Gene Section

Review

FGFR2 (fibroblast growth factor receptor 2)
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Identity

Other names: BEK; CD332; CEK3; ECT1; KGFR; K-sam; TK14; TK25
HGNC (Hugo): FGFR2
Location: 10q26.13
Local order: WDR11 - FGFR2 - ATE1 - NSMCE4A - TACC2.
Note: FGFR2 was independently cloned and characterized by several groups as a novel receptor-type tyrosine kinase BEK, KGFR, K-sam, or TK14.

DNA/RNA

Note
FGFR2 gene at chromosome 10q26.13 and FGFR1 gene at chromosome 8p12 are paralogs within the human genome.

Description
FGFR2 gene, consisting of at least 21 exons, encodes multiple isoforms due to alternative splicing. FGFR2b and FGFR2c with extracellular three Ig-like domains, transmembrane domain and cytoplasmic tyrosine kinase domain, are representative FGFR2 isoforms almost identical except the latter half of the third Ig-like domain. Exon 9 and 10, corresponding to the latter half of the third Ig-like domain, are incorporated into FGFR2b and FGFR2c in a mutually exclusive manner. Splicing silencer sequence within intron 8 and splicing activator sequence within intron 9 are implicated in the regulation of splicing preferentiality for FGFR2b and FGFR2c. Exons 20 and 21 of FGFR2 gene are alternative last exons encoding the C-terminal region of FGFR2 isoforms. Wild type FGFR2 transcripts with exon 21 are expressed in normal cells and most tumor cells, while aberrant FGFR2 transcripts with exon 20 are overexpressed in cases with FGFR2 gene amplification due to the exclusion of exon 21 from the FGFR2 amplicon. FGFR2 gene also encodes transmembrane-type FGFR2 isoforms lacking the first Ig-like domain, and secreted-type FGFR2 isoforms.

Structure and alternative splicing of FGFR2 gene.
**Transcription**

FGFR2b isoform is predominantly expressed in epithelial cells, while FGFR2c isoform preferentially in mesenchymal cells. FGFR2 is expressed in undifferentiated human ES cells, and also in ES-derived embryoid body, endodermal precursors, and neural precursors. FGFR2 is relatively highly expressed in fetal brain. Among adult human tissues, FGFR2 is relatively highly expressed in brain, retina, spinal cord, salivary gland, skin, kidney and uterus. FGFR2 is overexpressed in human breast cancer and gastric cancer due to gene amplification.

**Protein**

**Note**

FGFR2 functions as transmembrane receptor for FGF family members, such as FGF1 (aFGF), FGF2 (bFGF), FGF3, FGF4 (Kaposi's sarcoma-derived FGF or KGF), FGF6, FGF7 (keratinocyte growth factor or KGF), FGF9, FGF10, FGF16, FGF20 and FGF22. FGFR2b and FGFR2c are representative FGFR2 isoforms with distinct ligand specificity.

**Description**

FGFR2b and FGFR2c are representative FGFR2 isoforms, consisting of extracellular three Ig-like domains, transmembrane domain, and cytoplasmic tyrosine kinase domain. FGFR2b and FGFR2c are almost identical except the latter half of the third Ig-like domain. The divergence in the latter half of the third Ig-like domain leads to distinct ligand specificity between FGFR2b and FGFR2c. FGFR2b is a high affinity receptor for FGF1, FGF3, FGF7, FGF10 and FGF22, while FGFR2c is a high affinity receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16 and FGF20.

**Localisation**

FGFR2b and FGFR2c with the N-terminal signal peptide and a single transmembrane domain are localized to the plasma membrane.

**Function**

FGFR2 is a high affinity receptor for FGFs associated with heparan sulfate proteoglycans (HSPGs). Ligand-dependent FGFR2 dimerization releases FGFR2 from autoinhibition due to autophosphorylation of a key tyrosine residue within the activation loop of kinase domain. FRS2 (FRS2A) and FRS3 (FRS2B) are tyrosine phosphorylated by FGFR2 to recruit GRB2 and PTPN11 for the activation of SOS - RAS - RAF - MAP3K - MAP2K - MAPK and GAB1 - PI3K - AKT signaling cascades. Phospholipase C-gamma (PLCgamma) is recruited to FGFR2 through its interaction with phosphotyrosine residues on the C-terminal tail of activated FGFR2, which results in the catalysis of phosphatidylinositol diphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3). DAG activates protein kinase C (PKC) signaling cascade, while IP3 induces Ca\(^{2+}\) release from endoplasmic reticulum for the following activation of Calmodulin-Calciineurin-NFAT signaling cascade. FGFR2 transduces FGF signals to the MAPK and PI3K-AKT signaling cascades through FRS2 or FGF3, and to the PKC and NFAT signaling cascades through PLCgamma.

**Homology**

FGFR2b and FGFR2c are almost identical except the latter half of the third Ig-like domain as mentioned above. Among receptor-type tyrosine kinases, FGFR2 isoforms are more homologous to FGFR1 isoforms.
Mutations

**Germinal point mutations**

- Germinal missense mutations of FGFR2 gene occur in congenital skeletal disorders. Intronic single nucleotide polymorphisms (SNPs) of FGFR2 gene are associated with increased cancer risk. Somatic missense mutations or gene amplification of FGFR2 occur in several types of cancer.

**Somatic point mutations**

- Somatic missense mutations or gene amplification of FGFR2 occur in endometrial cancer, lung cancer, breast cancer, gastric cancer, and ovarian cancer. Genetic alterations of FGFR2 lead to aberrant activation of FGFR2 signaling cascades due to the creation of autocrine signaling loop or the release of FGFR2 from autoinhibition.

**Note**

Germinal missense mutations of FGFR2 gene occur in congenital skeletal disorders. Intronic single nucleotide polymorphisms (SNPs) of FGFR2 gene are associated with increased cancer risk. Somatic missense mutations or gene amplification of FGFR2 occur in several types of cancer.

**Germinal**

Germinal missense mutations of FGFR2 gene occur in congenital skeletal disorders, such as Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome, and Beare-Stevenson syndrome, which are featured by short-limbed bone dysplasia (craniosynostosis), and syndrome-specific abnormalities, such as Crouzonoid facies, bone syndactyly, limb abnormalities, and cutis gyrata. FGFR2 missense mutations around the third Ig-like domain result in altered ligand-receptor specificity to create the autocrine signaling loop. FGFR2 missense mutations within the tyrosine kinase domain lead to ligand independent activation of FGFR2. Germinal FGFR2 missense mutations cause congenital skeletal disorders due to aberrant FGFR2 signaling activation.

In addition, SNPs within intron 2 of FGFR2 gene are associated with increased risk of breast cancer, partly due to transcriptional upregulation of FGFR2.

**Somatic**

Somatic missense mutations or gene amplification of FGFR2 occur in uterus cancer (endometrial cancer), lung cancer, breast cancer, gastric cancer, and ovarian cancer. Genetic alterations of FGFR2 lead to aberrant activation of FGFR2 signaling cascades due to the creation of autocrine signaling loop or the release of FGFR2 from autoinhibition.

**Implicated in**

**Cancer**

**Disease**

Somatic missense mutations or gene amplification of FGFR2 occur in endometrial cancer, lung cancer, breast cancer, gastric cancer, and ovarian cancer as mentioned above. In addition, class switch from FGFR2b to FGFR2c occurs during malignant progression of prostate cancer and bladder cancer. Somatic mutations and class switch of FGFR2 isoforms...
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Mechanisms of oncogenic FGFR2 signaling activation.

induce aberrant FGFR2 signaling activation in tumor cells.

**Prognosis**

FGFR2 gene amplification accompanied by FGFR2 overexpression in breast cancer and gastric cancer is associated with poor prognosis. Class switch from FGFR2b to FGFR2c is associated with more malignant phenotype in prostate cancer and bladder cancer.

**Congenital skeletal disorder**

**Disease**

Germinal mutations of FGFR2 gene occur in Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome, and Beare-Stevenson syndrome. FGFR2 missense mutations cause congenital skeletal disorders due to aberrant FGFR2 signaling activation as mentioned above.

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