SUMMARY (Basic) 4/25/25 ciT1zen science

Exosomes in Systemic Autoimmune Diseases
ciT1zen science summary

Source: Excerpts from "A multitude of skills in exosomes: From biomarkers to therapeutic applications" - Specifically focusing on the sections "Exosomes in Systemic Autoimmune Diseases: Recent Advances in Diagnostic Biomarkers and Therapeutic Applications" and related foundational information.
https://doi.org/10.2147/IJN.S506221

Summary:
This document reviews the emerging role of exosomes, nanoscale extracellular vesicles, in systemic autoimmune diseases (SADs). The reviewed source highlights the multifaceted involvement of exosomes in the pathogenesis of SADs, including their roles in intercellular communication, immune modulation, antigen presentation, and inflammatory responses. Exosomes carry a diverse cargo of proteins, miRNAs, and lipids that significantly influence immune function. This review explores the potential of exosomes as non-invasive biomarkers for the diagnosis, monitoring, and prediction of therapeutic response in four common SADs: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome (SS). Furthermore, it discusses the therapeutic potential of both naturally derived (e.g., from mesenchymal stromal cells - MSCs) and engineered exosomes as cell-free immunotherapies and drug delivery vehicles for these challenging conditions. While promising, the clinical implementation of exosomes in SADs faces challenges related to production costs, technical complexity, lack of standardization, and the need for further research and clinical trials.

Main Ideas/Facts:
1. Introduction to Systemic Autoimmune Diseases (SADs):
- SADs are characterized by the immune system mistakenly attacking multiple body tissues and organs, leading to chronic inflammation and damage.
- They affect approximately 10% of the global population and pose significant healthcare challenges due to their complexity and increasing prevalence.
- Current treatments are often limited to symptomatic relief or broad immunosuppression, which can have poor efficacy and serious side effects.
- Understanding the molecular mechanisms underlying SADs is crucial for developing new diagnostic and therapeutic strategies.

2. The Role of Exosomes in Immunity and Intercellular Communication:
    - Exosomes are nanoscale extracellular vesicles (40-160 nm) secreted by cells that play a vital role in intercellular communication and immune modulation.
    - They possess strong immune regulatory properties essential for maintaining cellular homeostasis and mediating immune tolerance.
    - Exosomes carry molecular cargo (proteins, miRNAs, lipids) that can be transferred to recipient cells, modulating gene expression and signaling pathways critical for immune regulation.
    - "The cargo of exosomes, such as proteins, miRNAs, and lipids, are vital determinants of cellular and humoral immunity."
3. Biological Characteristics and Biogenesis of Exosomes:
    - Exosomes originate from multivesicular endosomes (MVEs) through a process involving membrane invaginations and fusion sorting.
    - Their membranes contain various proteins, including tetraspanins, transporters, signal transduction receptors, and integrins, which mediate immune cell communication.
    - Exosome biogenesis is a highly regulated process involving the endosomal sorting complex required for transport (ESCRT). Dysregulation of this process can contribute to autoimmune pathology by altering exosome composition and release.
    - "The formation of MVEs and the generation of ILVs depend critically on the endosomal sorting complex required for transport (ESCRT)."
4. Heterogeneity of Exosomes:
    - Exosomes exhibit significant heterogeneity in size, composition (nucleic acids, lipids, proteins, metabolites), cellular origin, and function.
    - This heterogeneity influences their targeting specificity and their diverse roles in either exacerbating or suppressing autoimmune responses.
    - "Exosomes exhibit variability across four aspects: size, composition, cellular origin, and function."
5. Exosomes as Biomarkers for SADs:
    - The molecular content of exosomes isolated from various body fluids (serum, plasma, urine) reflects the pathological state of their parent cells, making them potential non-invasive biomarkers for SADs.
    - Specific exosomal miRNAs, lncRNAs, mRNAs, and proteins are differentially expressed in patients with RA, SLE, SSc, and SS compared to healthy individuals.
    - In RA, upregulated exosomal miRNAs like miR-885-5p and miR-6894-3p, and dysregulated miR-451a and miR-25-3p show promise for early diagnosis, including ACPA-negative cases.

- In SLE, exosomal miRNAs such as miR-21, miR-155, and miR-451a correlate with disease activity and renal injury, while urinary exosomal tsRNAs are emerging as markers for lupus nephritis (LN).
- In SSc, aptamer proteomics of serum exosomes has identified differential proteins related to inflammation and immunity as potential early biomarkers. Circulating exosomal lncRNA-miRNA-mRNA networks are also being explored.
- In SS, differentially expressed proteins (related to ferroptosis) and circRNAs/miRNAs in plasma and saliva-derived exosomes show potential for early and non-invasive diagnosis.
- "Screening for differential exosomal contents can help elucidate the pathological mechanisms of SADs and provide new strategies for non-invasive diagnosis."

6. Therapeutic Potential of Exosomes in SADs:
    - Exosomes, particularly those derived from MSCs, exhibit immunomodulatory effects in SADs by influencing immune cells and joint cells.
    - MSC-derived exosomes can carry therapeutic miRNAs (e.g., miR-451a in RA, miR-29a-3p in SSc, miR-125b in SS) that target disease-relevant pathways.
    - Engineered exosomes with enhanced targeting and drug loading capabilities are emerging as promising drug delivery vehicles for targeted therapy in SADs.
    - Examples include exosomes loaded with anti-inflammatory drugs (e.g., glucocorticoids in RA), cfDNA scavengers, and molecules modulating immune cell polarization.
    - Exosomes expressing PD-L1 have shown therapeutic potential in animal models of autoimmune diseases by modulating the local immune microenvironment.
    - "Engineered exosomes, with enhanced targeting, bioavailability, low toxicity, are emerging as promising drug delivery vehicles."
7. Challenges and Future Directions:
    - Clinical application of exosomes in SADs is still in early stages, with no completed clinical trials specifically for exosome-based therapies reported in the reviewed source.
    - Challenges include high production costs, technical complexity in isolation and characterization, inefficiency in some aspects, and the lack of standardized protocols.
    - Further research is needed to fully understand the diverse roles of exosomes in SAD pathogenesis and to optimize their therapeutic applications.

- Large-scale clinical studies are necessary to validate exosome-based biomarkers and establish standardized detection protocols.
- Future research should focus on understanding how factors like ethnicity, gender, and aging influence exosome cargo and function in SADs.
- Engineered exosomes offer opportunities to overcome limitations by enhancing targeting, drug loading, and circulation half-life.
- Careful evaluation of the dual role of exosomal immune checkpoint molecules like PD-L1 in both autoimmunity and cancer is crucial.
- "Continued research and well-designed clinical trials will be crucial in refining exosome-based drug delivery systems and optimizing their therapeutic applications for SADs."

Key Quotes:

- "Systemic autoimmune diseases (SADs) encompass a spectrum of organ involvement, clinical heterogeneity, and therapeutic challenges meriting significant research."
- "Accumulating evidence indicates that exosomes have multifaceted roles in the pathogenesis of SADs through processes like cellular signaling, immune modulation, antigen presentation, and inflammatory response."
- "This review examines key signaling pathways in four common SADs, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome, and explores exosome as non-invasive biomarkers for diagnosis, disease monitoring, and therapeutic response prediction."
- "Additionally, the therapeutic potential of mesenchymal stromal cells (MSCs) or various type of mesenchymal stem cells derived exosomes as cell-free immunotherapies for SADs is highlighted."
- "However, challenges such as high production costs, technical complexity, and inefficiency, along with the lack of standardized protocols, limit clinical implementation in SADs."
- "A deeper understanding of exosome roles in SADs pathogenesis and innovative immunotherapies may provide valuable theoretical support for the diagnosis and treatment of these challenging conditions."

Implications:

- Exosomes hold significant promise for revolutionizing the diagnosis and treatment of SADs due to their involvement in disease pathogenesis and their potential as biomarkers and therapeutic agents.
- The development of non-invasive exosome-based diagnostic tools could lead to earlier detection, improved monitoring, and personalized treatment strategies for SADs.

- Cell-free therapies using MSC-derived or engineered exosomes offer a potentially safer and more targeted approach compared to traditional immunosuppressants.
- Addressing the current challenges in exosome research and translation, such as standardization and scalability, is crucial for realizing their clinical potential in SADs.

Further Research Needs:

- Comprehensive studies to further elucidate the specific roles of different exosome subtypes and their cargo in the pathogenesis of individual SADs.
- Development of standardized protocols for exosome isolation, characterization, and quantification for diagnostic and therapeutic applications.
- Rigorous preclinical studies and well-designed clinical trials to evaluate the safety and efficacy of exosome-based therapies for SADs.
- Research focused on optimizing the engineering of exosomes for enhanced targeting, drug loading, and stability.
- Investigation into the long-term effects and potential risks associated with exosome-based therapies, including their interaction with the tumor microenvironment.
- Studies exploring the influence of patient-specific factors (e.g., genetics, ethnicity, age, gender) on exosome profiles in SADs.