Breast Cancer RESEARCH

VIEWPOINT

Initiating breast cancer by *PIK3CA* mutation

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Abstract

PIK3CA mutations confer constitutive activation of PI3K, which initiates intracellular kinase signaling cascades that promote cell proliferation and survival. Recent studies by Meyer and colleagues and by Liu and colleagues demonstrate that expression of the H1047R exon 20 mutant of *PIK3CA* in luminal mammary epithelial cells induces tumorigenesis, implying that *PIK3CA* mutation is an early event in breast cancer. *PIK3CA*-H1047R-initiated tumors exhibit variable dependence on the oncogene and variable sensitivity to PI3K inhibition. Amplification of the oncogenes *MYC* and *MET* was observed in tumors that recurred following silencing of *PIK3CA*-H1047R, suggesting that these pathways represent mechanisms of escape from PI3K inhibition.

Phosphatidylinositol 3-kinase (PI3K) phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP_3) at the cytoplasmic face of the plasma membrane. PIP_3 promotes membrane recruitment and activation of several proteins that drive cell proliferation and survival, including AKT, PDK1, and SGK. Class IA PI3Ks are heterodimers composed of a p110 catalytic subunit and a p85/p55 regulatory subunit, each of which has several isoforms. The PI3K pathway is the most frequently mutated pathway in breast cancer, and mutations occur in signaling nodes both upstream and downstream of PI3K [1].

Activating mutations in *PIK3CA* (which encodes the p110α catalytic subunit) occur in approximately 30% of breast cancers and are more frequent in estrogen receptor-positive (ER^+) breast cancers [2,3]. Eighty percent of *PIK3CA* mutations occur in two 'hot spots' within exons 9 and 20, which encode the helical and kinase domains, respectively. The E542K and E545K (exon 9) mutations may confer a gain-of-function by disrupting an inhibitory interaction between p110α and p85 [4]. The H1047R (exon 20) mutation may induce an allosteric change that mimics Ras-GTP binding, making this mutant independent of interaction with Ras-GTP [5]. Both mutants are constitutively active, transform cells in culture, and promote tumorigenicity in xenograft models. Cancer cell lines harboring *PIK3CA* mutations are highly sensitive to PI3K pathway inhibitors [6,7], rendering this pathway a drug target of high interest for cancer therapy. *PIK3CA* mutations have been found at similar frequencies in breast ductal carcinoma *in situ* (DCIS) lesions, DCIS adjacent to invasive ductal carcinoma (IDC), and IDC [8], suggesting that these mutations are early events in breast tumorigenesis and therefore may promote transformation of normal breast epithelial cells.

A recent study by Meyer and colleagues [9] revealed that expression of the *PIK3CA*-H1047R mutant in mammary epithelial cells is sufficient to induce tumor formation in transgenic mice. *PIK3CA*-H1047R expression driven by Cre-mediated recombination induced by either the *WAP* promoter (which is active in alveolar progenitor and differentiated secretory luminal epithelial cells) or the *MMTV* promoter (which is active in differentiated luminal mammary epithelial cells) induced the formation of mammary tumors of varying histologic subtypes. Tumor cells expressed markers associated with both luminal and basal epithelial lineages, suggesting that tumors with basal characteristics can arise from luminal cells. The authors postulate that *PIK3CA*-H1047R may (a) transform multi-potent progenitor cells to allow both luminal and basal differentiation, (b) induce de-differentiation of luminal cells to multi-potent progenitors, which then give rise to both lineages, or (c) do both. Involuting mammary glands (which undergo ductal pruning following pregnancy and lactation) from *PIK3CA*-H1047R mice showed a reduction in the number of apoptotic cells and delayed involution in comparison with controls. *PIK3CA*-H1047R tumors also showed very low rates of apoptosis and higher levels of phosphorylated AKT than mammary tumors from another model (MMTV-*Neu*NT), suggesting that *PIK3CA*-H1047R prevents cell death by increased PI3K/AKT pathway activation.

In another study, Liu and colleagues [10] reported that *PIK3CA*-H1047R-induced mammary tumors exhibit

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variable dependence on this oncogene. Transgenic mice expressed *PIK3CA*-H1047R under the control of an MMTV-regulated, doxycycline-inducible system. Mice treated with doxycycline showed increased phospho-AKT levels in mammary epithelial cells and formed mammary tumors of varying histologic subtypes. Silencing of *PIK3CA*-H1047R by withdrawal of doxycycline decreased tumor phospho-AKT levels, decreased proliferation, increased apoptosis, and induced complete tumor regression in one third of the mice. Two thirds of tumors partially regressed and then resumed growth. Some recurrent tumors that maintained high levels of P-AKT and P-S6 were sensitive to the PI3K inhibitor GDC-0941, whereas tumors with low P-AKT and P-S6 were insensitive to this agent. This suggests that some *PIK3CA*-H1047R-induced tumors escape from dependence on PI3K. GDC-0941-resistant and *PIK3CA*-H1047R-independent tumors exhibited amplification of the oncogenes *MYC*, *MDM2*, and/or *MET*. The authors demonstrated tumor dependence on *MYC* (using short-hairpin RNA knockdown) and *MET* (using a kinase inhibitor) and showed that *MYC* overexpression circumvented dependence on PI3K.

These studies have important implications for the role of PI3K mutations in breast cancer. First, these works show that *PIK3CA*-H1047R induces mammary epithelial cell transformation *in vivo* and support the notion that *PIK3CA* mutation is an early event in breast cancer. Second, the paper by Liu and colleagues [10] affirms that *PIK3CA*-mutant tumors are dependent, in whole or in part, on this oncogene. Some tumors that recurred following silencing of *PIK3CA*-H1047R showed sensitivity to a PI3K inhibitor, indicating continued addiction to PI3K. Since PI3K pathway inhibitors preferentially inhibit the growth of cancer cells harboring *PIK3CA* mutations [6,7], such mutations are being used as an inclusion criterion in ongoing clinical trials with these agents to enroll patients who are most likely to benefit. The authors' findings support this concept. Third, in agreement with the existence of *PIK3CA* mutations in all subtypes of breast cancer, *PIK3CA*-H1047R expression induced mouse mammary tumors expressing both luminal and basal markers. Issues that remain to be addressed are the mechanism underlying the variable histologic subtypes of *PIK3CA*-H1047R-induced mammary tumors and the effects of *PIK3CA*-H1047R on luminal/basal cell differentiation. Fourth, the majority of *PIK3CA*-H1047R-induced mammary tumors recurred following an initial regression after oncogene silencing. Such recurrence was driven by *MYC* and *MET*, suggesting that therapies targeting the PI3K pathway may be most effective when used in combination with agents that block such escape mechanisms.

Abbreviations

DCIS, ductal carcinoma ***in situ***; IDC, invasive ductal carcinoma; PI3K, phosphatidylinositol 3-kinase; PIP_3, phosphatidylinositol 3,4,5-trisphosphate.

Competing interests

The author declares that he has no competing interests.

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