The synergistic role of prolactin and estrogen in breast cancer requires PAK1

In 2016, the American Cancer Society estimates about 40,000 deaths will result from breast cancer. This makes breast cancer the second leading cause of cancer-related among women. Despite the frightening statistics, the death rates from breast cancer have been declining since the late 1980s due to screening, increased awareness and improved treatments. One major setback to breast cancer treatment, however, has been resistance or acquired resistance to therapy. Therefore, understanding why drug resistance occurs in breast cancer will provide insight into how resistance can be circumvented.

About 70% of all breast cancers have functional estrogen receptor (ER) that mediate estrogen (E2) actions, hence referred to as ER positive (ER+) breast cancer. There are two types of ERs, namely ER? and ER?, with ER? being the predominant type expressed in breast cancers. It has been known for many years that ER? activation regulates the growth, survival and overall tumor features of breast cancers, but exactly how is not clear. Tamoxifen is an ER antagonist that is used in the clinics to block the actions of E2 in ER+ breast cancer. Unfortunately, several patients encounter tamoxifen resistance and stop responding to treatment.

Prolactin (PRL) is another hormone that is increasingly being recognized for its contribution to breast cancer pathogenesis. PRL receptor is highly expressed in many breast cancers as well, and increased circulating PRL has been correlated with increased risk of ER+ breast cancer. Interestingly, ER? can also be activated by stimulating cells with PRL in the absence of E2. Although PRL and E2 exert their independent actions in breast cancer, both hormones have been known to work together to synergistically enhance breast cancer growth.

We set out to answer the question of how the hormones PRL and E2 work together in breast cancer. We found that PRL and E2 independently activate a kinase protein called PAK1 through different mechanisms. When we combined PRL with E2 in the same assay, we found that activation of PAK1 was much greater than the response PRL or E2 alone. This suggested that PAK1 is a common node in PRL and E2 signaling in breast cancer. We observed that PAK1 activation in response to E2 or PRL was due to PAK1 phosphorylation on tyrosine residues (PAK1 phosphorylation is a modification in the PAK1 protein that switches on the protein). Because PAK1 has been previously implicated in different types of cancers including breast cancer, these finding suggested that E2 and PRL work through PAK1 to accelerate breast cancer growth. In order to confirm these results, PAK1 with mutation in the key tyrosine residues (PAK1 Y3F) was used. PAK1 Y3F showed decreased activation in response to PRL and no activation in response to E2. More interestingly, PRL and E2 stimulation of cells in which PAK1 Y3F was expressed showed significantly slower growth than cells with normal PAK1. Furthermore in *in vivo* studies, PRL and E2 stimulated cells expressing normal PAK1 to form significantly bigger tumors in mice than cells expressing PAK1 Y3F.

So what is the take home message from this study? ER+ breast cancers are treated with ER antagonist. Our study shows that PRL can take the place of E2 in driving breast cancer growth which explains resistance to anti-estrogen therapy; therefore, it is equally important to block the signals emanating from PRL receptors to effectively treat breast cancer. More importantly, PAK1 which is a common signaling node for PRL and E2 could be an effective therapeutic target for breast cancer treatment.

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