Secretome

- Transverse Myelitis Successfully Treated with Posterior Decompression Followed by Secretome and Mesenchymal Stem Cell Therapy
- In vitro and In vivo Studies on Mesenchymal Stem Cells for Ischemic Stroke Therapy: A Scoping Review of The Therapeutic Effect
- Optimizing mesenchymal stromal cells priming strategies for tailored effects on the secretome
- Innovating Glioma Therapy Using Secretions from Umbilical Cord Mesenchymal Stem Cells to Target Homeobox and Growth Factor Genes
- Gene expression profiles of angiogenesis markers and microRNA-128 from the secretome of umbilical cord mesenchymal stem cells from Macaca fascicularis
- In vitro models of microglia: a comparative study
- Traumatic Axonal Injury Successfully Treated with Secretome Followed by Mesenchymal Stem Cells Therapy
- IDH status dictates oHSV mediated metabolic reprogramming affecting anti-tumor immunity

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The secretome refers to the entire set of molecules actively secreted by a cell into the extracellular space. These molecules include:

Proteins: such as cytokines, - chemokines, growth factors, enzymes, etc.

Lipids

Non-coding RNAs: like microRNAs

Extracellular vesicles: including exosomes and microvesicles

Importance of the secretome

Cell-to-cell communication: Crucial for autocrine, paracrine, and endocrine signaling.

Immune modulation: Influences immune responses and inflammation.

Tissue regeneration: Involved in wound healing and stem cell-mediated repair.

Cancer biology: Tumor cells secrete factors that promote invasion, angiogenesis, and immune evasion.

Biomarker discovery: Secreted molecules are accessible in body fluids and are potential diagnostic/prognostic indicators.

Secretome Classification

The **secretome** refers to the set of molecules secreted by cells into the extracellular environment. It can be classified according to the **secretion pathway**, **molecular nature**, **function**, or **cellular origin**.

1. Based on Secretion Pathway

- **Classical Secretome**
  - Uses the ER-Golgi pathway
  - Requires a signal peptide
  - Examples:
    - Cytokines (e.g., IL-6)
    - Hormones (e.g., insulin)
    - Growth factors (e.g., VEGF)
- **Non-Classical (Unconventional) Secretome**
  - Does **not** use the ER-Golgi pathway
  - Lacks signal peptide
  - Examples:
    - FGF-1, FGF-2
    - IL-1β
    - HSP70

2. Based on Molecular Nature

- **Proteins**
  - Cytokines, enzymes, receptors, growth factors
- **Lipids**
  - Eicosanoids, sphingolipids
- **Nucleic Acids**
  - microRNAs, long non-coding RNAs (lncRNAs)
- **Extracellular Vesicles**
  - Exosomes (30–150 nm)
  - Microvesicles (100–1000 nm)

3. Based on Functional Role

- **Immunomodulatory**
  - IL-10, TGF-β
- **Pro-angiogenic**
  - VEGF, angiopoietins
- **Anti-apoptotic**
  - Survivin, HSPs
- **Pro-metastatic**

    - MMPs, integrins
- **Neurotrophic**
    - BDNF, GDNF

4. Based on Cellular Source

- **Stem Cell Secretome**
    - Mesenchymal stem cells (MSCs), iPSCs
- **Tumor Secretome**
    - Cancer cells, tumor microenvironment
- **Immune Cell Secretome**
    - Macrophages, T-cells, dendritic cells
- **Neural Secretome**
    - Neurons, astrocytes, microglia

`Note:` The study of the secretome is crucial in regenerative medicine, cancer research, and biomarker discovery.

Preclinical Experimental Studies

González-Rodríguez et al. evaluated the effects of hypoxia, pro-inflammatory cytokines, and spheroid culture conditions on ASC secretome composition and functionality. Gene expression analysis, nanoparticle tracking, protein quantification, and functional assays were performed to characterize the secretomes. RNA sequencing revealed significant differences in gene expression profiles across priming conditions, particularly in pathways related to osteogenesis, angiogenesis, inflammation, and neurotrophic factors. Notably, spheroid culture combined with hypoxia and inflammation resulted in a substantial increase in extracellular vesicle production and altered protein content. Functional assays demonstrated enhanced neutrophil inhibition by secretomes from hypoxia-primed ASCs. Our findings indicate that tailored priming strategies can significantly modulate the therapeutic properties of ASC secretomes, potentially enhancing their efficacy in various clinical applications. This study provides valuable insights for optimizing cell-free therapies in regenerative medicine and offers a basis for developing more targeted and effective treatments [1)]

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1. Strengths a. Relevance and Innovation The study addresses a highly topical area: cell-free therapies using the MSC secretome.

Shifts focus from cells to secreted factors, aligning with translational trends in regenerative medicine.

b. Comprehensive Priming Evaluation Tests multiple relevant priming conditions: hypoxia, inflammatory cytokines, and 3D spheroid culture.

The combination of hypoxia + inflammation + 3D culture is especially novel and clinically promising.

c. Robust Methodology Multi-omics and functional readouts:

RNA-seq for transcriptomic profiling.

Nanoparticle tracking for EV quantification.

Protein quantification for content analysis.

Functional assays (e.g., neutrophil inhibition) for immunomodulatory effect.

d. Biological Insights Demonstrates that priming strongly alters the secretome, both quantitatively and qualitatively.

Identifies inflammation- and angiogenesis-related pathways that could be targeted for therapy customization.

2. ⚠ Limitations a. Lack of In Vivo Validation The study is entirely in vitro, limiting conclusions about actual clinical efficacy or bioavailability in a living system.

No disease models were used to test therapeutic impact in context (e.g., osteoarthritis, wound healing, stroke).

b. Limited Functional Assays Although a neutrophil inhibition assay was used, broader functional validation (e.g., macrophage polarization, endothelial migration, neuroprotection) is missing.

No dose-response or kinetic data presented for secretome effects.

c. Heterogeneity of EVs Not Addressed EV characterization focused on particle count and size, but EV subtypes (e.g., exosomes vs microvesicles) were not well distinguished.

Lacks deep proteomic or miRNA profiling of EVs.

d. No Benchmarking with Unprimed Controls in All Assays While comparative, the study sometimes lacks a clear baseline of non-primed MSCs across every assay type for relative quantification.

3. Overall Assessment This is a solid preclinical study that advances understanding of how priming conditions alter MSC secretomes. The experimental design is strong, and the findings are biologically relevant. However, lack of in vivo work and limited functional breadth somewhat restrict the translational impact. Future studies should focus on disease models, EV subtype characterization, and functional assays relevant to clinical endpoints.

 Suggested Future Directions In vivo testing of optimized secretomes in animal models (e.g., ischemia, inflammation, degenerative diseases).

Proteomic and miRNA profiling of EVs under each priming condition.

Exploration of storage, stability, and bio-distribution of secretomes for real-world application.

Use of patient-derived immune cells or organoids for more translational functional assays.

1)

González-Rodríguez Y, Casado-Santos A, González-Cubero E, González-Fernández ML, Sellés-Egea A, Villar-Suárez V. Optimizing mesenchymal stromal cells priming strategies for tailored effects on the secretome. Biomed Pharmacother. 2025 May 29;188:118218. doi: 10.1016/j.biopha.2025.118218. Epub ahead of print. PMID: 40446445.