Review

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Careless talk costs lives: fibroblast growth factor receptor signalling and the consequences of pathway malfunction

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Since its discovery 40 years ago, fibroblast growth factor (FGF) receptor (FGFR) signalling has been found to regulate fundamental cellular behaviours in a wide range of cell types. FGFRs regulate development, homeostasis, and repair and are implicated in many disorders and diseases; and indeed, there is extensive potential for severe consequences, be they developmental, homeostatic, or oncogenic, should FGF–FGFR signalling go awry, so careful control of the pathway is critically important. In this review, we discuss the recent developments in the FGF field, highlighting how FGFR signalling works in normal cells, how it can go wrong, how frequently it is compromised, and how it is being targeted therapeutically.

Overview of FGF in physiology and pathology

FGFs are a family of 18 either locally or hormonally acting signalling factors that function through four FGF receptor tyrosine kinases (RTKs) to elicit a range of context-dependent cellular outcomes, including proliferation, survival, migration, and differentiation. FGFs are vital to a number of developmental and homeostatic processes and are also primary drivers in the repair response. Given their inherent complexity and critical roles in physiological processes, dysfunction in the FGF family leads to a number of developmental disorders and is consistently found to be a driving force in cancer. Deregulation of the FGF family can take many forms, including receptor amplification, activating mutations, gene fusions, and receptor isoform switching, which presents unique challenges to overcome in order to return FGF function to normal.

In this review, we cover recent studies that highlight new insights into how FGFs signal and their novel roles in development, homeostasis, and repair. We also cover the expanding field of how, and how frequently, FGF signalling goes awry in cancer. Finally, we discuss the many exciting approaches being taken to target aberrant FGF signalling and how they are currently performing in clinical trials.

FGF signalling and regulation

The 18 FGFs cluster into five paracrine subfamilies and one endocrine subfamily [1]. Paracrine FGFs are locally acting and are involved in a plethora of processes, ranging from organogenesis to tissue homeostasis, whereas endocrine FGFs act more globally and are involved in metabolic processes, such as glucose metabolism and phosphate homeostasis [1]. FGFs signal through FGFR tyrosine kinases, of which there are four signalling subtypes. FGFRs are composed of three extracellular immunoglobulin (Ig) like domains linked to an intracellular kinase via a transmembrane α-helix (Figure 1A). Alternate splicing of the extracellular Ig-like domains of FGFRs 1–3 creates 'b' and 'c' isoforms, which differ in their tissue distribution and ligand specificity (reviewed in [2]). A fifth subtype also exists, FGFRL1, which lacks an intracellular kinase domain but is still capable of binding to FGFs [3]. Mice deficient in FGFRL1 exhibit a number of malformations, including skeletal and heart defects [4]. Interestingly, mice lacking the intracellular portion of FGFRL1 do not exhibit any of these abnormalities, suggesting that FGFRL1 may function as a decoy receptor [5]. However, others have demonstrated that FGFRL1 has a signalling function, enhancing basal ERK signalling through the recruitment of the phosphatase SHP-1 in pancreatic beta cells [6].

Paracrine FGFs utilise heparan sulfate proteoglycans (HS) as binding partners, which stabilise the receptor–ligand structure and enhance resistance to proteolysis, while limiting the action of these FGFs to their site of initial release [7]. Endocrine FGFs exhibit weak interactions with HS, thereby allowing their diffusion away from the site of release and entry into the circulation where they can act hormonally [8]. In place of HS, endocrine FGFs utilise Klotho co-receptors in their receptor binding [8]. Thus, interaction with their respective binding partners provides tight control over the action of different FGF families. Indeed, removing the ability of a paracrine FGF to bind HS, coupled with the substitution of its C-terminal domain with that of an endocrine FGF to facilitate Klotho

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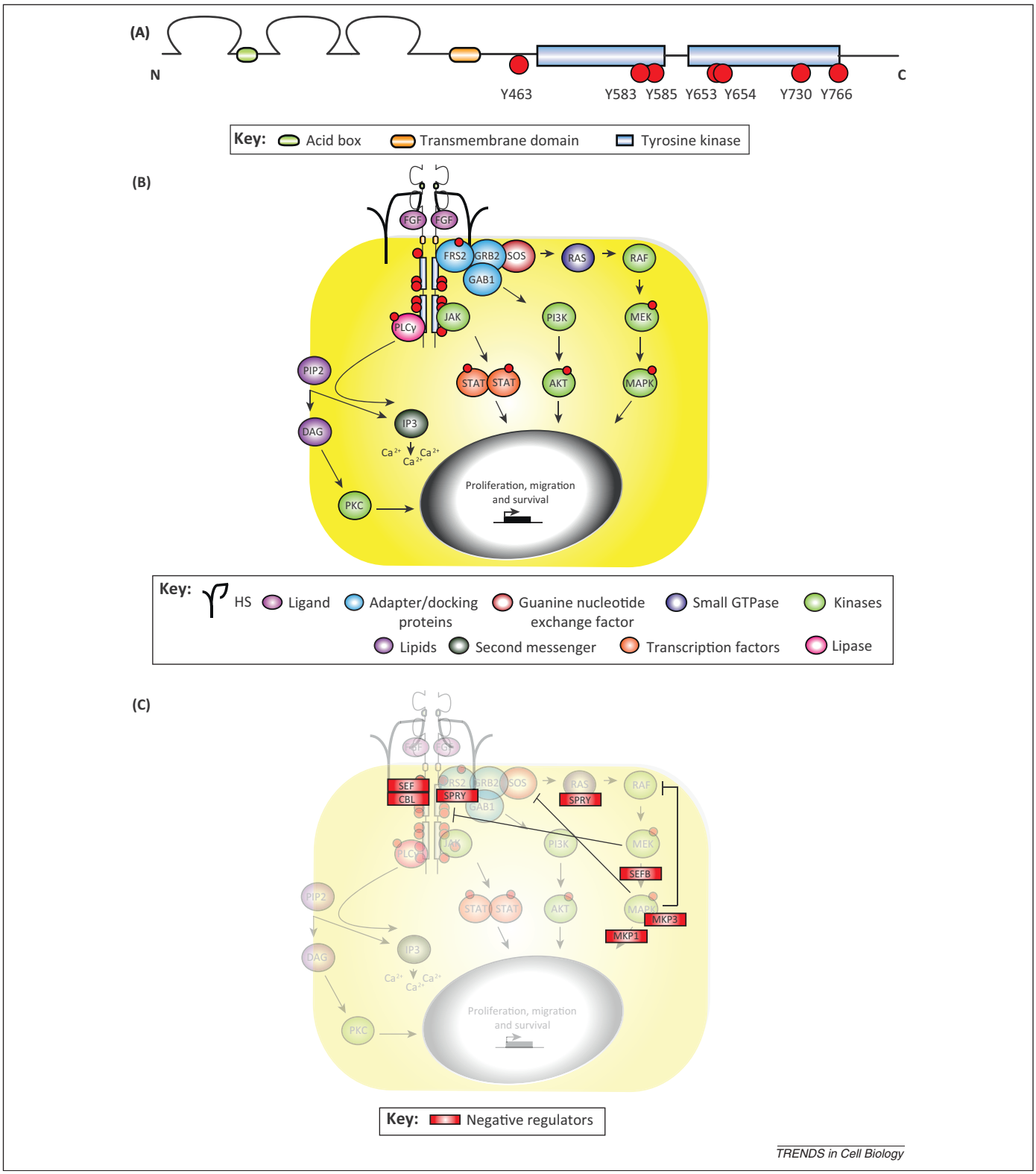

Figure 1. Fibroblast growth factor receptor (FGFR) signalling. **(A)** Schematic representation of FGFR1. The extracellular domain of FGFR1–4 is comprised of three Ig like loops. The region between the C terminal portion of the second loop and the N terminal portion of the third is responsible for ligand binding. Alternative splicing of these loops leads to varying affinity for different FGF ligands. The acid box (green) between the first and second Ig loops is involved in heparan sulfate proteoglycan (HS) binding. The transmembrane domain is shown in orange. The intracellular portion of the receptor consists of a split kinase domain (blue). Upon ligand binding, dimerisation and subsequent transphosphorylation of the receptor occurs on seven tyrosine residues (red circles). This induces four key downstream pathways: mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, phospholipase Cγ (PLCγ) and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) **(B)**. These pathways comprise a series of phosphorylation events, culminating in regulation of target genes, which dictate cellular processes, for example proliferation and migration. **(C)** A number of mechanisms exist to negatively regulate FGFR signalling, including upregulation and recruitment of signalling modulators (red boxes). Further, inhibitory feedback signals, from pathways such as MAPK, act to dampen upstream components of the FGFR signalling axis (black lines).