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Overcoming resistance in lung cancer using natural killer cell derived exosomes

Abstract:

We evaluated IL-15 stimulated natural killer cell-derived exosomes (NK-EVs) as therapeutic agents in vitro and in vivo in Osimertinib resistant lung cancer (H1975R) with EGFR mutations (L858R) in combination with carboplatin (CBP). NK-EVs were isolated by ultracentrifugation and characterized by nanoparticle tracking analysis and atomic force microscopy imaging revealed vesicles with a spherical form and sizes meeting the criteria of exosomal EVs. Further, western blot studies demonstrated the presence of regular EV markers along with specific NK markers (perforin and granzyme). EVs were also characterized by proteomic analysis which demonstrated that EVs had proteins for natural killer cell mediated cytotoxicity (Granzyme B) and T cell activation (Perforin and Plastin-2). Gene oncology analysis showed that these differentially expressed proteins are involved in programmed cell death and positive regulation of cell death. Further, isolated NK-EVs were cytotoxic to H1975R cells in vitro in 2D and 3D cell cultures. CBP's IC 50 was reduced by approximately 2 folds in 2D and 3D cell culture when combined with NK-EVs. The EVs were then combined with CBP and administered by i.p. route to H1975R tumor xenografts and significant reduction in tumor volume in vivo was observed(P<0.001). Further NK EVs were encapsulated with miR 593 and mIR 149-5p based on our gene ontology studies and further studied in PDX lung cancer models. Our findings show for the first time that NK-EVs target the PD-L1/PD-1 immunological checkpoint, induce apoptosis and anti-inflammatory response by downregulation of SOD2, PARP, BCL2, SET, NF-κB and TGF-ß. The ability to isolate functional NK-EVs on a large scale and using them with platinum-based drugs may lead to new clinical applications and suggest the possibility of the combination of NK-cell-derived EVs and CBP as a viable immunochemotherapeutic strategy for resistant cancer

Biography

Mandip Singh Sachdeva is a Professor of Basic Sciences and Pharmaceutics Section Leader at Florida A&M University's College of Pharmacy and Pharmaceutical Science. He also serves as the Editor in Chief of Critical Reviews in Therapeutic Drug Carrier Systems. Based in the Dyson Pharmacy Building, Dr. Sachdeva is recognized for his contributions to pharmaceutical sciences, with a particular focus on drug delivery systems and therapeutic innovations. His work fosters advancements in pharmacy education and research.