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Targeting the fibroblast growth factor receptor family in cancer

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ABSTRACT

Fibroblast growth factors (FGFs) regulate a plethora of biological functions, in both the embryonic and adult stages of development, binding their cognate receptors and thus activating a variety of downstream signalling pathways. Deregulation of the FGF/FGFR signalling axis, observed in multifarious tumor types including squamous non-small cell lung cancer, occurs through genomic FGFR alterations that drive ligand-independent receptor signalling or alterations that support ligand-dependent activation. Mutations are not restricted to the tyrosine kinase domain and aberrations appear to be tumor type dependent. As well as its complementarity and synergy with VEGF of particular interest is the interplay between FGFR and EGFR and the ability of these pathways to offer a compensatory signalling escape mechanism when either is inhibited. Hence there exists a rationale for a combinatorial approach to inhibition of these dysregulated pathways to reverse drug resistance. To date, several multi-target tyrosine kinase inhibitors as well as FGFR specific tyrosine kinase inhibitors (TKIs), monoclonal antibodies and FGF ligand traps have been developed. Promising preclinical data has resulted in several drugs entering clinical trials. This review explores aberrant FGFR and its potential as a therapeutic target in solid tumors.

Introduction

Deregulated receptor tyrosine kinases (RTKs) result in activated signal transduction pathways, that are characteristic of and essential to malignancy [1]. The fibroblast growth factor receptor (FGFR) family consists of four RTKs (FGFR1-4) which bind a diverse family of 18 FGF ligands and plays a role in development proven by gain-of-function mutations that result in dwarfism in model organisms and humans [2]. Similar to the epidermal growth factor receptor (EGFR), aberrant FGFR signalling has emerged as a key factor in the pathogenesis of multiple cancers. A study by Greenman et al. which screened the coding exons of 518 protein kinase genes from 210 different human cancers demonstrated that components of the FGF signalling pathway contained more non-synonymous mutations than all of the other kinases [3]. A recent analysis of 4,853 solid tumors found FGFR aberrations in 7.1% of cancers, gene amplification (66%), mutations (26%) and rearrangements (8%). FGFR1 (mostly amplification) was affected in 3.5% of patients; FGFR2 in 1.5%; FGFR3 in 2.0%; and FGFR4 in 0.5%. The cancers most commonly affected were urothelial (32%); breast (18%); endometrial (~13%), lung (squamous) (~13%), and ovarian (~9%) [4]. Activated FGFR signalling is also a key driver of resistance to several targeted therapies. It was previously shown to be synergistic with VEGF and involved in resistance to anti-VEGF inhibition [5]. However, more recently, an intricate relationship between the EGFR and FGFR families has also emerged with activated FGFR1 identified as a bypass escape mechanism to the EGFR tyrosine kinase inhibitor (TKI) afatinib [6], while comparably EGFR activation has been identified as a mechanism of resistance in FGFR3-mutant bladder cancers [7]. The FGFR inhibitor PD-173074 was shown to rescue fibroblast induced lapatinib resistance in esophageal squamous cell lines [8]. Hence, dual targeting of the EGFR and FGFR pathways may be a more effective therapeutic strategy, as discussed subsequently in this review. Targeting FGFR has shown potential in previously difficult to treat tumor types [9]. Herein we discuss the FGFR family and how deregulation of the FGFR signal transduction cascade contributes to cancer development, as well as the multiple targeted therapies in preclinical and clinical development.

FGF/FGFR signalling

FGFs are known to play a crucial role in the regulation of a plethora of developmental processes, in both the embryonic and adult stages of life. They are vital in the management of tissue repair, wound healing and tumor angiogenesis [10]. As such, it is crucial that FGF activity is tightly regulated in order to maintain homeostatic cellular proliferation. The mammalian FGF family

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comprises eighteen highly conserved ligands (FGF1-10, FGF16-23), grouped into five paracrine-acting subfamilies, one endocrine-acting subfamily [11] and four FGF homologous factors (FGF11-14), which have high sequence identity to FGF ligands but do not activate FGF receptors [10]. There is no human FGF15; rather murine FGF15 is orthologous to human FGF19 [10].

The human FGFR family to which FGF ligands bind comprises of four members, FGFR1-4. FGFRs are transmembrane tyrosine kinases belonging to the immunoglobulin (Ig) superfamily [12]. The extracellular region is composed of three Ig like domains (D1-D3), with a stretch of seven or eight acidic serine rich residues (acid box) located between D1 and D2. It is thought that the first Ig-like domain, D1, plays a role in receptor auto inhibition, while the second and third domains comprise the ligand-binding site [13]. In FGFR1-3 ligand-binding specificity is determined by alternative splicing of the third domain [14]. The N-terminal portion of D3 is encoded by a conserved exon (IIIa) while the C-terminal tail is encoded by one of two mutually exclusive exons, labelled IIIb and IIIc respectively. Alternative splicing does not occur in FGFR4 a lone isoform that is analogous to the FGFR2-IIIc isoform [15,16]. A fifth member of the FGFR family, fibroblast growth factor receptor like 1 (FGFRL1), was recently discovered. FGFRL1 lacks a tyrosine kinase domain and instead contains a short intracellular tail with a histidine rich motif [17]. FGFRL1 is thought to negatively regulate signalling, inhibiting cellular proliferation and promoting differentiation [18].

Phosphorylated tyrosine sites on the activated FGFR act as docking sites for various adaptor proteins that contain Src homology 2 (SH2) domains or phosphotyrosine binding (PTB) domains. These adaptor proteins are then phosphorylated directly by FGFR [19] and stimulate the activation of four downstream signalling pathways; Ras-Raf-MAPK, PI3K-AKT, STATs and PLCγ (Fig. 1) [16].

Deregulation of FGF–FGFR signalling in cancer

Deregulated FGF/FGFR activity has been reported in a plethora of different cancer types, including solid tumors and haematological malignancies (Table 1). Aberrant FGF/FGFR signalling may be the result of several different ligand-independent mechanisms; these include mutations, chromosomal translocations or amplifications of the genes encoding FGFRs, which may give rise to receptor overexpression and thus increased receptor signalling (Fig. 2). Alternatively impaired termination of FGF/FGFR signalling may result in increased levels of receptor on the cell surface and consequently may contribute to tumorigenesis. Moreover, ligand-dependent signalling has also been shown to play a role in the development of some cancers, via autocrine or paracrine production of ligand.

FGFR mutations

Germline gain-of-function mutations in FGFRs have been reported in a variety of human skeletal dysplasia as well as in numerous carcinomas. Mutations may occur in almost any part of the receptor [20]. Most mutations result in more active forms of the receptor, via enhanced ligand binding due to mutation of the extracellular domain (ECD), increased or constitutive receptor activation as a result of mutations in the ligand-binding domain and tyrosine kinase domain [21]. Other mutations have been shown to result in impaired degradation of the receptor and prolonged signalling, as discussed below.

FGFR1 mutations have been reported in melanomas but are a rather rare event. Analysis of the Catalog Of Somatic Mutations In Cancer (COSMIC) database identified rare somatic mutations of *FGFR1* (S125L and K566R) associated with basal-like triple negative breast cancer and somatic mutations have also been found in some lung cancers [22].

FGFR2 mutations are observed in 10–16% of endometrial carcinomas [23]. The majority of somatic mutations identified were identical to germline *FGFR* mutations associated with congenital craniofacial developmental disorders such as Apert Syndrome and Crouzon Syndrome [24]. 11 different *FGFR* mutations have been identified in endometrial cancer, with mutation S252W

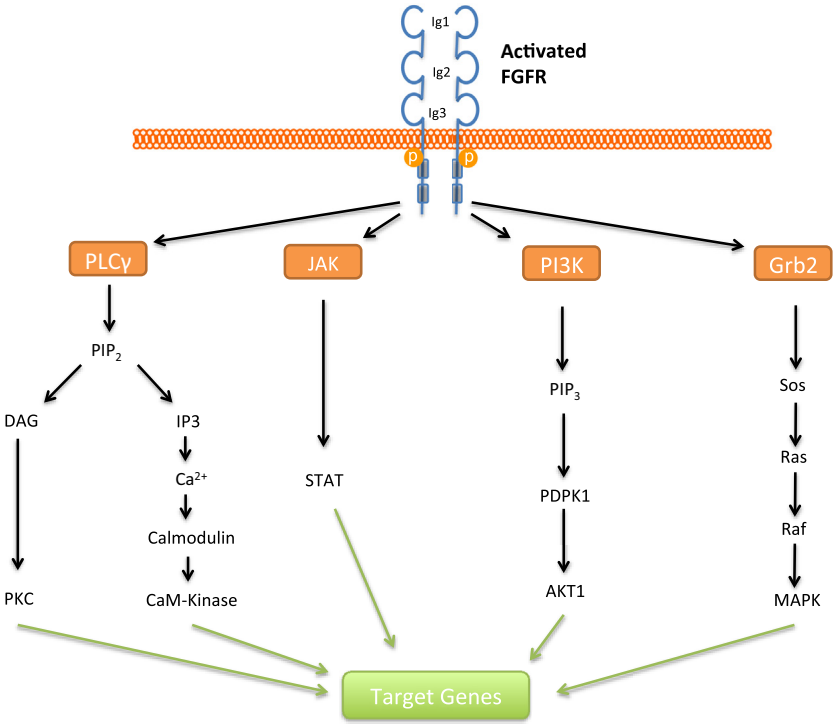

Fig. 1. Diagrammatic representation of the various signalling pathways that may be activated upon FGF ligand binding and receptor dimerization. Note: PLC – phospholipase C, JAK – Janus kinase, STAT – signal transducers and activators of transcription, PI3K – phosphoinositide 3-kinase, Grb2 – growth factor receptor-bound protein 2.