Docket #: S21-223

Blocking and Reversing Extracellular Vesicle-Driven Transcriptomic Transformation with Annexin V Treatment

Stanford researchers led by Dr. Francis Blankenberg have developed a novel therapeutic concept for blocking and reversing the transcriptomic changes induced by uptake of extracellular vesicles (EVs), including exosomes, by administration of Annexin V protein to a tumor microenvironment (TME). EVs continuously shed within the TME contain the cytoplasmic and membrane contents of their parental cells and are rapidly taken up by adjacent cells. It is known that tumor-derived EVs may interfere with immune therapies, and EV cross-talk can influence major tumor-related pathways such as hypoxia-driven epithelial-to-mesenchymal transition, cancer stemness, angiogenesis, and metastasis involving many cell types within the TME. The Stanford team has shown that infusion of rh-Annexin V (AnxV), a well-described safe human protein with nanomolar affinity for externalized membrane bound phosphatidylserine (PS), can block the uptake of PS+ EVs shed within the TME and inhibit EV-driven pro-tumoral transcriptomic transformation of tumor-associated immune, neo-angiogenic and stromal cells. They further show that irradiated orthotopic 4T1 murine mammary carcinomas transform the TME towards a pro-tumoral, immunosuppressive and neo-angiogenic transcriptome as determined by RNAseq analyses which can be reversed with systemic infusions of AnxV.

Stage of Development

The researchers have demonstrated that extracellular AnxV not only can inhibit PS-mediated phagocytosis/efferocytosis and PS receptor signaling pathways as described previously, but can reduce and/or reverse the pro-tumoral transcriptomic changes within the tumor microenvironment one week following a single 20 Gy dose of gamma radiation delivered to orthotopic 4T1 murine mammary carcinomas.

Applications

- Inhibition of pro-tumoral transformation of immune, stromal, and vascular cells mediated by EVs/exosomes shed by tumor cells
- AnxV treatment may be combined with a second anti-cancer therapy, e.g., radiation therapy, checkpoint inhibitor therapy, chemotherapy, CAR-T cell therapy, administration of anti-tumor antibodies, and targeted cancer therapy

Advantages

- New high potential therapeutic concept

Patents

- Published Application: WO2023130112

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