**Novel immunotherapeutic approach using engineered T cell-derived extracellular vesicles**

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**Abstract**

T cell-derived small extracellular vesicles (sEVs) exhibit anti-cancer effects. However, their anti-cancer potential should be reinforced to enhance clinical applicability. Herein, we generated interleukin-2-tethered sEVs (IL2-sEVs) from engineered Jurkat T cells expressing IL2 at the plasma membrane via a flexible linker to induce an autocrine effect. IL2-sEVs increased the anti-cancer ability of CD8+ T cells without affecting regulatory T (Treg ) cells and down-regulated cellular and exosomal PD-L1 expression in melanoma cells, causing their increased sensitivity to CD8+ T cell-mediated cytotoxicity. Its effect on CD8+ T and melanoma cells was mediated by several IL2-sEV-resident microRNAs (miRNAs), whose expressions were upregulated by the autocrine effects of IL2. Among the miRNAs, miR-181a-3p and miR-223-3p notably reduced the PD-L1 protein levels in melanoma cells. Interestingly, miR-181a-3p increased the activity of CD8+ T cells while suppressing Treg cell activity. IL2-sEVs inhibited tumour progression in melanoma-bearing immunocompetent mice, but not in immunodeficient mice. The combination of IL2-sEVs and existing anti-cancer drugs significantly improved anti-cancer efficacy by decreasing PD-L1 expression in vivo. Thus, IL2-sEVs are potential cancer immunotherapeutic agents that regulate both immune and cancer cells by reprogramming miRNA levels.

Keywords: Immunotherapy, EV, exosomes, PD-L1, IL2