Breast Cancer RESEARCH

EDITORIAL

FGFR1 amplification and the progression of non-invasive to invasive breast cancer

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See related research by Jang *et al.*, http://breast-cancer-research.com/content/14/4/R115

Abstract

The incidence of invasive breast cancer (IBC) can be dramatically reduced by improving our abilities to detect and treat ductal carcinoma *in situ* (DCIS). Progress will be based on a detailed understanding of molecular mechanisms responsible for tumor progression. An interesting study by Jang and colleagues evaluated and compared the frequency of amplification of four oncogenes (*HER2*, *c-MYC*, *CCND1* and *FGFR1*) in large cohorts of pure DCIS, in the DCIS component of IBC, and in corresponding IBC. Of particular interest, they found a twofold increase in *FGFR1* amplification in IBC versus pure DCIS, and significantly reduced disease-free survival in amplified versus unamplified IBC – leading the authors to conclude that FGFR1 plays an important role in the development and progression of IBC. These observations indeed provide hints that FGFR1 is important in this setting, although the issue is very complex and far from resolved.

Invasive breast cancer (IBC) evolves through a series of increasingly abnormal premalignant stages, over decades in most cases [1,2]. Ductal carcinoma *in situ* (DCIS) is a late stage in this evolution and the immediate precursor for most IBC. Currently, about 60,000 new cases of DCIS are diagnosed in the USA each year [3]. If undetected, at least one-third of cases will progress to IBC [4]. About 200,000 cases of IBC are also diagnosed [3], and nearly all evolve from DCIS that was not detected.

The incidence of IBC can be dramatically reduced by improving our abilities to detect and successfully treat DCIS, which will be based on a detailed understanding of molecular mechanisms responsible for tumor progression. Although there is much to learn, recent studies have begun to shed light on this important issue [5,6]. Among these is an interesting study by Jang and colleagues described in a recent issue of *Breast Cancer Research*, which evaluated and compared the frequency of amplification of four oncogenes (*HER2*, *c-MYC*, *CCND1*, and *FGFR1*) in large cohorts of pure DCIS (n = 175), in the DCIS component of IBC (n = 203), and in the corresponding IBC (n = 427) [1]. Amplification was carefully assessed by fluorescence *in situ* hybridization on tissue microarrays containing triplicate 2 mm cores/sample, which is far more tissue than used in most tissue microarray studies. Overall, they found reasonable rates of amplification for each oncogene in IBC consistent with many previous studies [7]. Far fewer studies of DCIS are available for comparison.

The main focus of the study was to compare amplification between pure DCIS and IBC, hypothesizing that differences may help identify genes that are important in the transition from *in situ* to invasive disease. In this regard, the most notable findings included significantly higher rates of *HER2* amplification in pure DCIS versus IBC (31% vs. 20%; P = 0.004), which has been shown before [8], and significantly lower rates of *FGFR1* in pure DCIS versus IBC (6% vs. 13%; P = 0.02), which is novel. These differences were more pronounced in lesions of high histological grade (*HER2* 60% vs. 34%; *FGFR1* 7% vs. 16%). Amplification frequencies in intrinsic molecular subtypes of IBC were also generally consistent with previous studies [7]. Jang and colleagues also looked at the relationship between amplification and clinical outcome. In these studies, amplification of *FGFR1* was associated with significantly reduced disease-free survival in patients with IBC (about 10% at 8 years), particularly in hormone-receptor-positive patients, although *HER2*, *c-MYC*, and *CCND1* were not prognostic in this cohort.

The twofold elevation of *FGFR1* amplification in IBC versus pure DCIS, and the poor prognosis in IBC, led the authors to conclude that activation plays an important role in the progression of breast cancer, including, in particular, the *in situ* to invasive transition. This is a reasonable conclusion in the sense that it is also

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consistent with previous studies showing that FGFR1 activation is oncogenic for breast cancer in transgenic mice [9], and is associated with increased invasion of breast cancer cell lines *in vitro* [10] and poor prognosis in IBC [7,11,12], especially in receptor-positive disease [11,12].

Although our understanding of *FGFR1* at the molecular level is incomplete, important aspects are known about its function and the consequences of gene amplification [13]. For example, the gene encodes a tyrosine kinase receptor that is part of a large family of fibroblast growth factors and receptors. In a normal setting, activation of *FGFR1* can lead to transactivation of mitogen-activated protein kinase and AKT, which collectively are essential for breast development, including the growth and differentiation of luminal epithelial cells. However, increased *FGFR1* activity, such as occurs through gene amplification, can result in increased luminal cell proliferation and, in transgenic mouse models, this hyperplasia may eventually evolve into *in situ* and invasive mammary carcinomas.

In humans, the chromosomal region where *FGFR1* resides, 8p11.2, is amplified in significant proportions of many types of cancers, including kidney cancer, lung cancer, prostate cancer, and leukemias. The region is also amplified in 10 to 20% of IBC [13]. However, the 8p11.2 amplicon is large and complex, and *FGFR1* is only one of several candidate oncogenes within the region [14] – others include *LSM1*, *PPAPDC1B*, *WHSC1L1*, and *BAG4*, which are also important in breast development and cell cycle regulation, among other relevant functions. To complicate matters more, only about 50% of *FGFR1*-amplified tumors appear to overexpress the transcript [15].

The study by Jang and colleagues provides additional evidence of an important role for *FGFR1* amplification in the progression of IBC [1]. The study also provides tantalizing hints that FGFR1 may be important in the *in situ* to invasive transition, which is a critical step in the progression of a nonlethal to potentially lethal disease – and this aspect of the study is entirely novel. Having said this, we need to be cautious about drawing conclusions regarding gene function and malfunction based on correlative studies of this nature alone. For example, the main evidence that FGFR1 is important in this study is elevated amplification in IBC versus DCIS. By analogous reasoning, the elevated amplification of *HER2* observed in DCIS versus IBC could be taken as evidence for suppression of tumor progression, which we know is wrong. Determining the molecular function, oncogenic potential, and clinical significance of FGFR1 at any stage of breast cancer evolution will require many additional comprehensive laboratory and clinical studies. These studies are particularly worthwhile in the sense that we have effective drugs to inhibit FGFR1 activity [13]. Jain and Turner have summarized recent interesting data in terms of the functional biology of the fibroblast growth factor receptors and development of inhibitors of these molecules, with emphasis on challenges to successfully target this pathway in breast cancer [16]. These could lead to new strategies for preventing the progression of DCIS to IBC, or restoring responsiveness of receptor-positive IBC to endocrine therapy if activation is confirmed to induce resistance [11,12] – perhaps *FGFR1* will be the next *HER2*.

Abbreviations

DCIS, ductal carcinoma *in situ*; FGFR1, fibroblast growth factor receptor 1; HER2, human epidermal growth factor receptor 2; IBC, invasive breast cancer.

Competing interests

The authors declare that they have no competing interests.

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