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Extracellular Vesicles as a Novel Immunotherapeutic Strategy in Hashimoto's Thyroiditis: Advances in Targeted Delivery Technologies

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Hashimoto's thyroiditis (HT), the leading cause of hypothyroidism, is characterized by a dysfunction of regulatory T cells (Tregs), resulting in a breakdown of self-tolerance and a chronic immune-inflammatory response driven by intra-thyroidal lymphocytic infiltration. The persistence of pro-inflammatory cytokines (e.g., IFN-γ, IL-17) and chemokines (e.g., MCP-1) fuels the autoimmune attack on the thyroid, highlighting the inflammatory cascade as a promising therapeutic target, particularly in the early stages of the disease.

In recent years, extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) have garnered increasing attention in regenerative medicine due to their ability to transfer the immunomodulatory properties of their cells of origin. Harnessing these properties, our study investigates the impact of Th1 priming on the cargo of small EVs (sEVs) derived from human fibroblast-like limbal mesenchymal stem cells (f-LSCs) and their capacity to modulate the activation state of peripheral blood mononuclear cells (PBMCs) in HT patients.

To this end, f-LSC-derived sEVs were isolated using tangential flow filtration (TFF) and extensively characterized through dynamic light scattering, flow cytometry, and western blot analysis. Furthermore, an optimized single-step freeze-drying protocol was developed to enable stable EVs storage, facilitating future clinical applications. PBMCs from HT patients and healthy controls were exposed to sEVs under pro-inflammatory conditions to assess their effects on T cell proliferation and immune modulation.

The *ex vivo* model developed in this study demonstrated that TFF isolation combined with lyophilization enhances EVs stability and preserves their bioactivity while reducing financial and instrumental constraints. Notably, Th1 priming enriched the bioactive protein cargo of sEVs, leading to a dose-dependent modulation of key inflammatory mediators (e.g., MCP-1, IL-2) and an increased presence of immunomodulatory proteins such as COX-2 and Hsp70. These molecular changes promoted Treg activity, suggesting that sEVs may serve as carriers of proteins capable of restoring a functional Treg population.

In conclusion, our findings position EVs as a promising immunotherapeutic tool for HT, leveraging cutting-edge delivery technologies to optimize their therapeutic potential. The ability to tailor EVs cargo through Th1 priming opens new avenues for precision medicine, offering innovative strategies to modulate immune dysregulation in autoimmune thyroid diseases.

Disclosure of interest: None declared