Extracellular Vesicle-Mediated Transfer of DOC2B: Unveiling Tumor-Suppressive Mechanisms in Cervical Cancer

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Abstract: Double C-2 Like Domain Beta (DOC2B) located on chromosome 17q13.3, has previously been associated with metastasis suppression by inducing senescence and decelerating the epithelial-to-mesenchymal transition (EMT). Extracellular vesicle (EV)-mediated intracellular trafficking exerts a significant impact on tumorigenesis, metastasis, and therapeutic resistance. Currently, targeting EVs is considered a novel therapeutic approach for the improved management of cancer. The localization of DOC2B into EVs and its associated tumor growth regulatory properties remains unexplored in CC. SiHa cells, lacking endogenous DOC2B expression, were manipulated to overexpress DOC2B via retroviral transduction. EVs derived from both DOC2B-SiHa and vector-SiHa cells were co-incubated with recipient cells, and subsequent cellular and biochemical assays were conducted. Interestingly, we observed that DOC2B localizes to EVs in calcium-dependent manner. Co-culturing SiHa cells with DOC2B EVs induced notable morphological changes, hindered growth and migration, potentially through G0/G1 arrest and anoikis. The recipient SiHa cells exhibited heightened intracellular levels of reactive oxygen species (ROS) and calcium, alongside increased lipid droplet accumulation and lipid peroxidation. Additionally, DOC2B EVs downregulated active AKT1 and ERK1/2, suppressed EMT markers, promoted cellular senescence, and enhanced the cytotoxic effects of cisplatin. Notably, the chelation of intracellular calcium substantially decreased the localization of DOC2B to EVs thereby influencing its tumor-suppressive properties. Our findings suggest that EV-mediated transfer of DOC2B holds promise in mitigating aggressive behaviours in SiHa cells. This contributes novel insights into the intricate interplay between DOC2B, EVs, calcium and cervical cancer progression, presenting a foundation for future clinical applications.

Keywords: DOC2B, Extracellular Vesicles, Calcium, Cervical Cancer, EMT, Senescence

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