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Rolf J. Craven
University of Kentucky, rolf.craven@uky.edu

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Editorial

PGRMC1: a new biomarker for the estrogen receptor in breast cancer

Rolf J Craven

Department of Molecular and Biomedical Pharmacology, Markey Cancer Center, University of Kentucky, MS-305 UKMC, Lexington, KY 40536, USA

Corresponding author: Rolf J Craven, rolf.craven@uky.edu

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Abstract

Estrogen receptor (ER) status is a critical biomarker in breast cancer, in large part because the ER is the target of tamoxifen and similar drugs. In the previous issue of *Breast Cancer Research*, Neubauer and colleagues used a proteomic approach to identify proteins that are differentially regulated by ER in breast tumors. The authors showed that ER-negative tumors have elevated levels of PGRMC1 (progesterone receptor membrane component-1), a hormone receptor component and binding partner for P450 proteins. In contrast, PGRMC1 was phosphorylated in ER-positive tumors. The staining patterns of ER and PGRMC1 were mutually exclusive in breast tumor sections, and PGRMC1 staining was sharply increased in hypoxic areas of the tumor. The results suggest that PGRMC1 is a candidate biomarker for ER status and hypoxia in breast cancer.

Hormones, acting through their receptors, drive the proliferation of some tumor types, including breast, ovarian, and prostate tumors. The estrogen receptor (ER) has a profound effect on breast tumor growth and is the target for the drugs tamoxifen and fulvestrant. In spite of the importance of ER as a therapeutic target, ER-negative tumors have a more aggressive character and a different metastatic pathway than ER-positive tumors. Thus, the proteins that are negatively regulated by ER may constitute biomarkers and therapeutic targets for breast cancer.

In the previous issue of *Breast Cancer Research*, Neubauer and colleagues [1] found that PGRMC1 (progesterone receptor membrane component-1) is elevated in ER-negative tumors. In spite of its name, PGRMC1 is not a progesterone receptor but binds to P450 proteins, an unknown steroid-binding protein, and PAIR-BP1 (plasminogen activator inhibitor mRNA-binding protein), and PGRMC1 is linked to pro-survival signaling in cancer [2]. One caveat with the study by Neubauer and colleagues [1] is that estrogen-containing hormone treatments repress PGRMC1 transcription [3,4], but PGRMC1 transcriptionin tumors was not tested.

Neubauer and colleagues also found that PGRMC1 is phosphorylated in ER-positive tumors, suggesting that there is an ER-regulated kinase that phosphorylates PGRMC1. Identifying this kinase will be an interesting future direction of the research. Another notable point in the tumor analysis is the co-induction of PGRMC1, transferrin, and apolipoprotein A-1 because PGRMC1 has been implicated in both iron transport and cholesterol synthesis in model organisms [5-8]. In contrast, cytochrome b_5 has the opposite expression pattern from PGRMC1 in tumors, even though PGRMC1 is related to cytochrome b_5 structurally [9].

Our laboratory has previously shown that PGRMC1 is over-expressed in breast tumors compared with corresponding non-malignant tissue [10]. PGRMC1 is also overexpressed in ovarian tumors in a manner that correlates with tumor stage [11]. Neubauer and colleagues suggest that PGRMC1 correlates with ER status, but their conclusions are limited by the small sample size, and it will be interesting to see this correlation tested in a larger study. Both ER-negative status and hypoxia correlate with poor outcome in breast cancer [12,13], and it is possible that PGRMC1 levels will have a similar predictive value. However, the results of Neubauer and colleagues suggest that microarray correlations are not sufficient to address this question since PGRMC1 may be de-stabilized by phosphorylation in ER-positive tumors.

Neubauer and colleagues have shown that PGRMC1 induction is linked to hypoxia. This is consistent with the earlier work of Dressman and colleagues [14], which included PGRMC1 in a signature of genes that predict hypoxia in breast cancer. Furthermore, a yeast PGRMC1 homologue is

ER = estrogen receptor; PGRMC1 = progesterone receptor membrane component-1.

transcriptionally induced by hypoxia, and induction requires the SREBP homologue, *Sre1*$^{+}$ [8]. Many important regulatory pathways are conserved between yeast and humans, and it is intriguing to speculate that an SREBP-dependent pathway might trigger PGRMC1 induction in hypoxic human cells.

One of the compelling links between PGRMC1 and cancer is the ability of the former to activate intracellular signaling, including the Akt kinase [15]. Interestingly, Ser56 and Ser180 are required to activate Akt after oxidative damage in a PGRMC1-overexpressing cell line. There are two likely mechanisms through which PGRMC1 activates Akt. First, PGRMC1 could activate P450 proteins and produce a metabolite or by-product (such as reactive oxygen species) that triggers Akt phosphorylation. Second, PGRMC1 may bind directly to an Akt activator [4]. If so, Ser56 and Ser180 could potentially be docking sites for proteins that activate Akt, such as PDK1. In such a scenario, we might envision PGRMC1 as a type of adaptor protein that is directly involved in cell signaling. In ER-negative tumors, increased PGRMC1-to-Akt activation could increase survival signaling, of which Akt is an important component, increasing anchorage-independent growth and drug resistance. The paper by Neubauer and colleagues represents an important step in understanding this pathway.

Competing interests

The author declares that he holds US Patent 7,342,100, entitled 'Hpr6 mutants and uses thereof'. However, he has no financial stake in the patent, and the subject of the patent does not overlap directly with this editorial.

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