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Targeting FGFR pathway in breast cancer

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ABSTRACT

Developments in breast cancer biology over the last years have permitted deconstructing the molecular profile of the most relevant breast cancer subtypes. This has led to an increase in therapeutic options, including more effective personalized therapy for breast cancer and substantial improvements in patient outcomes. Although currently there are only a few targeted therapies approved for metastatic breast cancer, the discovery of druggable kinase gene alterations has radically changed cancer treatment by providing novel and successfully actionable drug targets. Fibroblast growth factors and their receptors (FGFRs) participate in different physiologic processes and also play an essential role in cancer cell proliferation, survival, differentiation, migration, and apoptosis. This article summarizes the main molecular alterations of FGFRs, as well as the available preclinical and clinical data with FGFR inhibitors in breast cancer, and discusses new opportunities for the clinical development of these agents in patients with breast cancer.

1. Introduction

Breast cancer is a heterogeneous disease with multiple clinical presentations and tumor characteristics. In recent years, gene expression profiling studies have classified breast tumors into four different molecular subtypes (luminal A, luminal B, HER2 enriched, and basal-like), leading to a new classification of breast cancer with prognostic and therapeutic implications [1].

Developments in breast cancer biology over the last years have permitted deconstructing the molecular profile of the most relevant breast cancer subtypes. This has led to an increase in therapeutic options, including more effective personalized therapy for breast cancer and substantial improvements in patient outcomes [2]. To date, the US Food and Drug Administration (FDA) has only approved a limited number of targeted therapies for the treatment of breast cancer. In addition to endocrine therapy, these include: five anti-HER2 therapies (trastuzumab, lapatinib, neratinib, T-DM1, and pertuzumab), everolimus, palbociclib, ribociclib, and abemaciclib [3–12]. However, other strategies targeting different tyrosine kinase receptors are currently under way.

The fibroblast growth factor receptor (FGFR) family comprises five transmembrane receptors, all but one with tyrosine kinase activity. During the past few years, considerable research has confirmed the essential role of FGFR signaling in cancer cell proliferation, angiogenesis, and survival, and this pathway appears, therefore, to be an excellent target for cancer therapy [13].

In this review, we summarize the main molecular alterations of FGFRs, as well as the available preclinical and clinical data with FGFR inhibitors in breast cancer, and discuss new opportunities for the clinical development of these agents in patients with breast cancer.

2. The fibroblast growth factor (FGF)/FGFR signaling pathway

FGFs and FGFRs are involved in different physiologic processes, such as embryonic development, regulation of angiogenesis, and wound repair, among others. Additionally, the FGF/FGFR signaling network plays a critical role in cancer cell proliferation, survival, differentiation, migration, and apoptosis. For these reasons, dysregulation of the FGF/FGFR pathway consistently has been

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associated with human cancers as well as many other developmental disorders [13,14].

The human FGFR family contains four classical FGFRs (FGFR1, FGFR2, FGFR3, and FGFR4) encoded by four distinct genes (*FGFR1-4*). It is noteworthy to mention that in addition to the classical receptors encoded by FGFR genes, several isoforms with different ligand-binding affinities are generated through alternative splicing of FGFR1 through FGFR3. Each receptor comprises an extracellular domain, a transmembrane domain, and a tyrosine kinase cytoplasmic domain. The extracellular region consists of three immunoglobulin-like (Ig) domains (IgI, IgII, and IgIII) and an acid box, typically located between IgI and IgII. The IgII and IgIII domains constitute the FGF ligand-binding site [15]. Recently, a fifth member of the FGFR family has been discovered, the fibroblast growth factor receptor like 1 (FGFRL1 or FGFR5), that also contains three extracellular Ig-like domains but lacks the protein tyrosine kinase domain [16].

The FGF family of ligands comprises 18 members (FGF1–FGF10 and FGF16–FGF23) that may be categorized into two groups. The first consists of hormone-like FGFs (FGF19, FGF21, and FGF23) that function in an endocrine manner and can bind to FGFRs through the presence of klotho proteins. The second contains the canonical FGFs (FGF1–FGF10, FGF16–FGF18, FGF20, and FGF22) that are captured in the cell surface or in the extracellular matrix by heparan sulfate glycosaminoglycans and act as paracrine or autocrine growth factors.

Binding of FGFs to FGFRs leads to receptor dimerization, resulting in the transphosphorylation of a tyrosine in the activation loop of the kinase domain. Subsequently, the activated FGFRs phosphorylate their intracellular receptor substrates, particularly FGFR substrate 2 (FRS2) and phospholipase Cγ (PLCγ). On one hand, activated FRS2 promotes downstream signaling through the RAS–mitogen-activated protein kinase (MAPK) or the phosphoinositide 3-kinase (PI3K)–AKT pathways that regulate cell proliferation, differentiation, and survival. On the other hand, the activation of PLCγ leads to the release of calcium ions from the intracellular compartment and to the activation of calcium-dependent signaling, events that mediate cell motility. Moreover, there are other effector proteins activated by FGFRs, such as Signal Transducers and Activators of Transcription (STAT) factors, Src, and RAF, through the stimulation of protein kinase C (Fig. 1) [17].

Nevertheless, the regulatory mechanisms involved in the control of FGFR signaling are poorly understood and likely are different depending on tumor type and molecular context. Therefore, additional research in this area is warranted.

3. Genomic aberrations of the FGF/FGFR signaling pathway in breast cancer

The FGF/FGFR signaling pathway is frequently deregulated in human cancers. Overall, *FGFR* alterations have been found in 7.1% of cancers, with the majority being gene amplifications (66% of the aberrations), followed by mutations (26%) and rearrangements (8%) [18]. Tumor types most commonly affected are urothelial (32% *FGFR*-aberrant), breast (18%), endometrial (~13%), squamous lung cancers (~13%), and ovarian cancer (~9%). Moreover, ligand-dependent mechanisms are also responsible of the aberrant activation of FGFR signaling through the paracrine and/or autocrine production of FGFs proteins by stromal and/or tumor cells.

In breast cancer, *FGFR1* amplification represents the most frequent genomic aberration, whereas amplification of *FGFR2–4* genes and *FGFR* activating mutations are uncommon. These alterations are discussed further in the following sections (Table 1).

3.1. FGFR1 gene amplification

The 8p11-12 chromosomal region harboring the *FGFR1* gene locus is amplified in about 14% of breast cancer patients, with a range from 8.7% to 23% depending on the study, principally in the hormone receptor (HR)-positive/HER2-negative subtype [18–20]. It is important to highlight that genes other than *FGFR1* within the 8p11-12 amplicon also may promote breast cancer development. Furthermore, in up to one third of patients, the *FGFR1* gene is amplified simultaneously with an amplicon on chromosome 11q12-14 that contains additional oncogenes, such as *CCND1*, *FGF3*, *FGF4*, and *FGF19* [21,22]. However, *in vitro* studies have demonstrated that FGFR1 expression by itself is required for the survival of *FGFR1*-amplified breast cancer cell lines, supporting the oncogenic potential of *FGFR1* amplification [23].

3.2. FGFR2 gene amplification

The *FGFR2* gene located on chromosome 10q26 is amplified in approximately 4% of triple-negative breast cancers but appears to be a relatively rare event in other tumor subtypes, occurring in less than 1% of all breast cancers [18,24]. In contrast to *FGFR1* amplification, the presence of other important oncogenes in this amplicon is less relevant, and its coamplification with other chromosomal regions has not been reported. Nevertheless, breast cancer cell lines with high levels of amplification of *FGFR2* are also highly sensitive to FGFR inhibitors, indicating that *FGFR2* amplification could signify addiction to the FGFR pathway for growth [25].

3.3. FGFR3 and FGFR4 genes amplification

Amplification of the *FGFR3* and *FGFR4* genes has been detected in less than 1% and around 2.3% of breast cancer patients, respectively [18] However, another study has revealed the presence of increased FGFR4 mRNA levels in up to 30% of patients with breast cancer, suggesting a discrepancy between *FGFR* amplification and FGFR mRNA levels that will be further discussed in the manuscript in more detail [26].

3.4. FGFR mutations and fusions

Although *FGFR* mutations are common in other tumor types, such as endometrial (*FGFR2*) and urothelial cancers (*FGFR3*), their incidence is much lower in breast cancer [18]. However, *FGFR* mutations with unknown functional significance have also been identified in human breast cancers [27]. Moreover, the use of new tools for genome analysis has recently allowed the identification of *FGFR1* and *FGFR2* gene fusions with oncogenic potential in four breast cancer patients [28]. This implies that the implementation of next-generation sequencing (NGS) technologies will be critical for the detection of novel druggable oncogenic alterations in the coming years.

4. Role of the FGF/FGFR signaling pathway in the treatment of breast cancer

Preclinical data have consistently shown that *FGFR1*-and *FGFR2*-amplified breast cancer cell lines and xenografts are more sensitive than nonamplified models to growth inhibition by FGFR inhibitors [29,30]. Moreover, alterations in the FGF/FGFR signaling pathway may also have important clinical implications in breast cancer patients.

Despite the fact that the role of *FGFR2* amplification in the management of breast cancer remains unclear, several studies have confirmed the clinical and biological importance of *FGFR1*