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Current strategies for inhibiting FGFR activities in clinical applications: opportunities, challenges and toxicological considerations

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Aberrations in fibroblast growth factor receptor (FGFR) signaling are instrumental to the pathophysiology of several malignancies and disorders. Hence, FGFR inhibitors are explored in therapeutics with early candidates developed as competitors for the ATP-binding pocket in the kinase domain. More recent programs yielded compounds of diverse scaffolds with alternative binding modes. Concurrently, monoclonal antibodies and peptide-based agents provide independent options for clinical development. Notwithstanding this rapid progress, we contemplate the toxicological impact of FGFR inhibition based on the defined role of FGFR family members in physiology and homeostasis. The high homology among FGFR1–4 and also with other kinase subfamilies creates an additional challenge in developing selective inhibitors. It orchestrates an ongoing conundrum of moderating a balance between synergism through multitargeting kinase inhibition and minimizing off-target toxicities.

FGFRs as therapeutic targets

Structure and function

The fibroblast growth factor receptor (FGFR) family is a key lineage of the receptor tyrosine kinase superfamily with four distinct isoforms (FGFR1–4) found across several tissue types and expressed to different extents under varying conditions [1,2]. As a family, FGFRs regulate key cellular processes of cell growth, proliferation, wound healing, embryogenesis and angiogenesis [1], alluding to potential pathologies arising from their aberrations. FGFRs are positioned at the upper echelon of cell signaling where they can receive extracellular cues in the form of FGFs and, subsequently, transmit intracellularly to elicit biochemical responses. Structurally, FGFRs are characterized by three key domains: the extracellular domain with three immunoglobulin subunits forming a ligand-binding unit to associate with FGFs; a single-pass transmembrane domain; and two intracellular kinase domains [1]. Upon effective FGF binding, the receptor undergoes dimerization, phosphorylation of specific tyrosine residues and 'tagging' of the domains to create anchoring points for downstream adaptor proteins to bind. Key adaptor proteins FGFR substrate (FRS)2α and phospholipase C (PLC)γ play crucial parts in innervating second messengers, turning on a plethora of transcriptional events that propagate cell proliferative and antiapoptotic signals (Fig. 1a) [2]. This signaling is promoted by the presence of co-receptors: heparan sulfate or heparin present locally at the cell surface reinforcing FGF–FGFR interaction [3]; and the Klotho family is another class of co-receptors crucial for some FGFR signaling (Fig. 1b) [4]. From the perspective of drug design, the involvement of these co-receptors and protein–protein interactions in the FGF–FGFR signaling axis promulgates broader opportunities for pharmacological interventions during aberrations of signaling. Overall, the diverse downstream effects of FGFR activation present multiple points of regulatory controls and implication on diseases. The exact nature of the pathology depends on the tissue-specific expression of the FGFR pathways and the type of aberration being presented.

Pathophysiology involving FGFRs

Roles in cancer

The most notable disease state associated with FGFR dysregulation is that of malignancies. Cancer growth has been reported to be implicated by FGFR overexpression and/or genetic alteration in the form of somatic or germline mutations [2]. The outcome is an increased protein expression that can trigger a ligand-independent

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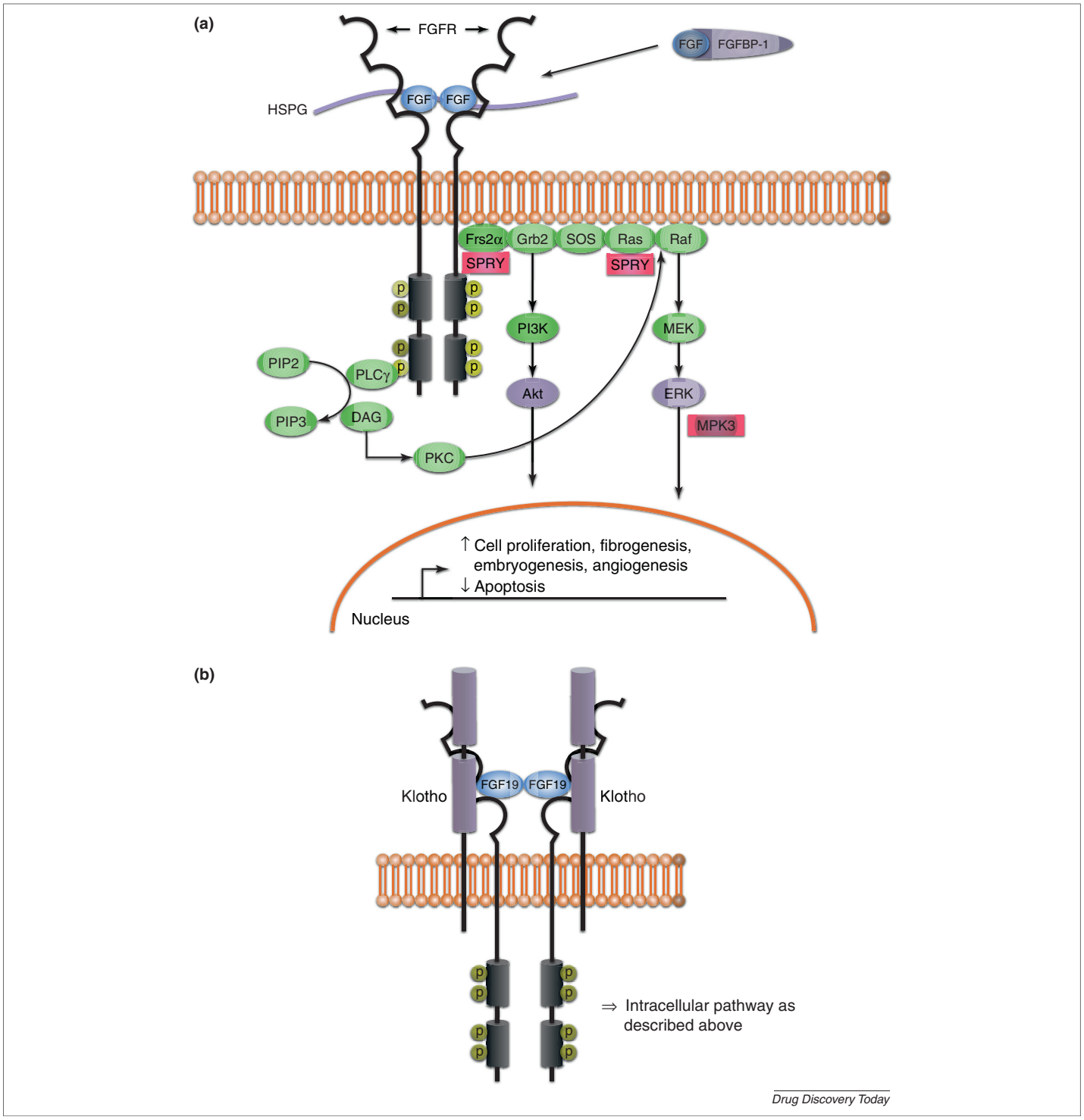

FIGURE 1

Fibroblast growth factor receptor (FGFR) signaling network. **(a)** FGFRs are single-pass transmembrane receptor tyrosine kinases with extracellular domains comprising of three IgG subunits and two intracellular kinase domains in tandem. FGF-binding protein 1 (FGFBP-1) releases FGFs from immobilized stores to bind to FGFR. FGF binds to the second and third extracellular domain of FGFR, mediated by heparan sulfate proteoglycan (HSPG). Upon FGF binding, the receptor dimerizes and phosphorylates at the kinase domains. Adaptor proteins FGFR substrate (FRS)2α and phospholipase C (PLC)γ then bind to activate the Ras/mitogen-activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K)/Akt signaling pathways. Sprouty (SPRY) and MAPK phosphatase 3 (MPK3) serve as negative regulators of these pathways. **(b)** FGFs belonging to the FGF19 subfamily bind heparan sulfate with low affinity and, instead of utilizing heparin or HSPG, require Klotho as a co-receptor for binding to FGFR. Abbreviations: DAG, diacylglycerol; Grb2, growth-factor-receptor-bound 2; PIP_2, phosphatidylinositol (4,5)-biphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PKC, protein kinase C; SOS, son of sevenless.