

for progestin-induced breast cancer growth, we hypothesized that EZH2 could function as a mediator in the pro-tumorigenic effects of progestins, targeting specific tumor suppressor and differentiating genes to allow ER/PR-positive BC growth. In the present work we found that progestin treatment of T47D cells induced EZH2 mRNA and protein expression, which was abolished by the use of the progestin antagonist RU486 and when PR expression was blocked by siRNAs. We also studied the participation of EZH2 in the regulation of PR-regulated genes TNF α (TNF α), cyclin D1 and TIMP2. By ELISA assays, we observed that progestin treatment of T47D cells for 24 h induced TNF α secretion. This effect was abolished when EZH2 expression was inhibited in the presence of EZH2 siRNAs and when EZH2 enzymatic activity was blocked by the use of GSK126. Regarding TIMP2, we observed that EZH2 canonical activity participates in TIMP2 downregulation exerted by progestin treatment. We showed that EZH2 non-canonical function is also involved in progestin modulation of TIMP2 given that blockage of EZH2 activity did not completely revert progestin effect. Finally, we demonstrated that progestin upregulation of cyclin D1 did not require EZH2 activity. Our results prove that EZH2 engagement in PR target genes may involve its canonical or non-canonical function and therefore support further studies on other progestin-regulated cancer genes implicated in tumor growth.

Presentation: No date and time listed

Abstract citation ID: bvac150.1481

Steroid Hormones and Receptors

ODP438

Canonical and Non-canonical Function of EZH2 in Progesterone Receptor Target Genes in Breast Cancer

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Enhancer of Zeste homolog 2 (EZH2) is a histone methyltransferase which catalyzes the trimethylation of lysine 27 of histone H3 (H3K27me3), an epigenetic mark associated with chromatin compaction and transcriptional repression of target genes. This constitutes its canonical mechanism of action. Several studies have shown that EZH2 is able to activate gene transcription by forming transcriptional complexes through mechanisms that do not involve histone methylation. Indeed, EZH2 can also act in a non-canonical function by regulating transcription independently of its enzymatic activity. We have previously described that progestins induce the interaction between Progesterone Receptor (PR) and EZH2 in breast cancer (BC) cells, which results in the downregulation of tumor suppressor GATA3 and in the increase in cell proliferation. Since EZH2 has been implicated in the progression of several types of cancer, including those of the breast, and our own previous results indicate that EZH2 is required