DOCTORAL THESIS

Elevated Extracellular Matrix Protein 1 in Circulating Extracellular Vesicles Enhances Obesity-associated Breast Cancer Progression: Apigenin as a Novel ECM1-targeted Therapeutic Agent

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ABSTRACT

Small extracellular vesicles (sEVs) mediate intracellular communication by transporting the cargo content to the target cells, which may be changed under pathological circumstances. Here, we found that extracellular matrix protein 1 (ECM1) protein levels were significantly increased in the circulating sEVs under obesity conditions. The loading of ECM1 protein into the sEVs was positively associated with integrin-β2 levels in the parental cells. Knockdown of integrin-β2 in the cells did not affect the cellular ECM1 protein levels but significantly reduced ECM1 protein in the sEVs released by the cells, while overexpression of integrin-β2 in the cells increased the sEV ECM1 protein levels. Treatments with the circulating sEVs purified from high-fat diet-induced obesity mice significantly enhanced breast cancer (BC) metastasis and growth *in vitro*, and *in vivo* with different mouse models and constitutive Rab27a knockout mice (B6/J-Rab27a-Cas9-KO). Identifying circulating sEVs ECM1 protein in promoting BC development under obesity conditions not only represents a novel mechanism but also suggests a novel sEVs-based strategy to treat obesity-associated BC.

Based on our findings, we have screened apigenin, an herbal compound, that could reduce ECM1 expression levels in BC. We also developed PD1-engineered sEVs as a drug delivery system to deliver apigenin to BC. Our

quantitative analysis demonstrated successful loading and encapsulation of apigenin into the vesicular structure of PD1-engineered sEVs. Moreover, treating BC with these sEVs could significantly increase apigenin levels in the cancer cells, hence reduced the cancer cell viability and ECM1 expressions. These findings suggest that PD1-engineered sEVs exhibit enhanced tumor-targeting capabilities by suppressing ECM1 expression and inhibiting BC growth. This highlights the therapeutic potential of PD1-engineered sEVs in cancer therapy, presenting a promising opportunity for clinical application.