Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Functions of Fibroblast Growth Factor Receptors in cancer defined by novel translocations and mutations

Leandro H. Gallo, Katelyn N. Nelson, April N. Meyer, Daniel J. Donoghue *

Department of Chemistry and Biochemistry, Moores UCSD Cancer Center, University of California San Diego, La Jolla, CA 92093-0367, United States

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Fibroblast Growth Factor Receptor
Translocation
Development
Rhabdomyosarcoma
Myeloproliferative syndrome

ABSTRACT

The four receptor tyrosine kinases (RTKs) within the family of Fibroblast Growth Factor Receptors (FGFRs) are critical for normal development but also play an enormous role in oncogenesis. Mutations and/or abnormal expression often lead to constitutive dimerization and kinase activation of FGFRs, and represent the primary mechanism for aberrant signaling. Sequencing of human tumors has revealed a plethora of somatic mutations in FGFRs that are frequently identical to germline mutations in developmental syndromes, and has also identified novel FGFR fusion proteins arising from chromosomal rearrangements that contribute to malignancy. This review details approximately 200 specific point mutations in FGFRs and 40 different fusion proteins created by translocations involving FGFRs that have been identified in human cancer. This review discusses the effects of these genetic alterations on downstream signaling cascades, and the challenge of drug resistance in cancer treatment with antagonists of FGFRs.

1. Overview of canonical FGFR signaling

Receptor tyrosine kinases (RTKs) represent important signal transducers in the cell membrane and are comprised of nearly twenty families of homologous proteins in humans, with almost 60 distinct members [1]. In the FGFR family, four homologous human receptors have been identified: FGFR1, FGFR2, FGFR3 and FGFR4. All of the FGFRs exhibit three extracellular immunoglobulin (Ig)-like domains, a membrane-spanning segment and a split tyrosine kinase domain. Fibroblast Growth Factors (FGFs), a large family of related growth factors, act in concert with heparin sulfate proteoglycans (HSPGs) as high-affinity FGFR agonists [2,3]. The splicing of FGFRs results in further distinction of ligand specificity accompanied by altered biological properties, in which the most studied splicing isoforms involve the third immunoglobulin-like domain of the receptors [4]. For FGFR2 and FGFR3, the first half of third Ig domain consists of an invariant exon (IIIa), and splicing of the second half of third Ig domain results in either IIIb isoform (exons 7 and 8) or IIIc isoform (exons 7 and 9). Generally, the IIIb isoforms of FGFRs are expressed in tissues of epithelial origin whereas the IIIc isoforms are expressed in mesenchymal tissues [5].

Binding of FGF/HSPG to FGFR induces the dimerization of receptor monomers in the plasma membrane, followed by trans-autophosphorylation of tyrosine residues located in the cytoplasmic kinase domain. This tyrosine phosphorylation triggers the binding of Src homology (SH2) domain of phospholipase C gamma (PLCγ) to the receptor, resulting in the activation of PKC. Activation also induces RAS–MAPK and PI3K–AKT signaling *via* FRS2 and GRB2 adaptor proteins. Additional pathways activated by FGFRs include Jun N-terminal kinase and JAK/STAT pathways. FGFR signaling results in cellular proliferation and migration, anti-apoptosis, angiogenesis and wound healing (Fig. 1) [6].

Abbreviations: ARMS, alveolar rhabdomyosarcoma; BSS, Beare Stevenson cutis gyrata syndrome; CFS, chromosomal fragile site; CC, coiled coil domain; EMS, 8p11 myeloproliferative syndrome (EMS); ERMS, embryonal rhabdomyosarcoma; FN, fibronectin domain; Ig, immunoglobulin-like domain; IMD, IRSp53/MIM domain; ITD, internal tandem duplication; JM, juxtamembrane domain; LIsH, LIS1-homologous domain; LZ, leucine zipper domain; KD, kinase domain; KI, kinase insert domain; LADD, lacrimo auriculo dento digital syndrome; ORF, open reading frame; RMS, rhabdomyosarcoma; SAM, sterile alpha motif; SADDAN, severe achondroplasia with delayed development and acanthosis nigricans; SP, signal peptide; SPFH, stomatin/prohibitin/flotillin/HflK/C domain; TK domain, tyrosine kinase domain; TD, thanatophoric dysplasia; TM, transmembrane domain; ZF, zinc finger domain.

* Corresponding author. Tel.: +1 858 534 7146.
E-mail addresses: legallo@ucsd.edu (L.H. Gallo), kanelson@ucsd.edu (K.N. Nelson), ameyer@ucsd.edu (A.N. Meyer), ddonoghue@ucsd.edu (D.J. Donoghue).

http://dx.doi.org/10.1016/j.cytogfr.2015.03.003

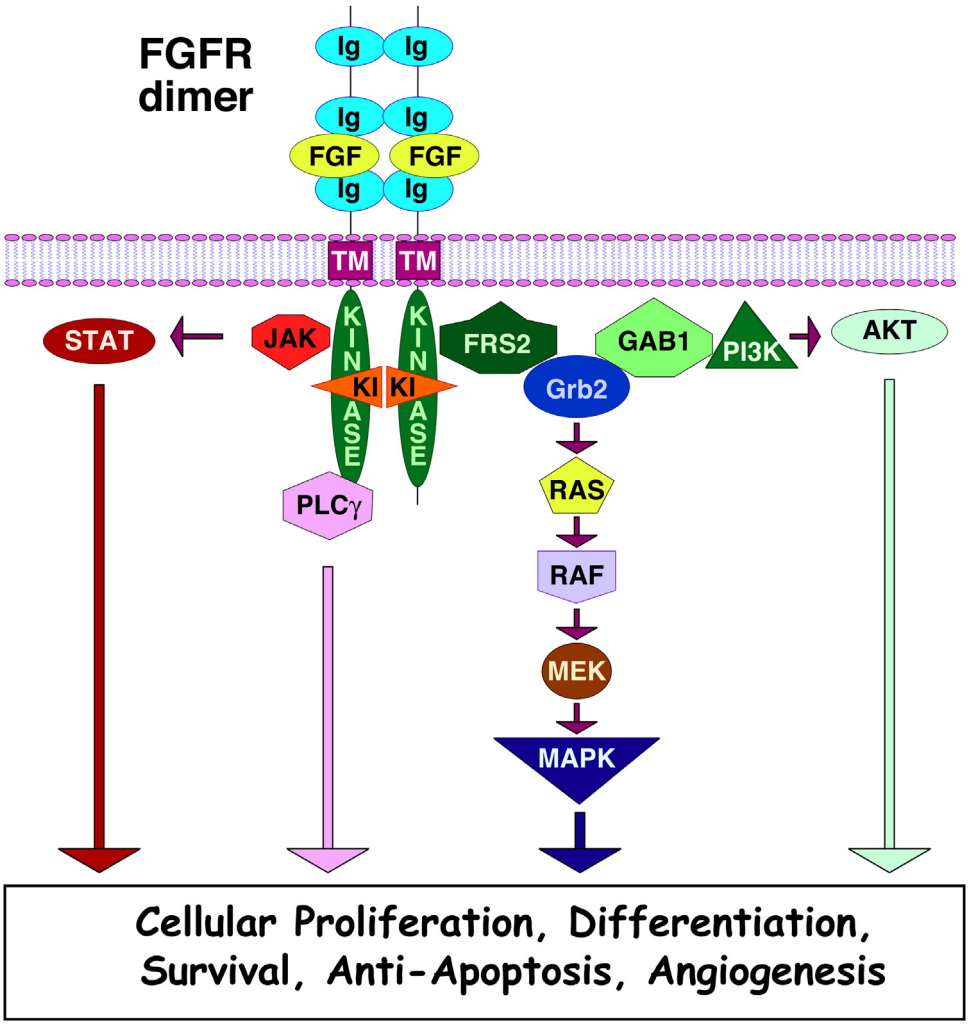

Fig. 1. FGFR signaling pathways. FGF ligand binds to FGFR monomers, leading to the dimerization and subsequent tyrosine autophosphorylation of the receptor. This event leads to activation of FGFRs and various downstream proteins, resulting in cellular proliferation, differentiation, survival, anti-apoptosis and angiogenesis.

2. FGFRs are mutated in human syndromes and cancers

2.1. Nomenclature of mutations with respect to isoforms

The alternatively spliced isoforms of FGFR1, FGFR2 and FGFR3 result in considerable confusion in numbering specific mutations, depending upon the convention employed by the original authors. In Table 1, we have presented the residue numbers in FGFR1 for both the αA1 and αB1 isoforms, in FGFR2 for the IIIb and IIIc isoforms, in FGFR3 for the IIIb and IIIc isoforms, and FGFR4 for the Uniprot P22455-1 and P22455-2 isoforms. Throughout this manuscript, we will refer to the numbering for the isoforms FGFR1 αA1, FGFR2 IIIb, FGFR3 IIIb, and full-length FGFR4 (Uniprot P22455-1), although a specific mutation may have been described initially in the other isoform. Rarely, a mutation may occur at a residue that is not present in either of the most common isoforms; in these unusual cases, this other isoform is identified in Table 1.

2.2. Cysteine mutations in the extracellular domain lead to aberrant activation of FGFRs

Many mutations in the extracellular domains of FGFRs induce tyrosine kinase activation by disulfide bond disruption. For instance, each Ig domain of FGFR2 is stabilized by a disulfide bond between pairs of cysteine residues: Cys62 and Cys107 in Ig-I, Cys179 and Cys231 in Ig-II, Cys278 and Cys340 in Ig-III [7]. Mutations in FGFR2 that perturb a disulfide bond in the extracellular domain result in increased receptor activation, such as the C278F mutation in Crouzon and Pfeiffer Syndromes, or the mutation of C340 to S or Y in Crouzon Syndrome. These are examples of craniosynostosis syndromes exhibiting premature closure of cranial sutures, accompanied by defects in chondrocyte signaling and brain development [8]. This same theme is recapitulated in somatic mutations involved in human cancer as exemplified by the C278F mutation and the mutations C340F/R/S/W/Y identified in spermatocytic seminoma [9]. Conceptually similar mutations that remove a critical Cys residue also occur in FGFR3 and FGFR4 (Table 1, Fig. 2).

Conversely, the *addition* of a single cysteine mutation creates an unpaired cysteine that can participate in abnormal intermolecular disulfide bond formation leading to receptor activation. One such example is FGFR2 W290C, a mutation causing Pfeiffer Syndrome, which has also been identified in lung squamous cell carcinoma and spermatocytic seminoma (Table 1). A conceptually similar mutation is that of FGFR2 S352C in Crouzon Syndrome [10,11], also identified in spermatocytic seminoma. Other examples of FGFR2 mutations that introduce a new cysteine residue in the extracellular domain include R203C, Y281C, S320C, Y338C, and S373C, which have been identified in various cancers including breast cancer, endometrial carcinoma, lung squamous cell carcinoma and

Please cite this article in press as: Gallo LH, et al. Functions of Fibroblast Growth Factor Receptors in cancer defined by novel translocations and mutations. Cytokine Growth Factor Rev (2015), http://dx.doi.org/10.1016/j.cytogfr.2015.03.003