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Trichinella spiralis extracellular vesicles induce anti-inflammatory and regulatory immune responses in vitro

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Abstract

The helminth Trichinella spiralis, through its excretory-secretory (ES L1) products, induces immune regulatory mechanisms that modulate the host's immune response not only to itself, but also to bystander antigens, foreign or self in origin, which can result in the alleviation of inflammatory diseases. Under the influence of ES L1, dendritic cells (DCs) acquire a tolerogenic phenotype and the capacity to induce Th2 and regulatory responses. Since ES L1 products represent a complex mixture of proteins and extracellular vesicles (TsEVs) the aim of this study was to investigate the impact of TsEVs, isolated from ES L1 products, on phenotypic and functional characteristics of DCs and to elucidate whether TsEVs could reproduce the immunomodulatory effects of the complete ES L1 product. Monocyte-derived DCs treated with TsEVs acquired semi-matured phenotypes, characterized by low expression of human leukocyte antigen - DR isotype (HLA-DR), cluster of differentiation (CD) 86 (CD86), and CD40, moderate expression of CD83 and C-C chemokine receptor type 7 (CCR7), and increased expression of tolerogenic markers indoleamine 2,3-dioxygenase 1 (IDO-1) and immunoglobulin-like transcript 3 (ILT3), together with the unchanged production of IL-12 and IL-23, and elevated production of IL-10 and transforming growth factor (TGF)-β, compared with controls. Gene expression analysis of TsEV-treated DCs revealed elevated levels of mTOR, Ahr, NF-κB2, RelB, SOCS1 and SOCS3, which participate in signaling pathways involved in DC maturation and the subsequent regulation of release of both anti-inflammatory and pro-inflammatory cytokines. TsEVs promoted the capacity of DCs to drive polarization of Th2 and anti-inflammatory responses, and impaired their capacity to induce Th1/Th17 polarization. Moreover, TsEV-treated DCs possessed a high capacity to induce conventional FoxP3 + regulatory T cells, as well as unconventional T regulatory (Tr1) cells. Tolerogenic properties of TsEV-treated DCs were retained even after challenge with a pro-inflammatory stimulus. These findings highlight the potential of TsEVs to induce immune tolerance, suggesting their potential use as therapeutics for the treatment of inflammatory disorders.

Keywords: ES L1 products; Exosomes; Extracellular vesicles; Immunomodulation; Regulatory T cells; Tolerogenic dendritic cells; Trichinella spiralis.