

FGFR

Key References

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Overview

Fibroblast growth factors (FGFs) comprise a large family of signaling polypeptides. In the adult organism, FGFs are homeostatic factors and function in tissue repair and response to injury. In the embryo, FGFs regulate cell proliferation, migration, differentiation and survival. When inappropriately expressed, some FGFs can contribute to developmental defects and to the pathogenesis of cancer and other diseases. Mutations in FGF receptor tyrosine kinases (FGFRs) in humans causes skeletal diseases such as Achondroplasia, the most common form of dwarfism in humans, and Craniosynostosis syndromes, a cluster of diseases that involves premature fusion of cranial bones. In vertebrates, 22 *Fgf* genes encode polypeptides that range in molecular mass from 17 to 34 kDa. Eighteen of the 22 FGFs bind and activate a subset of seven distinct high affinity FGFRs that are derived by alternative splicing of four genes. Affinity and specificity of FGFs for their receptors is regulated by alternative mRNA splicing in three of the four known *Fgfr* tyrosine kinase genes. FGF activity and specificity is further regulated by heparin sulfate proteoglycans, which serve as co-receptors for FGFs.

FGF receptors (FGFR) contain three extracellular immunoglobulin-like (Ig) domains and a heparin binding sequence. Alternative mRNA splicing in the carboxy-terminal half of Ig-domain III creates b and c isoforms of *Fgfrs* 1-3. *Fgfr* alternative splicing is regulated in a tissue-specific manner and dramatically affects ligand-receptor binding specificity. The b splice form is utilized in epithelial lineages and the c splice is utilized in mesenchymal lineages. Ligands specific for these receptor splice forms are expressed in adjacent tissues resulting in directional epithelial-mesenchymal signal-

ing. For example, FGFR2b is expressed in many epithelial tissues and can be activated by FGF7, FGF10 and FGF22, ligands produced in mesenchymal tissue. These ligands show no activity towards mesenchymally expressed FGFR2c. Conversely, ligands such as FGFs 4, 8 and 9 are expressed in epithelial-like tissue and activate c splice forms of *Fgfrs*.

An important feature of FGF biology involves the interaction between FGF and heparin and heparan sulfate proteoglycans (HSPG). Heparin and heparan sulfate stabilizes FGFs to thermal denaturation and proteolysis, limits the diffusion and release of FGFs into interstitial spaces, and regulates the binding affinity and specificity of FGFs for their receptors. Heparin or heparan sulfate is required for FGF to effectively activate an FGFR in cells that are deficient in or unable to synthesize HSPG or in cells pretreated with heparin degrading enzymes or inhibitors of sulfation. Mutations in enzymes involved in heparan biosynthesis also affect FGF signaling pathways during development.

FGFRs are receptor tyrosine kinases that are activated by ligand-induced dimerization and subsequent auto-phosphorylation. FGFs bind to FGFRs in a 1:1 complex that is facilitated by heparin/heparan sulfate, which makes numerous contacts with both the FGF and FGFR molecule. Heparin/heparan sulfate also interacts with an adjoining FGFR to promote FGFR dimerization. The activated FGFR interacts with intracellular signaling molecules allowing it to couple to several signal transduction pathways. The two primary pathways activated by the FGF receptor are the ras-raf-map kinase pathway and the phospholipase C-gamma (PLC- γ) pathway. An adapter protein,

FRS2 couples the FGFR to MAP kinase and phosphatidylinositol-3 (PI-3) kinase activation, chemotactic response, and cell proliferation. The mitogenic response to FGF is likely to require activation of map kinase and possibly p38; however, the ability of FGFs to regulate differentiation and embryonic patterning may involve the ras, PLC- γ or novel pathways. For example, the anti-proliferative effects of FGF on chondrocytes are likely to be mediated through STAT1. Feedback inhibition of FRS2 is regulated by MAP kinase phosphorylation of multiple threonine residues in response to FGF, insulin, EGF, and PDGF extracellular signals. Differential signaling in diverse cell types is also a consequence of sequence differences between the four FGF receptors and possible alternative splicing within the cytoplasmic domain.

Two main classes of small molecule inhibitors have been identified. The SU compounds contain a substituted oxindole core (indolinone) while the PD compounds have a substituted pyrido[2,3-*d*]pyrimidine core. Crystallographic studies show that both SU5402 and PD173074 bind in the ATP-binding cleft of the FGFR1 tyrosine kinase domain between the two lobes of the kinase. It is likely that these molecules inhibit all FGFRs.

FGFR

| FAMILY MEMBERS | FGFR1 | FGFR2 | FGFR3 | FGFR4 | FGFR5 |
|---|--|---|--|---|----------------------------------|
| OTHER NAMES | Fms-like tyrosine kinase 2, c-fgr, FLG, FLT2, Cek-1 | BEK, KSAM, Cek-3, KGFR | JTK4, Cek-2, flg-2 | JTK2, TKF | Not found |
| MOLECULAR WEIGHT/STRUCTURAL DATA | 91.8 kDa, 822 aa | 92 kDa, 821 aa | 87.7 kDa, 806 aa | 87.9 kDa, 802 aa | 54.5 kDa, 504 aa |
| ISOFORMS | 18 | 19 | 3 | Not known | Not known |
| SPECIES | Human, mouse, rat, chicken, <i>Xenopus</i> | Human, mouse, <i>Xenopus</i> | Human, mouse | Human, mouse | Human |
| DOMAIN ORGANIZATION | 3 Ig-like C2-type domains, protein kinase domain | 3 Ig-like C2-type domains, protein kinase domain | 3 Ig-like C2-type domains, protein kinase domain | 3 Ig-like C2-type domains, protein kinase domain | 2 Ig-like C2-type domains |
| PHOSPHORYLATION SITES | Tyr ⁴⁶³ , Tyr ⁵⁸³ , Tyr ⁵⁸⁵ , Tyr ⁶⁵³ , Tyr ⁶⁵⁴ , Tyr ⁷³⁰ , Tyr ⁷⁶⁶ | Tyr ⁶⁵⁷ | Tyr ⁶⁴⁸ | Tyr ⁶⁴³ | Not known |
| TISSUE DISTRIBUTION | Placenta, brain, liver, lung, uterus | Brain, kidney, skin, lung, liver | Brain, kidney, testis | Myoblasts, lung, liver, kidney | Mesenchymal, kidney, brain, lung |
| SUBCELLULAR LOCALIZATION | Plasma membrane | Plasma membrane | Plasma membrane | Plasma membrane | Plasma membrane |
| BINDING PARTNERS/ASSOCIATED PROTEINS | FGF2 | FGF1 and FGF2 | FGF1 | FGF19 | Not known |
| UPSTREAM ACTIVATORS | FGF-1,2,4 | FGF-1,2,4,7 | FGF-1,2,4,9 | FGF-1,2, ? | FGF-1,2, ? |
| DOWNSTREAM ACTIVATION | Sprouty 2, Shp2, PLC- γ , STAT1, STAT3, MAPK, PI3K | Sprouty 2, Shp2, PLC- γ , STAT1, STAT3, MAPK, PI3K | Shp2, PLC- γ , STAT1, STAT3, MAPK, PI3K | Shp2, PLC- γ , STAT1, STAT3, MAPK, PI3K | Not known |
| ACTIVATORS | Not known | Not known | Not known | Not known | Not known |
| INHIBITORS | SU5402, PD166285, PD173074, PD161570, PD166866 | SU5402, PD166285, PD173074, PD161570, PD166866 | SU5402, PD166285, PD173074, PD161570, PD166866 | SU5402, PD166285, PD173074, PD161570, PD166866 | Not known |
| SELECTIVE ACTIVATORS | Not known | Not known | Not known | Not known | Not known |
| PHYSIOLOGICAL FUNCTION | Cell activation, chemotactic response, cell proliferation, cell differentiation, embryonic patterning | Cell activation, chemotactic response, cell proliferation, cell differentiation, embryonic patterning | Cell activation, chemotactic response, cell proliferation, cell differentiation, embryonic patterning | Cell activation, chemotactic response, cell proliferation, cell differentiation, embryonic patterning | Not known |
| DISEASE RELEVANCE | Pfeiffer and Kallmann syndrome, stem cell leukemia, lymphoma | Crouzon, Jackson-Weiss, Apert and Pfeiffer syndromes, Beare-Stevenson cutis gyrata syndrome | Achondroplasia, Crouzon syndrome, thanatophoric dysplasia, bladder cancer, cervical cancer, craniosynostosis adelaide type, multiple myeloma | Thyroid cancer | Not known |

Abbreviations

PD161570: 1-Tert-butyl-3-[6-(2,6-dichloro-phenyl)-2-(4-diethylamino-butylamino)-pyrido[2,3-d]pyrimidin-7-yl]urea

PD166285: 6-(2, 6-dichlorophenyl)-2-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-8-methyl-Pyrido[2, 3-d]pyrimidin-7(8H)-one dihydrochloride

PD166866: 1-[2-Amino-6-(3,5-dimethoxy-phenyl)-pyrido[2,3-d]pyrimidin-7-yl]-3-tert-butyl-urea

PD173074: N-[2-[[4-(diethylamino)butyl]amino-6-(3, 5-dimethoxyphenyl)pyrido[2, 3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea

SU5402: 3-[4-Methyl-2-(2-oxo-1,2-dihydro-indol-3-ylidene)methyl]-1H-pyrrol-3-yl]-propionic acid