Decoding Regulatory T-Cell Subset–Specific Extracellular Vesicle Signatures and Their Roles in Immune Homeostasis

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Overview

RESEARCH DIRECTION

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INFORMATION

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ADMINISTRATIVE UNIT(S)

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LEVEL(S)

2e cycle
3e cycle

LOCATION(S)

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Project Description

Regulatory T cells (Tregs) are essential for maintaining immune balance. They prevent excessive or prolonged immune responses by controlling dendritic cells, which initiate and direct immune responses, and $CD4^+$ effector T cells, which coordinate inflammation. Tregs communicate through direct contact, soluble factors, and small extracellular vesicles (sEVs). These nanosized, membrane-bound particles transfer biological molecules—including RNA, proteins, cytokines, enzymes, lipids, and metabolites—between cells and can modify recipient-cell proliferation, activation, functional state, and secretion.

A landmark study by Okoye et al. provided the first mechanistic evidence that exosomes contribute to Treg-mediated immune suppression. However, this foundational work examined canonical $CD4^+CD25^+Foxp3^+$ Tregs as a general regulatory population. It did not determine whether distinct Treg subsets produce sEVs with different molecular cargo or specialized immunoregulatory functions. Thus, although Treg-derived exosomes are recognized as mediators of immune suppression, their potential heterogeneity according to Treg subset of origin remains largely unexplored.

Tregs comprise several subsets with distinct phenotypic properties and mechanisms of immune suppression. These include natural and induced Tregs, type 1 regulatory T cells, $ICOS^+$ and $CXCR5^+$ Tregs, and Th3 cells. Our preliminary findings show that sEVs released by these regulatory-cell subsets contain different lipid and cytokine profiles. This suggests that each subset may produce sEVs with a characteristic molecular cargo and a specialized capacity to regulate immune responses. However, it remains unknown how Treg subset identity determines sEV composition and whether molecular differences among sEVs translate into distinct effects on dendritic cells and $CD4^+$ effector T cells. We hypothesize that individual Treg subsets release molecularly specialized sEVs that differentially regulate these immune-cell populations.

Objective 1: we will define and compare the molecular cargo signatures of sEVs released by distinct Treg subsets. Treg subsets will be isolated from mouse spleens by cell sorting and cultured under standardized conditions. Their sEVs will be purified from culture supernatants and validated according to size, structure, and molecular markers. We will then use an integrated multi-omics strategy to characterize their cargo. Small RNA sequencing will identify vesicular miRNAs, quantitative proteomics will define protein composition,

multiplex assays will measure selected cytokines and enzymes, and mass spectrometry will characterize metabolites. Integrating these datasets will reveal shared and subset-specific molecular signatures and prioritize candidate molecules for functional studies.
Objective 2: we will determine how sEVs from each Treg subset directly and indirectly regulate dendritic cells and $CD4^+$ effector T cells. Purified immune cells will be exposed to standardized sEV doses, and changes in proliferation, activation, functional state, and production of immune mediators will be measured. We will assess whether sEVs influence distinct $CD4^+$ T-cell responses and alter dendritic-cell maturation and regulatory properties. Because dendritic cells direct $CD4^+$ T-cell responses, sEV-exposed dendritic cells will subsequently be co-cultured with $CD4^+$ effector T cells. Comparing these responses with those produced by direct T-cell exposure will distinguish effects acting directly on T cells from those mediated through changes in dendritic-cell function. Molecular and functional datasets will then be integrated to identify sEV cargo components associated with specific cellular responses.
We expect that these strategies will provide crucial insights into how the identity of individual Treg subsets determines the molecular composition and immunoregulatory functions of their sEVs. Building on the foundational demonstration of exosome-mediated suppression by canonical $CD4^+CD25^+Foxp3^+$ Tregs, this work will establish whether phenotypically and functionally distinct Treg subsets use specialized sEV cargo to regulate dendritic cells and $CD4^+$ effector T cells. This will provide a better understanding of how regulatory-cell diversity shapes extracellular-vesicle communication and coordinates immune homeostasis.

Discipline(s) by sector

Sciences de la santé

Biologie cellulaire, Biologie moléculaire, Immunologie

Funding offered

Yes

The last update was on 7 August 2026. The University reserves the right to modify its projects without notice.