermis show increased occurrence of squamous cell carcinoma (SCC) with oncogenic Hras mutations after DMBA/TPA treatment, indicating that loss of Fgfr2b in skin epidermis results in increased sensitivity to chemical carcinogenesis (44). Fgf7 and Fgf10 are in part secreted from γδT cells within epidermis during wound healing process (45), and mice lacking γδT cells also show enhanced sensitivity to skin carcinogenesis in the DMBA/TPA model (46). Together these facts indicate that inactivation of Fgfr2b signaling promotes mouse skin carcinogenesis (Fig. 1).

Nfe2l2 (Nrf2) is one of target genes of the Fgfr2b signaling pathway in the skin epidermis (18). *Nfe2l2* gene encodes a basic leucine zipper (bZIP) transcription factor Nfe2l2 homologous to Nfe2 and Nfe2l1 (Nrf1). Although Nfe2l2 is downregulated due to Keap1-mediated ubiquitylation under

non-stressed condition, Nfe2l2 is released from Keap1-induced degradation due to structural modification of Keap1 under environmental or endogenous reactive oxygen species (ROS) (47). Stabilized Nfe2l2 binds to antioxidant (ROS-detoxifying) response element of target genes encoding antioxidant enzymes to catalyze carcinogens to non-carcinogenic chemicals. Because Fgfr2b signaling upregulates Nfe2l2 involved in cytoprotection (18), loss of Fgfr2b signaling due to deletion or spliceosome dysregulation accelerates carcinogenesis.

4. FGFR2 in non-cancerous disorders

Missense activating mutations of *FGFR2* gene occur in Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome, and Beare-Stevenson syndrome, which are congenital skeletal disorders manifested by short-limbed bone dysplasia (craniosynostosis), and other features specific to each syndrome, such as Crouzonoid faces, bone syndactyly, limb abnormalities, and cutis gyrata (25,48-50). Missense mutations of *FGFR2* gene induce aberrant FGFR2 signaling activation during skeletal development.

One SNP (rs17101921) located in the 3'-flanking region of *FGFR2* gene is claimed to be associated with schizophrenia based on the analyses on 10 cases (51); however, confirmatory study using >1000 cases and controls are mandatory to reach the conclusion. Because *FGFR2* and *WDR11* genes are clustered around the recombination hot spot at human chromosome 10q26 (4), real causative gene associated with rs17101921 SNP remains unclear. It is noteworthy that Fgf22-Fgfr2b signaling cascade is involved in synapse formation during embryogenesis. Candidate approach to investigate SNPs of genes encoding FGF22-FGFR2b signaling components might be useful to identify novel causative SNPs associated with schizophrenia.

5. Small-molecule FGFR inhibitors

Protein kinases with conserved amino-acid sequence share the catalytic domain with similar three-dimensional structure. Small-molecule compounds fitting into the ATP-binding pockets of protein kinases have been developed for cancer therapeutics (52,53). PD173074, SU5402, AZD2171, and Ki23057 are representative small-molecule FGFR inhibitors (Fig. 2).

PD173074 with pyrido[2,3-*d*]pyrimidine core inhibits FGFR1 with IC_{50} value of 20 nM (54). PD173074 interacts with L484, V492, A512, K514, E531, M535, I545, V559, V561, Y563, A564, L630, A640, and F642 around the ATP-binding pocket of FGFR1, and inhibits tyrosine kinase activity and autophosphorylation of FGFR1. PD173074 blocks FGF2-induced angiogenesis *in vivo* (54). PD173074 also blocks mitogenesis of tumor cells through G1-arrest mediated by downregulation of Cyclin D1 and Cyclin D2 at the concentration of 2000 nM (55). PD173074 inhibits proliferation and survival of endometrial cancer cells with FGFR2 mutations (56,57).

SU5402 with indolin-2-one core inhibits FGFR1, PDGFRB and VEFGR2 tyrosine kinases with IC_{50} values of 30 nM, 510 nM and 20 nM, respectively (58). The indolin-2-one core
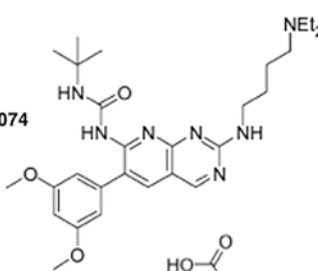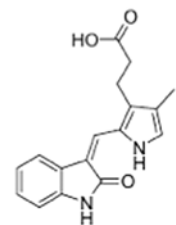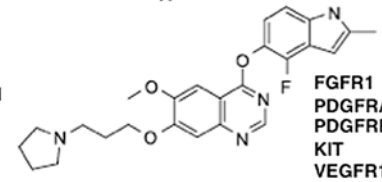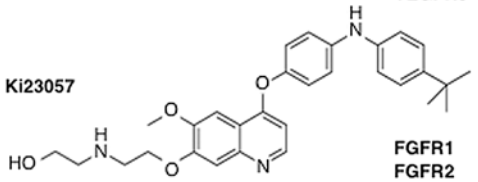

Figure 2. Small-molecule FGFR inhibitors.

of SU5402 interacts with the ATP-binding site of FGFR1 kinase domain, while substituted moieties interact with the hinge region between two lobes of FGFR1 kinase domain (59). Because selectivity of indolin-2-one compounds against receptor tyrosine kinases are determined by substituents extending from the indolin-2-one core, SU5402 is a narrow-range tyrosine kinase inhibitor.

AZD2171 is a broad-range tyrosine kinase inhibitor (60). AZD2171 inhibits FGFR1, PDGFRB and VEFGR2 tyrosine kinases with IC_{50} values of 26 nM, 5 nM, and <1 nM, respectively. AZD2171 also inhibits other receptor tyrosine kinases, such as PDGFRA, KIT, VEGFR1, and VEGFR3. Oral administration of AZD2171 (1.5 mg/kg/day) significantly inhibits growth of various human tumor cells transplanted into athymic mice (60). AZD2171 inhibits VEGF-induced proliferation of human umbilical vein endothelial cells at concentrations less than nM, and proliferation of human tumor cells at concentrations around mM. AZD2171 inhibits tumor growth *in vivo* due to indirect effects on endothelial cells rather than direct effects on tumor cells themselves (60).

Ki23057 is also a broad-range tyrosine kinase inhibitor (61). Ki23057 inhibits FGFR1, FGFR2 and VEGF2 tyrosine kinases with IC_{50} values of 89 nM, 91 nM, and 38 nM, respectively. Ki23057 inhibits proliferation of OCUM-2MD3

and OCUM-8 gastric cancer cells with *FGFR2* gene amplification, but not MKN7, MKN45 and MKN74 gastric cancer cells without *FGFR2* gene amplification (61). Oral administration of Ki23057 (25 mg/kg/day) inhibits growth and peritoneal dissemination of OCUM-2MD3 cells. Antitumor effects of Ki23057 are mainly due to FGFR2-RAS-ERK signaling inhibition rather than FGFR2-PI3K-AKT signaling inhibition (61).

6. Other therapeutics targeted to FGFR2

Human antibody, peptide mimetic, RNA aptamer, small interfering RNA (siRNA), and synthetic microRNA (miRNA) are emerging technologies to be applied for molecular cancer therapy (41,62).

Peptide mimetic is a promising strategy to develop agonist or antagonist for transmembrane receptors. Dekafins are FGF mimetic peptides associating with FGFR1c or FGFR2b (63). Dekafin1 and Dekafin10 are partial agonists of FGFR1c, and the association between dekafin1 and FGFR1c is modulated by heparin sulfate moiety. Peptide mimetics functioning as FGFR2 antagonists will be potent lead compounds.

RNA aptamers are short RNA oligonucleotides forming a stable three-dimensional structure for specific tight binding to target protein (64-67). RNA aptamers binding to target proteins are selected from combinatorial libraries by using SELEX method. RNA aptamers targeted to FGFR2 kinase domain or FGFR2-FRS2 interface will be developed as novel FGFR2 signaling inhibitors, while those targeted to FGFR2 extracellular region will be developed as substitutes of human antibody for immunotherapy or tumor-targeted drug delivery.

Fire *et al* reported RNA repression by using double-stranded RNA in 1998 (68). Elbashir *et al* reported RNA repression by using siRNA in 2001 (69). Liang *et al* reported RNA repression by using synthetic miRNA in 2007 (70). siRNA and synthetic miRNA controlling protein expression through target-mRNA degradation or translational repression are promising technologies for cancer therapeutics; however, avoidance of off-target effects and development of tumor-specific delivery system should be addressed before clinical application (62).

7. Conclusion and perspectives

FGFR2 plays oncogenic and anti-oncogenic roles in a context-dependent manner (Fig. 1). Because novel sequence technology and peta-scale supercomputer are opening up the sequence era following the genome era (71), personalized medicine prescribing targeted drugs based on germline and/or somatic genomic information is coming reality (72,73). Application of FGFR2 inhibitors for cancer treatment in patients with *FGFR2* mutation or gene amplification is beneficial; however, that for cancer prevention in people with *FGFR2* risk allele might be disadvantageous due to the impediment of a cytoprotective mechanism against oxidative stress induced by smoking, irradiation, and chronic inflammation.

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