Editorial

# NHERF1: molecular brake on the PI3K pathway in breast cancer

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## Abstract

The adaptor protein NHERF1/EBP50 (Na/H exchanger regulatory factor 1/ezrin-radixin-moesin-binding phosphoprotein 50) emerged recently as an important player in breast cancer progression. Consisting of two tandem PDZ domains linked to a carboxyl-terminal ezrin-binding region, NHERF1 assembles macromolecular complexes at the apical membrane of epithelial cells in many epithelial tissues, including the mammary gland. Involved initially in trafficking and regulation of transmembrane ion transporters and G protein-coupled receptors, NHERF1 also couples molecules involved in cell growth, such as the platelet-derived growth factor receptor (PDGFR) and PTEN (phosphatase and tensin homolog deleted on chromosome 10). In the previous issue of *Breast Cancer Research*, Pan and colleagues show an inhibitory action of NHERF1 on the phosphoinositide-3 kinase (PI3K)/Akt pathway in breast cancer cells via interaction of NHERF1 with PTEN, the physiological antagonist of the PI3K. Additionally, they show that NHERF1 expression confers susceptibility to PDGFR pharmacological inhibition depending on the presence of PTEN tumor suppressor.

Breast cancer is a complex disease comprising multiple pathological types and molecular profiles that determine various clinical outcomes and responses to therapy. Molecular cancer treatments recently came into focus, and targeted molecular therapies, such as trastuzumab, have already provided effective new drugs against breast cancer. New oncogenic pathways are studied for their potential to become therapeutic molecular targets, one such pathway being the phosphoinositide-3 kinase (PI3K)/Akt pathway that is physiologically repressed by the PTEN (phosphatase and tensin homolog deleted on chromosome 10) tumor suppressor in normal tissues and cells. In the previous issue of *Breast Cancer Research*, Pan and colleagues [1] show that Na/H exchanger regulatory factor 1 (NHERF1), an adaptor protein recently shown to be involved in the progression of breast cancer, acts as a brake on the PI3K signaling downstream of the platelet-derived growth factor receptor (PDGFR) in the mammary gland. These findings extend and confirm previous studies in mouse embryonic fibroblasts that have exemplified a ternary complex bridged by NHERF1 between PDGFR and PTEN tumor suppressor exerting an inhibitory action on the PI3K signaling [2]. Pan and colleagues further substantiate the negative role of NHERF1 on the PI3K pathway by showing significant activation of Akt in the mammary gland of NHERF1-deficient mice. The group then explores the role of this inhibitory loop in the sensitivity of breast cells to the PDGFR (and Bcr-Abl) inhibitor STI-571, a drug that is in clinical trial for the treatment of metastatic breast cancer [3], among other types of cancer. They find that NHERF1 expression confers sensitivity to STI-571 treatment in PTEN-positive breast cancer cells but does not affect the response to the drug in PTEN-negative breast cancer cells. Alternatively, expression of NHERF1 in a normal breast cancer cell line (MCF10A) renders cells sensitive to STI-571 only in the presence of wild-type endogenous PTEN. Thus, it is tempting to correlate the sensitivity of breast cancer cells to STI-571 with the presence of these two biomarkers, NHERF1 and PTEN, and the study by Pan and colleagues clearly suggests this connection.

Dai and colleagues previously have reported an increased deletion rate (58%) of one *NHERF1* allele and also mutation with loss of heterozygosity in 3% of breast cancer cell lines and primary tumors [4]. Similarly to the observation that mutations in the PI3K catalytic subunit (*PIK3CA*) are mutually exclusive with *PTEN* mutations in breast cancer [5], Pan and colleagues observe an inverse correlation between the deletion of *NHERF1* allele and mutations of either *PTEN* or *PIK3CA* genes in breast cancer cell lines [1]. These data bring genetic evidence for NHERF1 integration in the PI3K pathway and point to a tumor-suppressor role of NHERF1 in

ER = estrogen receptor; NHERF1 = Na/H exchanger regulatory factor 1; PDGFR = platelet-derived growth factor receptor; PI3K = phosphoinositide-3 kinase; PIK3CA = phosphoinositide-3 kinase catalytic subunit; PTEN = phosphatase and tensin homolog deleted on chromosome 10.

breast cancer. Further functional validation of the anti-proliferative role of NHERF1 in breast cancer cells has been provided by NHERF1 silencing experiments [6].

Interestingly, recent reports described an overexpression of NHERF1 in breast cancer as compared with normal mammary tissue [7,8]. The human *NHERF1* gene promoter contains estrogen receptor (ER) response elements [9], and the increased NHERF1 expression has been detected in more than 90% of ER-positive tumors [7,8,10]. Conversely, NHERF1 is completely absent in approximately two thirds of the more aggressive ER-negative breast tumors [8,10], again suggesting a tumor-suppressor role for NHERF1. The apparently opposing situations may be reconciled by the notion that NHERF1 is an adaptor protein that assembles signaling proteins in complexes, and its loss or its overexpression equally disrupt these complexes, the former by lack of scaffolding and the latter by titrating down other components of the complex. The latter appears to be even more conspicuous if the overexpression of the adaptor protein occurs in a cell compartment different from its normal intracellular distribution. Indeed, all of the reports showing NHERF1 overexpression in breast tumors point to an accumulation of NHERF1 in the cytoplasm as opposed to the physiological membrane localization of the molecule in normal breast tissue [7,8,10]. The possibility that delocalized NHERF1 may scaffold complexes in the cytoplasm, thus sequestering signaling molecules away from the plasma membrane, deserves future consideration. On the other hand, *in vivo* data from NHERF1-deficient animals have clearly shown that the lack of NHERF1 from the membrane destabilizes both membrane-associated and transmembrane proteins [11,12]. It is very likely that in the ER-positive breast tumors displaying NHERF1 overexpression, a combination of cytoplasmic overexpression and delocalization from the plasma membrane contributes to the reported enhanced invasiveness of these tumors [7,8]. In this respect, the matter regarding the mechanism of NHERF1 recruitment to the plasma membrane is open. Many membrane-targeting mechanisms have been proposed, including phosphorylation of the first PDZ domain [13], direct binding to lipids via the tandem PDZ domains [14], or recruitment by the cortical ezrin [15], and the predominance or contribution of these mechanisms for NHERF1 membrane localization in mammary cells awaits further study.

In view of the preliminary pharmacological studies presented by Pan and colleagues in this issue, the presence of subsets of breast tumors that present distinct expression patterns of NHERF1 raises a number of questions about the possibility of using NHERF1 as a biomarker. Are these tumor subsets reacting differently to PDGFR inhibitors, and is this reactivity correlated with PTEN or PDGFR expression levels? Are other PI3K/Akt pathway-targeted therapies effective on the cells that have upregulated PI3K activity due to loss of NHERF1? Could the NHERF1-deficient mice be used as a model, perhaps in combination with other genetic alterations occurring in human breast cancer, to test the efficacy of new therapies? It becomes increasingly apparent that the understanding of the tumor-suppressive functions of NHERF1 and of the mechanism pertaining to its subcellular localization will provide the necessary foundation for designing personalized effective breast cancer therapeutic solutions.

## Competing interests

The author declares that they have no competing interests.

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