Full Form of FGF: Fibroblast Growth Factor

FIBROBLAST GROWTH FACTOR (FGF)

Introduction

The fibroblast growth factor (FGF) is a growth factor that potentially acts on the repair and regeneration mechanism of tissue. It is pretentious in nature and promotes the proliferation of fibroblast and this growth factor comprises 22 protein members. FGFs are multifunctional and act through the binding and activation of the fibroblast growth factor receptors (FGFRs). The FGFRs are stimulated by the RAS/MAP kinase signalling pathway.

FGF has potential biological functions like it has been utilized for damaged tissue regeneration, which includes skin, blood vessel, cartilage, bone, tooth, ligament/tendons, muscles, adipose tissues, and nerve. The potential of tissue regeneration using FGF with respect to recombinant human FGF family is immense; several studies on FGF incorporation has been done. These include experiments like previous days FGF administrated directly to the site of wound, later study suggests that free FGF are degradable and lose their biological activity so after that FGFs are absorbed onto or encapsulated within the material to protect its biological activity. Nowadays, many types of material have been developed for carrying FGFs with their therapeutic potential.

Types and Biological Description:

Discovered in pituitary extracts in the year 1973, FGFs are widely expressed in cells and tissues.

- Two types of FGFs identified by nature: Acidic FGFs (FGF1) and the basic FGF (FGF 2) which were isolated from the brain and pituitary gland as fibroblast growth factors, and was found in both vertebrates and nonvertebrate both.
- In Zebrafish *(Danio rerio)*, ten FGFs have been found that is FGF2–4, 6, 8, 10, 17a, 17b, 18, 24.
- In *Xenopus*, six FGFs identified which are FGF2–4, 8–10; Chicken has 13 FGFs; FGF1–4, 8–10, 12, 13, 16, 18–20; mice have 22; FGF1–18, 20–23, and humans have 22 different FGF1–14, 16–23, whereas only three *Drosophila* FGF genes and two *Caenorhabditis elegans* FGF genes have been observed in invertebrates.
- The Human FGF family has 22 members: FGF1, FGF2, FGF3 (INT2), FGF4, FGF5, FGF6, FGF7 (KGF), FGF8 (AIGF), FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, and FGF23.
- Following phylogenetic analysis, human FGF family has been classified into seven subfamilies; FGF1, FGF4, FGF7, FGF8, FGF9, FGF11, and FGF19.

- The FGF1- FGF1 and 2,
- FGF4, 5, and 6,
- FGF3, 7, 10, and 22,
- FGF8, 17, and 18,
- FGF9, 16, and 20,
- FGF11, 12, 13, and 14, and
- FGF19, 21, and 23

- Alternatively, gene location analysis revealed that the human FGF gene family can be divided into six subfamilies: FGF1/2/5, FGF3/4/6/19/21/23, FGF7/10/22, FGF8/17/18, FGF9/16/20, and FGF11/12/13/14.

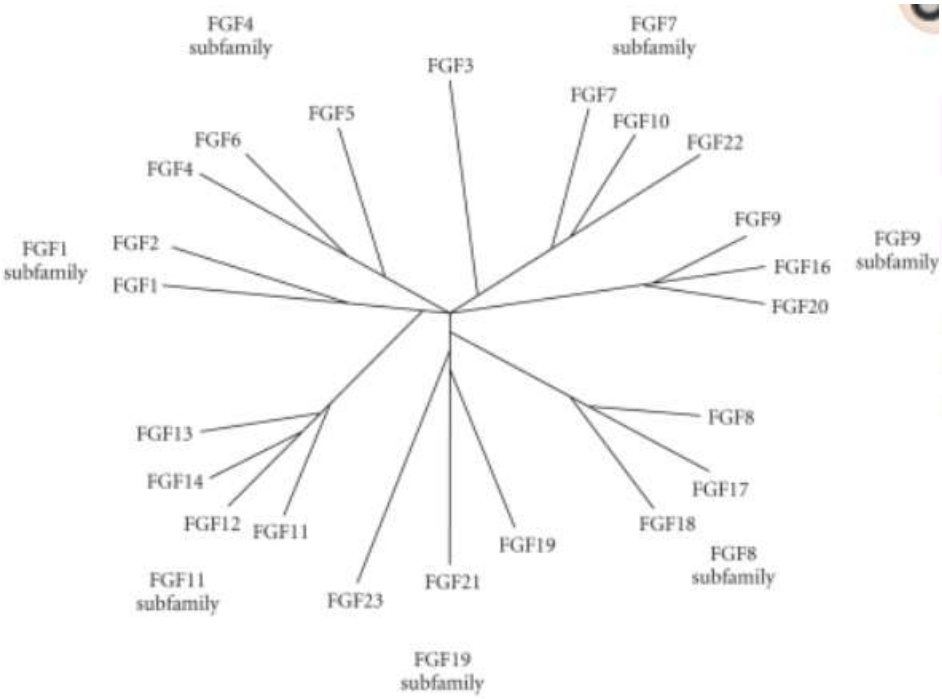

Fig. Phylogenetic analysis of FGF families

FGF Signalling Dynamics:

FGFs act as signalling molecules that binds and activates FGFRs.

i) Activated FGFRs mediates the signalling pathway by collecting specific molecules which are able to bind with phosphorylated tyrosine at the cytosolic part of the receptor which triggers a number of signalling pathway that leads to specific cellular responses.

ii) Then these serve as docking sites for the collection of Src homology -2(SH2) or phosphor tyrosine binding (PTB) domains of adaptors for proteins or signalling enzymes.

iii) Formation of signalling complex occurs by recruiting active receptors which result in a cascade of phosphorylation events.

iv) The most understandable pathways for FGFs are the RAS/MAP kinase pathway, PI3 kinase/AKT pathway, and PLCγ pathway. The figure below schematically describes the three pathways of the FGF signal, the RAS/MAP kinase pathway, PI3 kinase/AKT pathway, and PLCγ pathway.

v) Also, the figure demonstrates that FGFs stimulate tyrosine phosphorylation of the docking protein FRS, followed by forming the GRB2-SHP2-GAB-1 complex resulting in activation of RAS-MAP kinase pathway and PI3 kinase/AKT pathway.

vi) In PLCγ pathway, PLCγ upon its activation, brings about the hydrolysis of phosphatidylinositol, a process that yields IP3 and DAG and culminates by the activation of PKC.

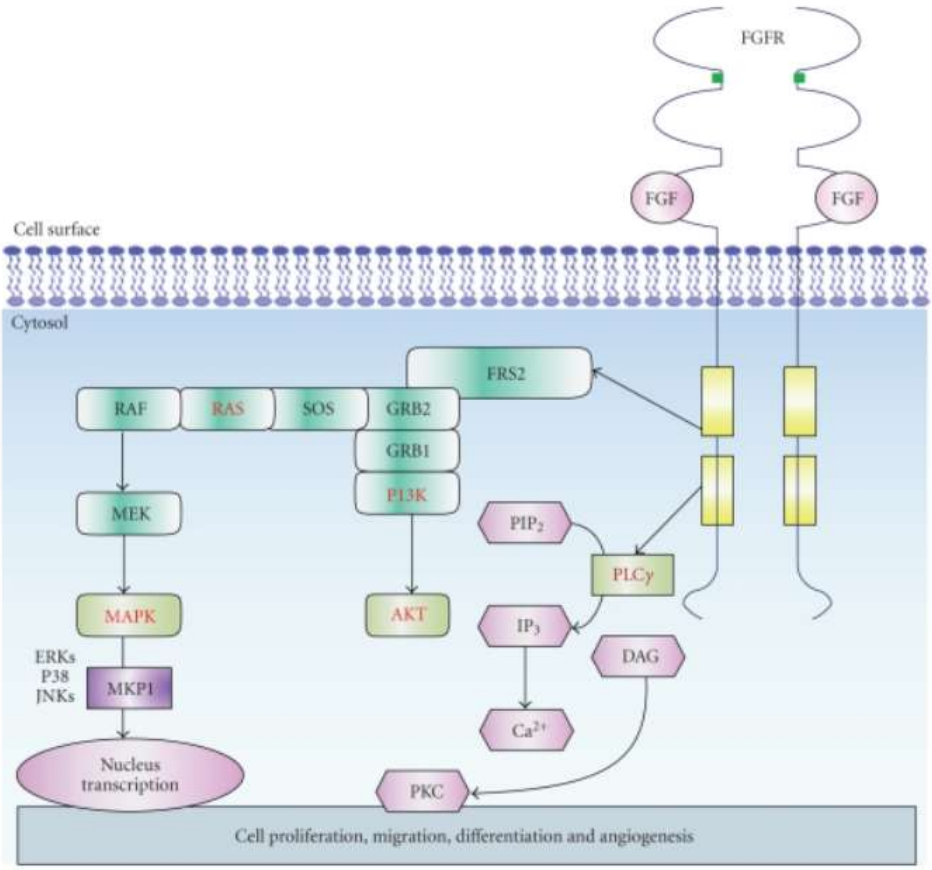

Fig. The FGF signalling pathway

Legend: FRS2: fibroblast growth factor receptor substrate 2, GRB: guanine nucleotide exchange factor, SOS: son of sevenless, RAS: monomeric G-protein, RAF: kinase, MEK: kinase, MKP1: MAP kinase phosphatase, PIP2: phosphatidylinositol (4,5)-bisphosphate, IP3: inositol triphosphate, DAG: diacylglycerol, PKC: protein kinase C.

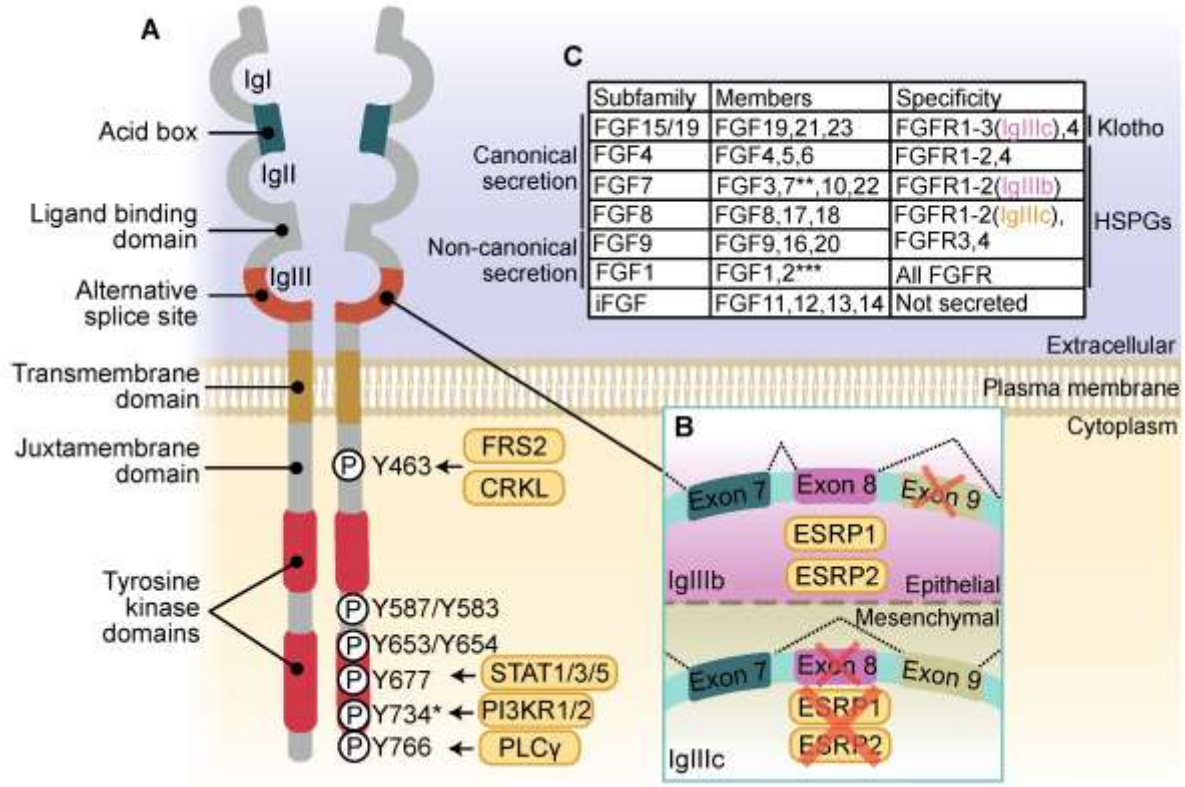

Fig. FGFR structure, activation and FGF interaction.

A. FGFR Structure. B. Activation: Alternative splicing gives rise to FGFR isoforms with diverse ligand binding affinities. ESRP1/2- Epithelial splicing regulatory proteins. C. FGF Subfamilies with their different FGFR-biding affinities and secretion mechanisms; intracellular FGFs (i-FGFs) are not secreted. FGFR need coreceptors, either Klotho or HSPG- Heparan sulfate proteoglycan to activate the various isoforms.

Biological Functions of FGFs:

FGFs have their physiological role by binding it to high-affinity tyrosine kinase FGFRs on the target cell surface, so the function of FGFs totally depends on the signalling pathway of FGFs between the FGFRs and FGFs family. Several studies have reported that FGFs functions in cell proliferation, migration, and differentiation and also are known to play a significant role in angiogenesis.

i) **Cell proliferation**

Following FGFs have functional roles in cell proliferation: FGF1, FGF2 target Preadipocyte, Endothelial cell, epithelial cell, fibroblast cell, neural stem cell; FGF4 targets Trophoblast stem cell; FGF7, FGF10 target Epithelial cell, and FGF18, Osteoblast, chondrocytes, osteoclast.

ii) **Cell migration**

In cell migration, FGF2 targets Astrocyte, myogenic cell; FGF4 targets Myogenic cell; FGF7 targets Epithelial cell, keratinocyte, and FGF8 Neural crest cell.

iii) Cell differentiation

In cell differentiation, FGF1, FGF2 take part which targets Neuroepithelial, FGF7 target Keratinocyte, and FGF20 targets Monkey stem cell.

iv) Angiogenesis

In angiogenesis, FGF1, FGF2 play a role in Endothelial cell targeting.

Inhibitors of FGFs:

FGFRs are crucial in the development of embryos, wound healing, angiogenesis cell proliferation and differentiation, FGFRs deregulation is known to be a driving factor for the development of tumours. Inhibitors of FGFRs can generally be divide into two groups, in accordance to their binding behaviour- type I, and type II.

Inhibitors of the Type-I category bind FGFRs in the DFG-in enzymatic active conformation in an ATP-competitive manner, while the binding of type II necessitates the DFG-motif to be flipped to the DFG-out state . Some chemical structure of FGFRs are given in the below figure.

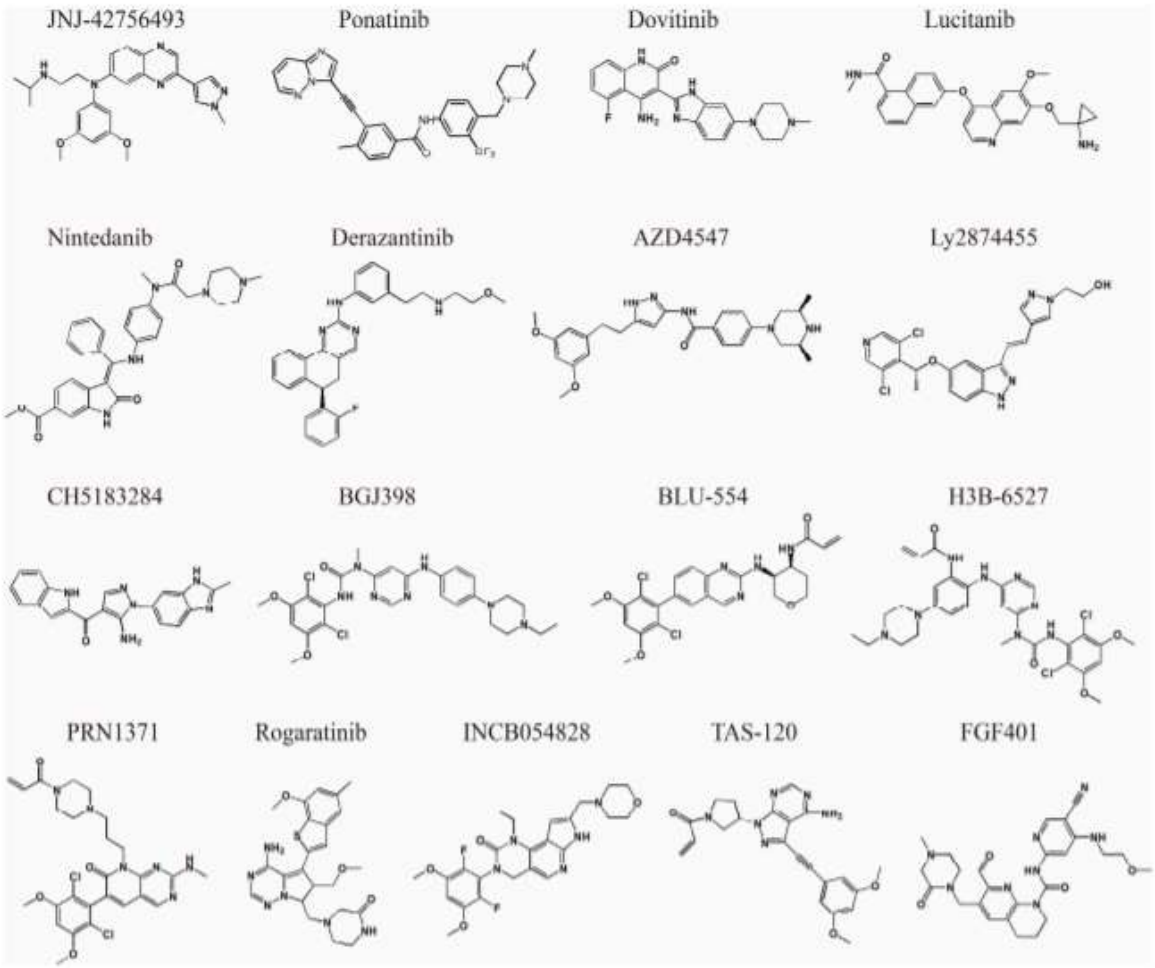

Fig. Structures of FGFR inhibitors

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