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Progesterone Receptor Membrane Component-1 is Phosphorylated upon Progestin Stimulation and Binds to Estrogen Receptor ?-Coregulators PHB1 and PHB2 in Breast Cancer Cells

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Combined menopausal hormone therapy, using estrogen and synthetic progestins, is associated with an increased risk of developing breast cancer. The effect of progestins on breast cells is complex and not fully understood yet. In previous in vitro and in vivo studies, we found different progestins to increase the proliferation of Progesterone Receptor Membrane Component-1 (PGRMC1)-overexpressing MCF7 breast cancer cells, revealing a potential role of PGRMC1 in forwarding membrane-initiated progestin signals into the cell.

Therefore, the aim of this study was to further investigate the activation mechanism and downstream signaling of PGRMC1 after progestin binding.

To identify posttranslational modifications and potential interaction partners of the receptor after progestin binding, co-immunoprecipitation experiments were performed using MCF-7/PGRMC1 cells, followed by mass spectrometry analysis. To further validate the results, western blot analysis, proximity ligation assay and co-localization studies were conducted. Further, proliferation of MCF-7/PGRMC1 cells and MCF7/PGRMC1 cells, possessing point mutations at PGRMC1 phosphorylation sites, was investigated upon treatment with progestins.

Treatment of MCF7/PGRMC1 cells with the progestin norethisterone (NET) induces phosphorylation of the receptor at Casein Kinase 2 (CK2) phosphorylation site Ser181. Point mutation of the Ser181 phosphorylation site in MCF7/PGRMC1 cells impairs proliferation upon NET treatment. Further, the Estrogen Receptor ? (ER?)-coregulators Prohibitin 1 (PHB1) and Prohibitin 2 (PHB2) were identified as interaction partners of PGRMC1 after progestin treatment and upregulation of ER?-dependent genes could be observed.

This study gives further insight into the mechanism of differential phosphorylation of the receptor and confirms our earlier hypothesis that phosphorylation of the CK2 binding site is essential for activation of the receptor upon progestin binding. It further suggests an important role of PGRMC1 in the progression of breast cancer in progestin-based hormone replacement therapy.

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