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EZH2 Promotes Migration and Invasion of Triple-negative Breast Cancer Cells via Regulating TIMP2-MMP-2/-9 Pathway.

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Purpose: Enhancer of zeste homologue 2 (EZH2) is the catalytic core protein in the polycomb repressive complex 2 (PRC2), which catalyses the trimethylation of histone3 lysine27 and mediates gene silencing of the target genes that are involved in fundamental cellular processes, such as cell fate decision, cell cycle regulation, senescence, cell differentiation and cancer formation. But the consistent association between triple negative breast cancer (TNBC) metastasis and EZH2 has not been confirmed. The aim of this study was to investigate the role of EZH2 in regulation of metalloproteinases (TIMPs)/matrix metalloproteinases (MMPs) to promote metastasis of TNBC and the metastasis-associated genes regulated by EZH2 in TNBCs.

Materials and Method: The EZH2 was knockdown by the specific shRNAs delivered by the lentivirus system from National RNAi Core Facility in MDA-MB-231 and MDA-MB-468 of TNBCs, and then analyzed with trans-well assay, chromatin immunoprecipitation assay, gelatin zymorgraphy assay, and RT-PCR to confirm the role of EZH2 in regulation of tissue inhibitors of TIMPs/MMPs to promote metastasis of TNBCs.

Results: Our data shows that high levels of EZH2 expression promote invasion and migration of TNBCs. Also, expression of TIMP2 and EZH2 is inversely correlated, probably due to down regulation of TIMP2 expression by EZH2. And, transcriptional repression of the TIMP2 gene occurs through the EZH2-mediated histone H3 on lysine 27 trimethylation for repression in TNBCs. Some results also indicated that EZH2-mediated transcriptional repression of TIMP2 directly leads to activation of MMP-9 and MMP-2.

Conclusion: In this study, we showed that aberrant up regulation of EZH2 expression in TNBCs shift this balance towards MMPs and promote degradation of the metastasis is extracellular matrix (ECM). Therefore, the transcriptional repression of TIMP2 by EZH2, which acts as a potential oncogene in various malignancies, plays an active role in the up regulation of MMP activity and promotes ECM degradation and invasion and migration of TNBCs.