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Review

Fibroblast growth factors, old kids on the new block

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ABSTRACT

The fibroblast growth factors (FGFs) are a family of cell intrinsic regulatory peptides that control a broad spectrum of cellular activities. The family includes canonic FGFs that elicit their activities by activating the FGF receptor (FGFR) tyrosine kinase and non-canonic members that elicit their activities intracellularly and via FGFR-independent mechanisms. The FGF signaling axis is highly complex due to the existence of multiple isoforms of both ligands and receptors, as well as cofactors that include the chemically heterogeneous heparan sulfate (HS) cofactors, and in the case of endocrine FGFs, the Klotho coreceptors. Resident FGF signaling controls embryonic development, maintains tissue homeostasis, promotes wound healing and tissue regeneration, and regulates functions of multiple organs. However, ectopic or aberrant FGF signaling is a culprit for various diseases, including congenital birth defects, metabolic disorder, and cancer. The molecular mechanisms by which the specificity of FGF signaling is achieved remain incompletely understood. Since its application as a druggable target has been gradually recognized by pharmaceutical companies and translational researchers, understanding the determinants of FGF signaling specificity has become even more important in order to get into the position to selectively suppress a particular pathway without affecting others to minimize side effects.

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It has been gratifying for early basic researchers on fibroblast growth factors (FGF) that their Cinderella in the growth factor arena is now drawing so much attention as a druggable target by pharmaceutical companies and translational researchers. The first two prototype FGFs, FGF1 and FGF2, discovered in the early seventies, were designated acidic and basic FGF (aFGF and bFGF) based on

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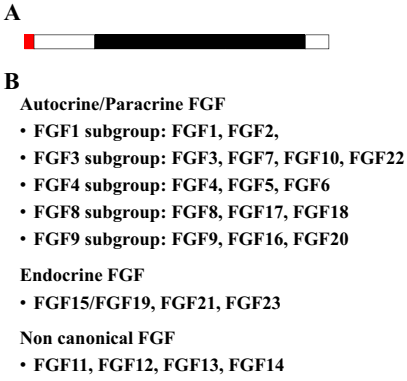

Fig. 1. The FGF family. (A) Schematic of the FGF. Red box, signal peptide; open boxes, non-conserved, N- and C-terminal domains; solid box, conserved core domain. (B) FGF sub-families. The 22 FGFs are grouped into 7 subfamilies based on sequence homology and function. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

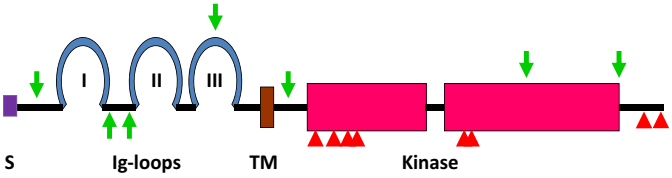

Fig. 2. Topology of a prototypical FGF receptor tyrosine kinase. S, signal peptide; I, II, III, immunoglobulin-like domain 1, 2, and 3; TM, transmembrane domain. Red box, tyrosine kinase domain that is separated by a kinase insertion sequence; green arrows, alternative splice sites; triangles, tyrosine phosphorylation sites. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

their activity to stimulate fibroblast proliferation and their isoelectric point [1,2]. Subsequently 20 more FGF homologues have been identified as the family members in mammals [3–20]. Genes coding for a large number of FGFs were cloned based on homology in the amino acid sequence. It was soon found that the name "fibroblast growth factor" was not the best name to describe the diverse functions of the family members and their receptors since many FGFs do not even have receptors expressed in fibroblasts and elicit no activity in fibroblasts. In addition, many FGFs induce diverse cellular responses beyond growth promoting signals in different target cells. Despite being misleading to some degrees, the name "fibroblast growth factor" followed by a number (FGF1, 2, 3, 4, etc.) has been preserved and replaced numerous other names used to describe either tissue origin, target, function, or properties of the FGF molecule. FGF signaling has long not been a favorite of pharmaceutical companies largely because of the diversity of both ligands and receptors in the family, its wide range of target cell types, diverse functions, and complexity of FGF signals that intersect either directly or indirectly with multiple pathways. The complexity of the multi-subunit transmembrane FGF signaling complex in both the extracellular and the intracellular portions has also been a major factor. Several cofactors are integral regulatory components of the FGF signaling complex. These include the chemically heterogeneous heparan sulfate (HS) cofactors, and in the case of endocrine FGFs, the Klotho coreceptors. These cofactors and coreceptors not only participate in FGF receptor-binding specificity and affinity, but also in specifying signaling activities. Therefore, a full understanding of the molecular mechanisms underlying the specificity of FGF signaling is important for therapeutic usage of FGFs.

1. FGF signaling axis

1.1. FGFs

The FGFs are single chain polypeptides that are tissue regulatory molecules controlling a broad spectrum of cellular processes in both embryonic and adult tissues. The polypeptides have one conserved domain flanked by non-conserved extensions (Fig. 1A). Most FGFs have an N-terminal signal peptide that facilitates secretion through classical mechanisms. However, several FGFs, including FGF1 and FGF2, do not have a cleavable signal peptide and are secreted in a non-conventional manner. Seven FGF subfamilies have been defined based on their sequence homology and function (Fig. 1B). These FGF subfamilies can also be divided into two general groups, the canonical FGFs comprising paracrine or autocrine-acting FGF1-10, FGF16-18, FGF20, and FGF22 and the endocrine-acting FGFs, FGF15 (mouse)/FGF19 (human), FGF21, and FGF23; and the non-canonical FGFs comprising FGF11-14. The canonical FGFs elicit regulatory functions through high affinity binding to and activating FGF receptors (FGFR). An autocrine canonical FGF acts on the cells of origin as a self-stimulator, and a paracrine FGF is secreted by one cell and acts on another locally within tissues. In contrast, the endocrine FGF originates at a distal organ site and reaches the target through the blood circulation in a classical endocrine mode of action. The non-canonical FGFs do not bind to the FGFR but elicit their activities intracellularly, such as through interaction with voltage-gated sodium channels and calcium channels [21–23].

1.2. FGFRs

The FGFR is a single chain transmembrane tyrosine kinase that consists of a ligand binding extracellular domain, a single transmembrane domain, and an intracellular tyrosine kinase domain that is separated into two parts by an insertion domain (Fig. 2). The mammalian FGFR is encoded by four highly homologous genes [24–27]. Except for the Fgfr4 gene for which only one splice isoform occurs naturally [28], other three Fgfrs have been found to encode multiple splice variants. These splice variants generate diversity of sequence and function in the ligand-binding extracellular domain and the intracellular substrate-binding and kinase domains [29]. It has been speculated that the combination of FGFR1 splice variation sequences can potentially encode up to 256 splice isoforms [29]. FGFR3 and FGFR4 have 3 immunoglobin (Ig)-like domains in the extracellular domains. As a consequence of alternative splicing, the extracellular domain of both FGFR1 and FGFR2 can contain either 2 or 3 Ig-like loops. The presence of the first Ig-loop modulates the affinity for both FGF and FGFR-binding heparin/heparan sulfate [30–32]. Two major isoforms generated by alternative splicing in the second half of Ig-loop III, namely IIIb and IIIc in FGFR1, FGFR2, and FGFR3 have been reported. This variation defines ligand-binding affinity and specificity of FGFR1-3 [33,34]. Several other splice variations at the extracellular domain have been found in FGFR2, although the functional significance of these variants remains unknown [35]. The role of the alternatively spliced dipeptide VT (valine-threonine) in the intracellular juxtamembrane domain of FGFR is controversial. It has been shown that the presence of VT is required for FGFR to bind FRS2α and FRS2β and therefore contributes to signaling specificity [36,37]. However, other reports show that the dipeptide is dispensable for the binding of FRS2α and FRS2β to FGFR1 even though it enhances the binding affinity between substrate and the receptor kinase [38]. The variations in the kinase domain and C-terminal tail following the kinase domain of FGFRs have only been found in cancer cells [29,39]. Although the kinase domains of the four FGFR isotypes are highly homologous (>80%) in the primary amino acid sequence and share common tyrosine phosphorylation sites (Fig. 2), the four FGFRs elicit receptor-, cofactor-, coreceptor-, and cell type-specific

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