

Title: Allogeneic Tumor Extracellular Vesicles Stimulate CD8 T Cell Response in Colorectal Cancer

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The majority of colorectal cancer (CRC) patients present with a microsatellite-stable (MSS) phenotype, rendering them highly resistant to immune checkpoint inhibitor (ICI) therapies. Among the contributors to intrinsic ICI resistance, tumor-derived extracellular vesicles (TEVs) have emerged as critical players. Our prior investigations have demonstrated that the autologous transfer of TEVs without functional miR-424 can induce tumor antigen-specific immune responses. Therefore, we postulated that allogeneic TEVs, modified to lack miR-424 and derived from an MC38 background, could incite CD8⁺ T cell responses while restraining CT26 tumor growth. Here we show that the prophylactic administration of MC38 TEVs, without functional miR-424, showed a significant augmentation in CD8⁺ T cells within CT26 CRC tumors. This allogenic TEV effect was evident in CT26 tumors but not B16-F10 melanoma tumors. Furthermore, we demonstrated the capacity of dendritic cells (DCs) to internalize TEVs, a possible mechanism to elicit an anti-tumor immune response. Moreover, our investigation of autologously administered DCs, which had been exposed to MC38 modified TEVs, underscores their potential to dampen tumor growth while elevating CD8⁺ T cell levels vis-à-vis MC38 wild-type TEVs exposed to DCs. Notably, the modified TEVs were well tolerated and did not increase peripheral blood cytokine levels. Our findings underscore the potential of allogeneic-modified TEVs without immune-suppressive miR-424 to elicit robust CD8⁺ T cell responses and limit tumor growth in CRC.