The Role of Fibroblast Growth Factor-Receptor Pathway Aberrations in Pediatric Diseases

Abstract

The fibroblast growth factor receptors play a crucial role in binding to fibroblast growth factor and are involved in various pathological conditions. These receptors consist of an extracellular ligand domain, a transmembrane helix domain, and an intracellular domain with tyrosine kinase activity. There are over 48 different isoforms of FGFR. Each FGF receptor in ligand-binding properties and kinase domains. The FGF/FGFR signaling pathway is implicated in various pediatric cancers and therefore are both non-selective and selective FGFR inhibitors available.Additionally, there are five distinct membrane FGF receptors dentified in vertebrates. All belonging to the tyrosine kinase superfamily. In this manuscript, the focus is based on ananalysis of the role of FGF receptor signaling pathways and aberrationsespecially in pediatric diseases. Erk 1 and Erk 2 seem to have an important role as a mediator of FGF signaling in different biological and developmental processes. FGF signaling plays an important role in conserved developmental functions in skeletal growth, palate closure, ear development, cranial suture ossification and neuronal development in the child. Aberrant FGF signaling causes different congenital disorders and different forms of cancer in childhood. Modulating FGF signaling is of great importance for the treatment of rare diseases in childhood.

Keywords: FGF-receptor-signaling pathway-aberration-pediatric-disease

Introduction

The fibroblast growth factors are a group of growth factors known as the FGF family. A total of 23 members of the FGF group are known to date: FGF-1 to FGF-23. FGFs are single-chain polypeptides with a mass usually between 16 and 22 kDalton. They are signaling proteins that are important and potent regulators of cell growth and differentiation. They play a key role in embryonic development. Accordingly, disturbances of FGF functions lead to severe developmental disorders in the embryonic period. In the adult organism, FGFs control tissue repair processes and are actively involved in the processes of wound healing and the formation of new blood vessels, as well as in the regeneration of nerves and cartilage tissue. FGFs have been detected in almost all tissues of the organism. FGFs control and alter or usually stimulate the proliferation, migration and differentiation of cells, especially endothelial cells, but also smooth muscle cells and fibroblasts. The complex process of angiogenesis is essentially controlled and influenced by growth factors of the FGF family. Prototypes of the FGF family are FGF-1 (acidic-FGF) and FGF-2 (basic-FGF). FGF molecules bind to their specific receptors (FGFR = FGF receptor) on the cell surface. FGFRs are receptor tyrosine kinases which -after binding the ligand FGF-are activated by autophosphorylation and initiate an intracellular signaling cascade with subsequent gene activation. FGFRs consist of an extracellular region containing three immunoglobulin-like (IG-like) protein domains (D1-D3), a single transmembrane helix, and an intracellular protein domain with tyrosine kinase activity. There are four FGFRs: FGFR1, FGFR2, FGFR3, FGFR4. Alternative mRNA splicing of the FGFR1-3 receptors results in additional forms of FGFRs (a total of seven FGFRs are known), which are designated "b" and "c". FGF-1 is the only ligand that binds to all seven cell surface receptors. The actual signaling complex formed at the cell membrane after binding of FGF and FGFR is called a ternary complex, which consists of two identical FGF ligands, two identical FGF receptor units and either one or two heparan sulfate chains. A special feature of the mechanism of action of FGFs is that it is significantly enhanced by the particularly high affinity of FGFs for proteoglycans, heparan sulphates and heparin (glycosaminoglycan). This is why the growth factors of the FGF family were previously also referred to as heparin-binding growth factors (HBGFs).

23 Fibroblast Growth factorsand Co-Factors

FGF-1 is the most active growth factor of the FGF family (1-53). It consists of 141 amino acids (1-52). The FGF-1-encoding gene is located on chromosome 5. Due to its comprehensive binding capacity with all FGF receptors, the biological, mitogenic cell effects are particularly pronounced and characterized by the initiation of cell proliferation, migration and differentiation. FGF-1 has a particular effect on endothelial cells, but also on many other cell types. Due to the particularly pronounced angiogenic activity of FGF-1, FGF-1 has recently been studied more intensively in clinical research and used in various clinical studies in human medicine (1-53). The plasma half-life of FGF-1 after intramyocardial injection is between 0.4 and 4.6 hours. High purification of FGF-1 by SDS-polyacryamide gel electrophoresis.*FGF-2 (b-FGF)* has a similar molar mass to FGF-1; its structure is more than 50 % identical to that of FGF-1. The FGF-2 coding gene is localized on chromosome 4. The effects of FGF-2 are similar to those of FGF-1, but not quite as pronounced. It is also produced by adipocytes and influences bone metabolism.

FGF-3 consists of 240 amino acids, its structure is approximately 40 % homologous with FGF-1; the coding gene is located on chromosome 11 (1,6,7). The physiological effects of FGF-3 are still poorly understood, butit is possible that FGF-3 may be particularly important during embryonic development. *FGF-4 (formerly K-FGF or hst1)* consists of 206 amino acids, is 40 % homologous with the structure of FGF-1-3, and the coding gene is located on chromosome 11. FGF-4 is frequently found in tumors, especially in gastric tumors. In healthy adult tissues, FGF-4 is only present in low concentrations. FGF-5 consists of 251 amino acids, the coding gene is located on chromosome 4. *FGF-5* apparently plays an important role during embryonic development, but in adult tissues, FGF-5 is only present in very low concentrations. *FGF-6* is 70 % homologous with FGF-4. The coding gene is located on chromosome 12. Little is known about its effects, but FGF-6 may play a role in wound healing. *FGF-7* was first called keratinocyte growth factor; it has a specific proliferative effect on epithelial cells. The coding gene is located on chromosome 15.*FGF-8* (gene localization on chromosome 10) may play a key role in the formation of the extremities during embryonic development. *FGF-9*, initially referred to as glioma-derived growth factor

(GDGF), stimulates in particular the proliferation and activation of glial cells in the brain.*FGF-10 to FGF-22*: Although the structures and amino acid sequences of these growth factors have been described, little is known about the detailed functions of these proteins.FGF-18 stimulates the formation of cartilage in model organisms when injected intraarticularly. A recombinantly produced human FGF-18 is currently undergoing clinical trials.*FGF-23* is secreted by osteocytes and is an important regulator of the phosphate and vitamin D balance. FGF-23 stimulates the excretion of phosphate by the kidneys. The task of FGF-23 is to keep phosphate levels in the blood constant despite varying phosphate intake with food. Increased blood levels of FGF-23 lead to a drop in the phosphate level in the blood (hypophosphatemia), reduced production of 1,25(OH)2 vitamin D and rickets or bone softening.Reduced blood levels of FGF-23 lead to increased phosphate levels in the blood (hyperphosphatemia), increased production of 1,25(OH)2 vitamin D, soft tissue calcification, excessive bone formation (hyperostosis) and reduced life expectancy. In kidney patients who have to start dialysis treatment, increased FGF-23 levels are associated with increased mortality. FGF-23 binds to the FGF receptor 1c and the co-receptor Klotho.Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phos-Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phos-Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phosphoric effect.

Co-Factors

Eight factors belonging to the fibroblast growth factor family are known (1-53). These are acidic FGF (aFGE), basic FGF (bFGF), int-2, Kaposi sarcoma FGF (K. FGF), also known as the product of hst-l oncogene, FGF5, FGF6, keratinocyte growth factor (KGF) and androgeninduced growth factor (AIGT). These polypeptides are 35-55% identical in their amino acid sequence and the aquainted genes have similar exon- intron structures. In contrast to the other members of the family, aFGF and bEGF lack a signal sequence, and the mechanism of their secretion is not yet fully understood. The most widely studied FGEs, aFGf and bFGE, appear to elicit very similar biological responses inmost target cell types. These two factors have effects in vito on a wide variety of cells of mesodermal, neutroectodermal as well as endodermal origin. They support the survival of neural cells and stimulate the proliferation of many cell types including fibroblasts, endothelial cells, smooth muscle cells, hepatocytes and skeletal myoblasts. aFGF and bFGE can also affect cellular differentiation: both factors stimulate the outgrowth by Polz rat pheochromocytoma cells and are capable of blockingmyoblasts of the skelet differentiation. In addition, bFGF has been claimed to enhance the cloning efficiency of hematopoietic progenitor celis. Other PGEs may have more specific functions. The mitogenic activity of KGF seems to be restricted to epithelialcelllines.In vitrobFGE has been implicated in mesoderm induction in Xenopus embryos. Disruption of the FGF signaling by expression of a dominant negative mutant of the Xenopus FGF receptor has recently been shown to inhibit the formation of mesodermal tissues. Other members of the FGF l family also seem to function in developmental processes. In addition to inducing proliferation and migration of endothelial cells in culture, bFGF and aFGF also induce neovascular structures in vivo. It was recently claimed that the progression and neovascularization of fibro sarcomas of transgenic mice carrying the bovine papillomavirusgenome is correlated with enhanced secretion of bFGF.

Ligand binding specificity

The ligand binding represents the first step in activating the FGFR signaling cascade. FGFR`s are based on three immunoglobulin-like domains (IgI-III) (48). The ligand binding specificity depends on splicing of the C terminus of the Ig III domain, which will be encoded by exon 8 and 9 to produce FGFRb or FRGFRc isoforms, which correlate to receptors of epithelial or mesenchymal tissues (48).

Intracellular signaling with protein interactions (modulators)of FGFR 1-4

Known intracellular protein interactions of FGFR1-4 are Frs2 and 3, CrkL and II, Shb, SH2, Grb14, Stat1 and 3, Src, SH2, SH3 and p85 protein (48). Some interactions depend on additional FGFR1-4 mutations (48). FGF signaling seems to be the major driver of Erk1 and 2 activation in many different developmental processes. For example, FGF4-Erk 1 and 2 regulate the primitive endoderm specification. Erk 1 and 2 signaling is necessary for primitive endoderm formation (48). FGF-Erk1/2 signaling regulates epithelial-mesenchymal interactions in the limb (48). Genetic disruption of FGF-10 or FGFR2b results in complete agenesis of the limbs (49).Conditional disruption of FGF8 and FGF4 or FGFR2 in epithelial tissue causes complete agenesis of the hindlimb (50). FGFR3 functions through Erk1/2 for inhibiting chondrocyte hypertrophic differentiation (48). Loss of FGFR3 function causes long bone overgrowth, activated mutations in FGFR3 cause skeletal dwarfism like achondroplasia in childhood (48). Erk1/2 and STAT 1 seem to regulate FGFR3 mediated inhibition of chondrocyte proliferation (51,52).FGFR1 is part of complex binding with FGF23 and Klotho in X-linked hypophosphatemia (53). *Klotho-FGFR1-FGF23 trimeric complexsignaling* plays an important role in X-linked hypophosphatemia in childhood and inhibition of this complex could diminish the level of FGF in the kidney in this disease (53).

Chemical structures of FGFs

The first FGFs were discovered and their chemical structures are described in the 1970s (1-53). Initially, it was assumed that they acted exclusively on fibroblasts. However, it was later discovered that FGFs have much more general functions - especially proliferation and differentiation - and can act on almost all cells. Today, even FGFs are known that there is no effect on fibroblasts, FGF-7 and FGF-9. FGF-1 and FGF-2 were initially obtained and isolated from the brain of cattle, and later the structures of the human growth factors FGF-1 and FGF-2 were also described. The enhancing effect of heparin and heparan sulphates on the function of FGFs was recognized early on. To date, 23 different sub-types of the FGF family have been described. The different FGF types have intensive mitogenic activities and are of great importance for organ differentiation and development in the embryonic period. They regulate cell proliferation, migration and differentiation. Regular cell and tissue differentiation is not possible without FGFs. In adult tissues and organs, FGFs - especially FGF-1 - have an extremely intensive activity on the induction of angiogenesis.This property of FGFs has recently aroused the interest of medical research, as angiogenesis can be used as a therapeutic principle in disease states and disorders in which arterial blood flow is impaired, coronary heart disease (CHD) and peripheral artery disease (PAD). Coronary heart disease (CHD) and peripheral arterial occlusive disease (PAD). Hypoxia and ischemia trigger the secretion of FGF-1 and

FGF-2, resulting in an up-regulation of FGF receptors in the tissue. Hypoxia and ischemia trigger the secretion of FGF-1 and FGF-2, resulting in an up-regulation of FGF receptors in the tissue.Clinical studies with patients suffering from severe coronary heart disease have demonstrated FGF-1-induced new vessels in the human heart muscle, as well as a local increase in blood flow with a reduction in angina pectoris symptoms. FGFs, especially FGF-1, also have a wound healing-promoting effect in cases of wound healing disorders. FGFR signaling can also lead to the activation of various downstream effectors, such as cell, survival, migration, and differentiation (8,25,51). These functions are essential for normal development and tissue homeostasis. Dysregulation of FGFR signaling can lead to various diseases, including cancer, skeletal dysplasia, and developmental disorders (1,4,7,9). Understanding the complex functions of FGFR signaling is crucial for developing targeted therapies for different pediatric diseases in the future (1-53).

Conclusion

The fibroblast growth factor family plays a key role in various developmental processes such as brain patterning, branching morphogenesis, and limb development. Researchers are currently exploring the therapeutic potential of FGFs in promoting cell growth, protecting cells, and stimulating blood vessel formation. Recent studies have highlighted the important functions of the endocrine-acting FGF19 subfamily in regulating bile acid, glucose, and phosphate levels, leading to increased interest in the potential medical applications of these molecules. There is a potential in treating metabolic syndromes, skeletal dysplasia, cancer and hypophosphatemic disorders in childhood by altering fibroplast growth factor signaling pathways.

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