



Salivary Extracellular Vesicles as Early Biomarkers of Autoimmune Oral Diseases

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ABSTRACT

Salivary extracellular vesicles (sEVs), including exosomes and microvesicles, have emerged as promising non-invasive biomarkers for the early detection and monitoring of autoimmune oral diseases. These nanoscale vesicles contain diverse biological cargo, including proteins, lipids, messenger RNAs, microRNAs, and other regulatory molecules that reflect physiological and pathological changes occurring within oral and systemic tissues. Their presence in saliva provides an accessible opportunity to identify molecular alterations associated with immune dysregulation before substantial clinical manifestations develop. In autoimmune conditions such as primary Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis, disease-associated changes in extracellular vesicle composition may provide valuable information regarding inflammation, salivary gland dysfunction, tissue injury, and disease activity. Advances in extracellular vesicle isolation, molecular profiling, multi-omics analysis, and artificial intelligence may facilitate the identification of highly specific biomarker signatures and improve diagnostic accuracy. Salivary EVs may also support disease monitoring, treatment-response assessment, and personalized clinical management. However, variability in saliva collection, EV isolation, characterization, molecular heterogeneity, and biomarker validation remains a major barrier to routine clinical implementation. Standardized methodologies and large-scale prospective studies are therefore required to establish clinically reliable diagnostic panels. Overall, salivary extracellular vesicles represent a promising foundation for minimally invasive, precision-oriented diagnosis of autoimmune oral diseases.

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INTRODUCTION AND BIOLOGICAL BASIS

Autoimmune oral diseases represent a clinically important group of disorders characterized by dysregulated immune responses that can affect salivary glands, oral mucosa, periodontal tissues, and dental structures. Primary Sjögren's syndrome (pSS) is particularly significant because autoimmune destruction of salivary glands can produce xerostomia, impaired oral defense mechanisms, recurrent infections, and progressive oral complications. Early identification of immune-mediated changes is therefore essential for timely intervention and prevention of tissue damage (Shahsavari & Liu, 2024).

Salivary extracellular vesicles (sEVs) are membrane-enclosed nanoparticles released by different cell types and include exosomes, microvesicles, and other vesicular populations. They transport biologically active cargo such as proteins, lipids, messenger RNA, microRNAs, and other regulatory molecules, allowing them to participate in intercellular communication and reflect disease-associated cellular changes. Their molecular contents have consequently attracted considerable interest as potential biomarkers of oral and systemic diseases (Hadavand & Hasni, 2019; Xu et al., 2020).

Saliva provides an especially attractive medium for extracellular-vesicle-based diagnostics because it can be collected non-invasively, repeatedly, and with relatively low patient burden. Salivary EVs may capture molecular information originating from oral tissues and systemic circulation, creating opportunities for early detection, disease monitoring, and personalized assessment (Cui et al., 2024). In pSS, EV-associated molecular signatures may reflect inflammatory activity and salivary gland dysfunction, supporting their potential as complementary diagnostic tools (Shahsavari & Liu, 2024).

The increasing application of artificial intelligence in dentistry provides additional opportunities to analyze complex EV-derived molecular datasets and identify disease-specific patterns (Singh, 2022). Likewise, biologically focused dental research, such as evaluation of pulpal responses to therapeutic interventions, emphasizes the importance of molecular indicators for understanding oral tissue responses (Singh et al., 2026). Collectively, these developments establish a strong biological and technological foundation for investigating salivary EVs as early biomarkers of autoimmune oral diseases.

Salivary EV Biomarkers and Diagnostic Applications

Salivary extracellular vesicles (sEVs), particularly exosomes and microvesicles, provide a biologically informative source of disease-associated molecules because their cargo reflects cellular signaling, immune activation, inflammation, and tissue injury. Their detection in saliva offers a minimally invasive approach for identifying molecular changes associated with autoimmune oral diseases. Exosomal proteins, messenger RNAs, microRNAs, lipids, and cytokine-related molecules may therefore serve as candidate biomarkers for disease detection and monitoring (Hadavand & Hasni, 2019; Cui et al., 2024).

Molecular Biomarker Potential

The diagnostic value of sEVs is primarily related to their protected molecular cargo. Alterations in EV-associated miRNAs may indicate dysregulated immune pathways, while proteins and nucleic acids can reflect inflammatory activity and salivary gland dysfunction. Because extracellular vesicles participate in intercellular communication and immune regulation, their molecular profiles may provide information about systemic autoimmune processes as well as localized oral pathology (Xu et al., 2020).

Diagnostic Applications in Primary Sjögren’s Syndrome

Primary Sjögren’s syndrome (pSS) represents an important target for salivary EV diagnostics because salivary gland dysfunction is a central clinical feature. EV-associated molecular signatures may assist in distinguishing autoimmune-mediated xerostomia from non-autoimmune causes and potentially identify disease-associated changes earlier in the disease course (Shahsavari & Liu, 2024).

Broader Diagnostic and AI Applications

Beyond pSS, salivary EV profiling may support investigation of systemic autoimmune diseases with oral manifestations.

Integration of EV-derived multi-omics data with artificial intelligence could improve biomarker selection, disease classification, and individualized risk prediction. AI-based approaches are increasingly relevant to data-driven diagnostic development in dentistry (Singh, 2022). Biologically informed oral diagnostics are also supported by emerging research evaluating tissue responses to dental interventions (Singh et al., 2026).

Overall, salivary EVs offer considerable potential for developing non-invasive, molecularly precise diagnostic strategies for autoimmune oral diseases, although clinical translation requires standardized EV characterization and validation in larger patient populations (Cui et al., 2024; Shahsavari & Liu, 2024).

CLINICAL TRANSLATION, AI INTEGRATION, AND CHALLENGES

Clinical Translation and Diagnostic Applications

Salivary extracellular vesicles (sEVs) offer a minimally invasive platform for detecting molecular alterations associated with autoimmune oral diseases. Their proteins, miRNAs, mRNAs, and other cargo may reflect immune activation, salivary gland dysfunction, and tissue injury, supporting early diagnosis and longitudinal monitoring (Hadavand & Hasni, 2019; Xu et al., 2020). In primary Sjögren’s syndrome, EV-based biomarkers may complement conventional serological and clinical assessments and potentially distinguish autoimmune xerostomia from non-autoimmune conditions (Shahsavari & Liu, 2024). Broader advances in salivary EV diagnostics further support their application in disease monitoring and therapeutic evaluation (Cui et al., 2024).

AI Integration and Precision Diagnostics

Artificial intelligence can analyze complex EV-derived proteomic, transcriptomic, and miRNA datasets to identify multidimensional biomarker signatures. Machine-learning models could integrate molecular findings with clinical characteristics, laboratory parameters, and imaging data to improve disease classification and individualized risk prediction. Such computational approaches align with the

Table 1: Salivary EV Biomarkers and Diagnostic Utility

EV biomarker/ component	Diagnostic information	Potential application
miRNAs	Immune and inflammatory regulation	Early disease detection
EV proteins	Inflammation and tissue injury	Disease classification
mRNAs	Altered cellular gene expression	Molecular profiling
Lipids	Cellular signaling changes	Disease characterization
Cytokine- associated cargo	Immune activation	Disease activity monitoring
Combined EV signatures	Multidimensional disease patterns	AI-assisted precision diagnosis

Table 2: Clinical Translation, AI Integration, and Key Challenges

Area	Clinical potential	Major challenge
Early diagnosis	Detect autoimmune molecular signatures	Biomarker specificity
pSS assessment	Complement conventional diagnosis	Disease heterogeneity
Monitoring	Track disease activity and treatment response	Temporal variability
AI integration	Multimarker prediction and classification	Dataset quality and validation
Precision medicine	Individualized risk stratification	Clinical standardization
Routine implementation	Non-invasive saliva-based testing	Cost, protocols, and reproducibility

expanding role of AI in dentistry and diagnostic decision-making (Singh, 2022).

Challenges and Translational Barriers

Clinical implementation remains limited by variability in saliva collection, EV isolation, characterization, storage, and analytical platforms. Biological heterogeneity and differences related to medications, oral health, age, and systemic conditions may also affect biomarker reproducibility. Large, standardized, prospective cohorts are required for validation. Furthermore, AI models require high-quality datasets and external validation. Evidence-based oral tissue assessment, including investigations of pulpal responses to dental interventions, emphasizes the importance of linking molecular biomarkers with clinically meaningful outcomes (Singh et al., 2026).

Overall, standardized EV methodologies combined with validated AI-driven analyses could accelerate the transition of salivary EV biomarkers from experimental discovery to clinically useful precision diagnostics (Cui et al., 2024; Xu et al., 2020).

FUTURE PERSPECTIVES

Future research should focus on establishing standardized protocols for salivary extracellular vesicle (sEV) collection, isolation, characterization, and molecular analysis to improve reproducibility and facilitate clinical translation. Because EVs contain proteins, lipids, mRNAs, and microRNAs capable of reflecting immune and tissue alterations, multimodal profiling may enable the development of sensitive biomarker panels for autoimmune oral diseases (Hadavand & Hasni, 2019; Xu et al., 2020). Particular attention should be given to primary Sjögren’s syndrome, where EV-based approaches may complement conventional clinical, serological, and imaging assessments and potentially support earlier diagnosis and treatment monitoring (Shahsavari & Liu, 2024).

Integration of sEV biomarkers with proteomics, transcriptomics, metabolomics, and artificial intelligence could further improve disease classification and individualized risk prediction. AI-based approaches may identify complex biomarker patterns that are difficult to recognize using conventional statistical methods, supporting data-driven diagnostic strategies in dentistry (Singh, 2022). Prospective multicenter studies are nevertheless required to validate candidate biomarkers across diverse populations and establish clinically meaningful diagnostic thresholds.

Broader biologically informed approaches to oral disease assessment, such as the evaluation of pulpal responses to dental interventions, further emphasize the importance of integrating molecular evidence into clinical decision-making (Singh et al., 2026).

CONCLUSION

Salivary extracellular vesicles represent a promising, minimally invasive platform for the early detection and monitoring of autoimmune oral diseases. Their molecular cargo can provide information about immune dysregulation, inflammation, and tissue dysfunction, while their accessibility through saliva offers considerable clinical advantages (Cui et al., 2024). Although methodological variability and insufficient clinical validation remain important challenges, continued advances in EV biology, multi-omics, and AI may enable reliable precision-diagnostic tools. Ultimately, standardized validation and integration with established diagnostic approaches could establish sEVs as valuable biomarkers for early diagnosis, disease monitoring, and personalized management of autoimmune oral diseases.

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