FGFR2 Abnormalities Underlie a Spectrum of Bone, Skin, and Cancer Pathologies

Masaru Katoh[1]

Fibroblast growth factor receptor (FGFR)2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycans, FGFR2 isoforms, endogenous inhibitors, and microRNAs. FGFR2 signals cross-talk with hedgehog, bone morphogenetic protein, and other regulatory networks. Some cases of congenital skeletal disorders with an *FGFR2* mutation show skin phenotypes, including acne, cutis gyrata, and acanthosis nigricans. Gain-of-function mutations or variations of human *FGFR2* occur in estrogen receptor-positive breast cancer, diffuse-type gastric cancer, and endometrial uterine cancer. Oral administration of AZD2171 or Ki23057 inhibits *in vivo* proliferation of cancer cells with aberrant FGFR2 activation in rodent therapeutic models. However, loss-of-function mutations of *FGFR2* are reported in human melanoma. Conditional *Fgfr2b* knockout in the rodent epidermis leads to increased macrophage infiltration to the dermis and adipose tissue, epidermal thickening accompanied by basal-layer dysplasia and parakeratosis, and the promotion of chemically induced squamous-cell carcinoma. Dysregulation of FGFR2 results in a spectrum of bone and skin pathologies and several types of cancer.

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INTRODUCTION

FGFR1, *FGFR2*, *FGFR3*, and *FGFR4* genes encode receptors for fibroblast growth factors (FGFs) that are involved in fetal morphogenesis, adult tissue homeostasis, and tumorigenesis (Dailey *et al.*, 2005; Eswarakumar *et al.*, 2005; Grose and Dickson, 2005; Wilkie, 2005; Chaffer *et al.*, 2007). The *BAG4–PPAPDC1B–FGFR1–TACC1* locus at human chromosome 8p11–p12 and the *BAG3–PPAPDC1A–FGFR2–TACC2* locus at human chromosome 10q26.12–q26.13 are syntenic blocks generated by ancient whole-genome duplications during vertebrate evolution (Katoh and Katoh, 2003b; Itoh and Ornitz, 2004). *FGFR1* and *FGFR2* are paralogs in the *FGFR* gene family.

The *FGFR2* gene encodes several splice variants by alternative splicing (Dionne *et al.*, 1990; Miki *et al.*, 1991; Savagner *et al.*, 1994; Katoh and Katoh, 2003a). Fibroblast growth factor receptor (FGFR)2b and FGFR2c are representative FGFR2 isoforms among several splice variants derived from the *FGFR2* gene. FGFR2b, in epithelial cells, and FGFR2c, in mesenchymal cells, are almost identical transmembrane-type receptors with extracellular immunoglobulin-like domains and cytoplasmic tyrosine-kinase domain. FGFR2b functions as the receptor for FGF1, FGF3, FGF7, FGF10, and FGF22, whereas FGFR2c functions as the receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16, FGF17, FGF18, and FGF20 (Ornitz *et al.*, 1996; Eswarakumar *et al.*, 2005; Zhang *et al.*, 2006). As the latter half of the third immunoglobulin-like domain of FGFR2b and FGFR2c is completely different because of alternative splicing of mutually exclusive exons, FGFR2b and FGFR2c show distinct ligand specificity.

Heparan-sulfate proteoglycan is a scaffolding protein that mediates the interaction of FGFs and FGFR2 in a tissue-specific manner (Mohammadi *et al.*, 2005; Luo *et al.*, 2006). FGFs that are associated with heparan sulfate proteoglycan induce dimerization and autophosphorylation of FGFR2 on Y657 in the activation loop of the tyrosine kinase domain to release FGFR2 from autoinhibition (Dailey *et al.*, 2005; Eswarakumar *et al.*, 2005; Chen *et al.*, 2007). FGFR2 then phosphorylates fibroblast growth factor receptor substrate (FRS)2/FRS2α/Sucl-associated neurotrophic factor target 1 (Wang *et al.*, 1996; Hadari *et al.*, 2001) to recruit growth factor receptor-bound protein 2 for the activation of the SOS—Ras–Raf—MEK(MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) kinase)–ERK (extracellular signal-regulated kinase) or the Gab1–phosphoinositide-3 kinase –Akt signaling cascade. Activated FGFR2 directly recruits phospholipase *C*-γ to catalyze phosphatidylinositol diphosphate to inositol triphosphate and diacylglycerol. Inositol triphosphate induces Ca^{2+} release from the endoplasmic reticulum,

[1]*Genetics and Cell Biology Section, National Cancer Center, Tokyo, Japan*

Correspondence: 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

Abbreviations: BCC, basal cell carcinoma; ER, estrogen receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; miRNA, microRNA; SCC, squamous cell carcinoma; SNP, single nucleotide polymorphism

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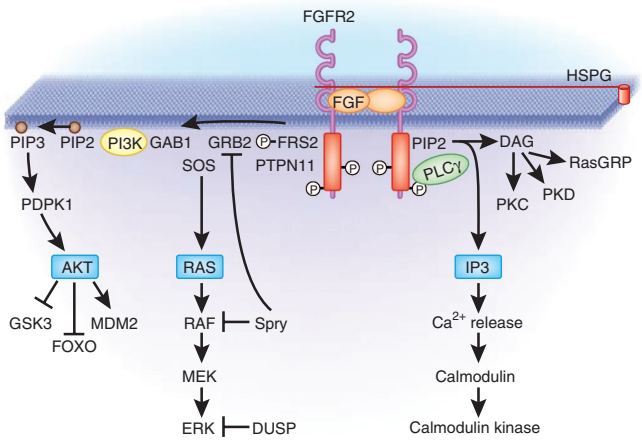

Figure 1. FGFR2 signaling cascades. Fibroblast growth factor receptor (FGFR)2b functions as a receptor for fibroblast growth factor (FGF)1, FGF3, FGF7, FGF10 and FGF22, whereas FGFR2c functions as a receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16, FGF17, FGF18 and FGF20. FGFR2 transduces FGF signals to Ras-extracellular signal-regulated kinase(ERK), phosphoinositide-3 kinase (PI3K)-Akt, Ca^{2+}, and diacylglycerol (DAG) signaling cascades. The FGF–ERK signaling cascade is involved in cell proliferation. The FGF–PI3K signaling cascade is involved in cell survival and polarity control. Sprouty inhibits the FGF–ERK signaling cascade at growth factor receptor-bound protein 2 and Raf, whereas dual-specificity phosphatase inhibits the FGF–ERK signaling cascade at ERK. FGFR2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycan (HSPG), FGFR2 isoforms, and endogenous inhibitors.

whereas diacylglycerol activates protein kinase C, protein kinase D, or RasGRP (guanyl nucleotide-releasing protein) signaling cascades. FGFR2 transduces FGF signals to Ras-extracellular signal-regulated kinase, phosphoinositide-3 kinase-Akt, Ca^{2+}, and diacylglycerol signaling cascades (Figure 1).

FGFR2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycans, FGFR2 isoforms, and endogenous inhibitors (Figure 1). Sprouty inhibits the FGF-extracellular signal-regulated kinase signaling cascade at growth factor receptor-bound protein 2 and Raf, whereas dual-specificity phosphatase inhibits the FGF-extracellular signal-regulated kinase signaling cascade at extracellular signal-regulated kinase. microRNAs (miRNAs) are emerging as crucial regulators of various signaling networks (Bartel, 2004; Negrini *et al.*, 2007; Grosshans and Filipowicz, 2008; Katoh and Katoh, 2008). MiR-433 represses translation of FGF20 in individuals with the *C* allele of the rs12720208 single nucleotide polymorphism (SNP) (Wang *et al.*, 2008), whereas miR-21 represses translation of functions of FGFR signaling inhibitor, Spry1 (Thum *et al.*, 2008).

Germline Fgfr2b-knockout mice die shortly after birth because of multiple-organ abnormalities, such as agenesis of the lungs, limbs, anterior pituitary gland, and thyroid gland and dysgenesis of the skin, glandular stomach, pancreas, and thymus (De Moerlooze *et al.*, 2000; Revest *et al.*, 2001). Genetic alterations of *FGFR2* at germline or somatic level gives rise to congenital disorders and acquired diseases through dysregulation of FGFR2 signaling cascades (Grose and Dickson, 2005; Wilkie, 2005; Katoh, 2008). Genome-wide association studies are opening up new opportunities for research on FGFR2-associated diseases (Easton *et al.*, 2007; Hunter *et al.*, 2007). Here, FGFR2-associated disorders or diseases are summarized in Table 1, and then skin manifestations caused by *FGFR2* genetic alterations are reviewed. As melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are representative skin malignancies, perspectives on these malignancies are also described with an emphasis on *FGFR2* genetics.

HUMAN DISORDERS OR DISEASES ASSOCIATED WITH *FGFR2*

Congenital skeletal disorders

FGFR2c is expressed on mesenchymal cells during the early phase of long-bone formation, known as the mesenchymal condensation process. FGFR2 is also expressed on preosteoblasts and osteoblasts during the later phase of bone formation (Eswarakumar *et al.*, 2002). The nuclear factor-Y transcription factor binds to the evolutionarily conserved CCAAT motif in the proximal promoter region of *FGFR2* gene, and is involved in basal expression of *FGFR2* (Sun *et al.*, 2009). Bone morphogenetic protein 2 induces FGFR2 upregulation in C3H10T1/2 embryonic-fibroblast cells; however, the mechanism of the FGFR2 induction by bone morphogenetic protein-Smad signaling remains unclear. As FGFR2 is involved in bone formation, *FGFR2* is a causative gene for several congenital skeletal disorders manifested by short-limbed bone dysplasia or craniosynostosis (Passos-Bueno *et al.*, 1999; Kan *et al.*, 2002; Wilkie, 2005).

The *FGFR2* gene is mutated in Crouzon syndrome (Reardon *et al.*, 1994), Jackson–Weiss syndrome (Jabs *et al.*, 1994), Apert syndrome (Wilkie *et al.*, 1995), Pfeiffer syndrome (Rutland *et al.*, 1995), Beare–Stevenson syndrome (Przylepa *et al.*, 1996), and Saethre–Chotzen syndrome (Paznekas *et al.*, 1998). Missense mutations of FGFR2 in congenital skeletal disorders are clustered around the third immunoglobulin-like domain or within the tyrosine kinase domain (Figure 2). Amino-acid substitutions around the third immunoglobulin-like domain induce autocrine FGFR2 activation through altered FGF-binding specificity (Yu *et al.*, 2000), whereas those in the tyrosine kinase domain induce ligand-independent FGFR2 activation by the releasing FGFR2 from autoinhibition (Chen *et al.*, 2007).

Breast cancer

Gene amplification of the *FGFR2* gene occurs in primary breast cancer (Adnane *et al.*, 1991). *FGFR2* gene amplification results in overexpression of the *FGFR2* gene products, especially C-terminally truncated FGFR2 protein, because of the exclusion of the last exon from the amplicon during the gene amplification process (Katoh and Katoh, 2003a). C-terminally truncated FGFR2 induces constitutive activation of FGFR2 signaling cascades in a