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REVIEW ARTICLE

Fibroblast growth factor (FGF) signaling in development and skeletal diseases

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Abstract Fibroblast growth factors (FGF) and their receptors serve many functions in both the developing and adult organism. Humans contain 18 FGF ligands and four FGF receptors (FGFR). FGF ligands are polypeptide growth factors that regulate several developmental processes including cellular proliferation, differentiation, and migration, morphogenesis, and patterning. FGF-FGFR signaling is also critical to the developing axial and craniofacial skeleton. In particular, the signaling cascade has been implicated in intramembranous ossification of cranial bones as well as cranial suture homeostasis. In the adult, FGFs and FGFRs are crucial for tissue repair. FGF signaling generally follows one of three transduction pathways: RAS/MAP kinase, PI3/AKT, or PLCγ. Each pathway likely regulates specific cellular behaviors. Inappropriate expression of FGF and improper activation of FGFRs are associated with various pathologic conditions, unregulated cell growth, and tumorigenesis. Additionally, aberrant signaling has been implicated in many skeletal abnormalities including achondroplasia and craniosynostosis. The biology and mechanisms of the FGF family have been the subject of significant research over the past 30 years. Recently, work has focused on the therapeutic targeting and potential of FGF ligands and their associated receptors. The majority of FGF-related therapy is aimed at age-related disorders. Increased understanding of FGF signaling and biology may reveal additional therapeutic roles, both in utero and postnatally. This review discusses the role of FGF signaling in general physiologic and pathologic embryogenesis and further explores it within the context of skeletal development.

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Introduction

The fibroblast growth factor (FGF) family consists of structurally related polypeptides involved in several physiologic processes. Highly conserved, these growth factors are found in thousands of animal species, ranging from nematode and zebra fish to mouse and human.[1] FGFs play a role in cellular proliferation, migration, and differentiation, mitogenesis, angiogenesis, embyrogenesis, and wound healing.[2] It is by the activation of various signal transduction pathways that FGFs mediate multiple developmental processes.[3]

Mammals contain 18 FGF types (FGF1—FGF10 and FGF16—FGF23), which have been grouped into six distinct subfamilies based on phylogeny and sequence homology.[4] FGFs share a similar internal core and have a characteristically high binding affinity for both heparin and fibroblast growth factor receptors (FGFRs). FGFRs are tyrosine kinase receptors that contain a heparin-binding sequence, three extracellular immunoglobulin-like domains (D1—D3), a hydrophobic transmembrane domain, and a split intracellular tyrosine kinase domain.[5–7] The mammalian FGFR family consists of four members (FGFR1—FGFR4). The amino acid sequences of each receptor are highly conserved, with differentiation occurring only in their ligand affinity and tissue distribution.[8] Characteristic of FGFRs is the acid box, which is a serine-rich, acidic sequence in the linker between D1 and D2.[4] The acid box and D1 domain are thought to play a role in receptor autoinhibition.[9] The D2—D3 fragment is required for ligand specificity and binding. In vertebrates, four genes encode the FGFRs (*FGFR1-4*), and undergo alternative splicing in their extracellular domain to produce many varieties of FGFR1-4 with varying affinities for their ligands.[10]

Many data suggest the role of FGF signaling in fundamental developmental pathways, including embryogenesis and the development of organ systems.[11] Aberrations in this pathway have been associated with human disease. Cancers from various tissue types have been linked to dysregulated FGF signaling.[12] Faulty signaling is also associated with many congenital syndromes. Many other conditions, including skeletal dysplasias,[13] deafness,[14] and lacrimo-auriculo-dento-digital syndrome,[15] result from FGF signaling errors. Pathological conditions are mostly due to gain- or loss-of-function mutations in the ligands themselves or their receptors.[4]

The degree of involvement of FGF signaling in both normal and pathologic development has led to considerable research on the therapeutic applications and targeting of the FGF family. Recombinant FGFs and small-molecule FGF receptor kinase inhibitors have been used in the treatment of cancer and cardiovascular disease. Emerging research has also demonstrated their potential pharmacologic role in preventing chemotherapeutic side effects as well as treating metabolic syndrome.[16] In this article, we review the current knowledge of FGF signaling in both physiologic and pathologic development and also address recent discoveries regarding its therapeutic potential.

The FGF signaling system

Positive regulation of signaling

The FGF signaling cascade is initiated by the binding of FGF ligands to FGFRs. Following FGF binding, a ligand-dependent dimerization event takes place in which a complex is formed that consists of two FGFs, two heparin sulfate chains, and two FGFRs. Each ligand binds to both receptors, and the receptors make contact with one another via a patch on the D2 domain.[4] This facilitates the transphosphorylation of each receptor monomer by an intrinsic tyrosine kinase domain. At least seven phosphorylation sites have been identified for FGFR1 (Tyr^{163}, Tyr^{583}, Tyr^{585}, Tyr^{653}, Tyr^{654}, Tyr^{730}, and Tyr^{766}).[17–19] Phosphotyrosine groups serve as docking sites for adaptor proteins that regulate downstream signaling.[20] The FGF system is associated with several downstream signaling pathways; the best understood are the RAS/mitogen-activating protein (MAP) kinase pathway, the phosphoinositide 3 (PI3) kinase/AKT pathway, and the phospholipase C gamma (PLCγ) pathway (Fig. 1).[21]

The main downstream pathway associated with FGF signaling is the RAS/MAP kinase pathway. This pathway is implicated during cellular proliferation and differentiation.[22] MAP kinases are serine/threonine-specific protein kinases that act in response to extracellular stimuli and regulate various cellular processes. Examples of MAP kinase effectors include c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated kinase.[23] After an FGF ligand binds to its receptor, an integral step in the signaling pathway is the phosphorylation of the tyrosine residues on the docking protein fibroblast growth factor receptor substrate 2 alpha (FRS2α). This permits binding of adaptor proteins that are associated with signal activation.[24,25] An FRS2 complex consisting of FRS2α, guanine nucleotide exchange factor 2 (GRB2), GRB2-associated binding protein 1 (GAB1), the son of sevenless (SOS), and tyrosine phosphatase (SHP2) is then formed that facilitates activation of the RAS/MAP kinase[26] and also PI3 kinase/AKT pathways.[27]

The PI3 kinase/AKT pathway is associated with cellular survival and cell fate determination.[26,28] This pathway may also impact cell polarity.[29] Like the RAS/MAP kinase pathway, the PI3 kinase/AKT pathway is initiated when an FRS2 signaling complex forms. GAB1 protein then links activated FGFRs with PI3 kinase. Downstream of PI3 kinase, phosphoinositide-dependent kinase and AKT (an anti-apoptotic protein kinase) are activated.[21]

Another target molecule of activated FGFR is PLCγ. This pathway is activated upon the binding of the PLCγ molecule to the phosphorylated Tyr^{766} of the receptor.[21] Inositol triphosphate (IP3) and diacylglycerol (DAG) are then generated by the hydrolysis of activated PLCγ. DAG and cytoplasmic calcium released from the endoplasmic reticulum in response to IP3 together activate protein kinase C (PKC).[21] Though it has not been completely elucidated, the PLCγ kinase pathway influences cell morphology, migration, and adhesion.[26,28]