Salivary Exosome Biomarkers for Predicting Delayed Wound Healing after Oral Surgery

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Abstract

Delayed wound healing following oral surgical procedures remains a significant clinical challenge, often resulting in prolonged recovery, increased risk of infection, and compromised treatment outcomes. Early identification of patients at risk requires reliable, minimally invasive biomarkers capable of reflecting biological changes within the healing environment. Salivary exosomes, nanosized extracellular vesicles containing proteins, lipids, messenger RNA, and microRNA, have emerged as promising diagnostic tools due to their stability, accessibility, and ability to mediate intercellular communication. These vesicles provide valuable molecular information related to inflammation, immune regulation, angiogenesis, extracellular matrix remodeling, and tissue regeneration. Alterations in exosomal cargo may serve as predictive indicators of impaired healing responses after oral surgical interventions, including tooth extraction, implant placement, and periodontal procedures. Advances in molecular profiling technologies have enabled the identification of potential exosome-derived signatures associated with wound repair dynamics. The integration of salivary exosome analysis with digital diagnostics and predictive modeling may facilitate personalized postoperative care and early intervention strategies. Despite current limitations related to standardization, validation, and clinical implementation, salivary exosome biomarkers represent a promising approach for improving the prediction and management of delayed oral wound healing.

Keywords: Salivary exosomes; extracellular vesicles; oral surgery; wound healing; biomarkers; microRNA; regenerative dentistry; personalized medicine.

Introduction

Successful wound healing after oral surgical procedures is essential for restoring tissue integrity, preventing complications, and ensuring predictable clinical outcomes. However, delayed healing remains a common concern following procedures such as tooth extraction, periodontal surgery, implant placement, and regenerative interventions. Impaired healing is often associated with prolonged inflammation, microbial challenges, altered immune responses, and reduced tissue regeneration capacity. Current clinical methods primarily rely on visual assessment and symptomatic evaluation, which may not detect early molecular alterations responsible for delayed repair. Therefore, the development of sensitive and non-invasive biomarkers is essential for improving postoperative monitoring and personalized treatment strategies.

Exosomes, a subtype of extracellular vesicles released by various cells, have gained significant attention due to their ability to transport functional biological molecules, including proteins, lipids, messenger RNA, and microRNA. These vesicles participate in intercellular communication and regulate important processes

involved in inflammation, angiogenesis, immune modulation, and tissue regeneration. Their presence in saliva provides a convenient and minimally invasive platform for biomarker discovery, particularly in oral and craniofacial applications (Han et al., 2018; Xing et al., 2020). Salivary extracellular vesicle analysis has demonstrated potential for identifying disease-associated molecular changes through proteomic and molecular profiling approaches (Aqrawi et al., 2017).

In oral regenerative processes, molecular signaling plays a crucial role in controlling tissue repair and maintaining biological balance. Similar to the importance of biological modulation in endodontic and regenerative therapies, understanding cellular communication pathways may enhance approaches for improving healing outcomes (Singh, 2019; Singh, 2020). Exosomal biomarkers, including specific proteins such as Alix and regulatory microRNAs, have shown diagnostic potential in oral diseases and may provide insights into abnormal healing responses (Nakamichi et al., 2021; Manzano-Moreno et al., 2021).

Therefore, salivary exosome biomarkers represent a promising strategy for predicting delayed wound healing after oral surgery by enabling early molecular detection, risk assessment, and personalized postoperative management. Further research is required to establish standardized detection methods and validate their clinical applicability.

Biological Basis of Salivary Exosomes in Wound Healing

Exosome Formation and Molecular Cargo

Salivary exosomes are small extracellular vesicles, typically ranging from 30–150 nm, released through the endosomal pathway by various oral and systemic cells, including epithelial cells, immune cells, fibroblasts, and mesenchymal cells. During oral wound healing, these vesicles function as important mediators of intercellular communication by transferring biologically active molecules such as microRNAs (miRNAs), messenger RNAs, proteins, lipids, and growth-related factors to recipient cells. Their stable lipid bilayer protects molecular cargo from degradation, making saliva an effective medium for non-invasive biomarker detection (Han et al., 2018; Aqrawi et al., 2017). Exosomal proteins such as Alix, CD63, and CD81 contribute to vesicle identification and reflect cellular activity during tissue repair processes (Nakamichi et al., 2021).

Role in Inflammation and Tissue Regeneration

Successful oral wound healing requires coordinated regulation of inflammation, angiogenesis, fibroblast activation, epithelial migration, and extracellular matrix remodeling. Salivary exosomes influence these processes by modulating immune responses and transferring regulatory molecules that control inflammatory pathways. Altered exosomal miRNA and cytokine profiles may indicate excessive inflammation or impaired regenerative activity, contributing to delayed wound closure (Manzano-Moreno et al., 2021). Furthermore, exosome-mediated signaling can enhance tissue regeneration by promoting cell proliferation, vascular formation, and repair mechanisms, supporting their potential application in regenerative dentistry (Xing et al., 2020).

Application in Oral Surgical Healing

In oral surgery, exosomal biomarkers provide insights into the biological status of healing tissues following procedures such as tooth extraction, implant placement, and periodontal surgery. Their ability to reflect local wound conditions may allow early identification of patients with compromised healing responses. Integration of exosome analysis with regenerative approaches, including bioactive materials and biologically driven therapies, may improve postoperative outcomes by supporting controlled inflammation and tissue restoration (Singh, 2019; Singh, 2020). Thus, salivary exosomes represent a promising molecular platform for predicting and managing delayed oral wound healing.

Table 1: Potential Exosomal MicroRNA Biomarkers Associated with Oral Wound Healing

Biomarker	*Biological Function*	*Predictive Role in Delayed Healing*
miR-21	Regulates inflammation and tissue repair pathways	Indicates altered regenerative responses
miR-146a	Controls immune and inflammatory signaling	Reflects persistent inflammatory activity
miR-155	Modulates immune responses	Associated with excessive inflammation
Other salivary miRNAs	Influence cellular communication and remodeling	Potential indicators of healing progression

Salivary Exosome Biomarkers for Predicting Delayed Healing

Salivary exosomes provide a promising molecular platform for predicting delayed wound healing by reflecting cellular responses involved in inflammation, immune regulation, angiogenesis, and tissue remodeling. These extracellular vesicles contain stable biological molecules, including microRNAs, proteins, and cytokines, which can indicate alterations in the wound-healing environment following oral surgical procedures (Han et al., 2018; Xing et al., 2020). Changes in exosomal cargo may identify patients with impaired regenerative capacity before clinical signs of delayed healing become evident.

MicroRNA-Based Exosomal Biomarkers

Exosomal microRNAs regulate gene expression associated with inflammatory control, fibroblast activity, epithelial migration, and vascular formation. Dysregulated microRNA profiles may indicate persistent inflammation or inadequate tissue repair after oral surgery. Salivary microRNA analysis has demonstrated diagnostic and prognostic value in oral diseases, supporting its potential application in monitoring postoperative healing responses (Manzano-Moreno et al., 2021).

Exosomal Protein and Cytokine Biomarkers

Exosomal proteins such as Alix, CD63, and CD81 serve as indicators of exosome activity and cellular stress. Salivary exosomal Alix detection has demonstrated the diagnostic potential of exosome-derived proteins in oral conditions (Nakamichi et al., 2021). Additionally, exosomal cytokines and inflammatory mediators may reveal abnormal immune responses contributing to delayed wound closure (Aqrawi et al., 2017).

Integration of salivary exosome profiling with regenerative approaches and biologically active dental materials may enhance personalized management of postoperative healing outcomes (Singh, 2019; Singh, 2020). However, standardized detection methods and clinical validation remain essential before routine application.

Table 2: Exosomal Biomarker Categories for Predicting Delayed Oral Healing

Biomarker type	*Examples*	*Clinical significance*
exosomal proteins	Alix, CD63, CD81	Reflect exosome release and cellular stress
Cytokines	IL-6, TNF-α, TGF-β	Indicate inflammatory imbalance
Growth factors	VEGF-related molecules	Assess angiogenesis and regeneration
Regenerative markers	Tissue repair-associated proteins	Predict healing capacity

Clinical Applications, Challenges, and Future Perspectives

Clinical Applications

Salivary exosome biomarkers have significant potential for improving postoperative monitoring and predicting delayed wound healing following oral surgical procedures. Their ability to provide molecular information through non-invasive saliva collection allows early identification of abnormal inflammatory responses, impaired angiogenesis, and delayed tissue regeneration. Exosomal microRNAs, cytokines, and proteins may assist clinicians in evaluating healing progression after tooth extraction, implant placement, periodontal surgery, and regenerative procedures. The diagnostic potential of salivary extracellular vesicles has been demonstrated in various oral and systemic conditions, supporting their application as reliable biomarkers for disease and tissue response monitoring (Han et al., 2018; Aqrawi et al., 2017). Furthermore, exosome-based approaches may complement regenerative dental strategies by improving understanding of cellular communication involved in repair processes (Xing et al., 2020).

Challenges

Despite promising applications, several limitations must be addressed before routine clinical adoption. Variations in saliva composition, patient-related factors, and differences in exosome isolation techniques may influence biomarker accuracy. Standardized protocols for sample collection, purification, and molecular analysis are required to ensure reproducibility. Additionally, establishing specific exosomal signatures that accurately distinguish normal healing from delayed wound repair remains challenging. Integration with existing clinical approaches, including infection control and tissue-preserving strategies, will require further validation (Singh, 2019; Singh, 2020).

Future Perspectives

Future research should focus on developing rapid point-of-care salivary exosome diagnostic platforms and combining exosome profiling with artificial intelligence-based predictive models. Identification of specific exosomal proteins, such as Alix, and salivary microRNA patterns may enhance personalized monitoring of oral healing outcomes (Nakamichi et al., 2021; Manzano-Moreno et al., 2021). With continued advances in molecular dentistry, salivary exosome biomarkers may become valuable tools for precision-based postoperative care and regenerative oral medicine.

Conclusion

Salivary exosome biomarkers represent a promising non-invasive approach for predicting delayed wound healing after oral surgical procedures. Their ability to carry biologically active molecules, including microRNAs, proteins, and cytokines, provides valuable insight into the complex processes involved in inflammation, immune regulation, angiogenesis, and tissue regeneration. By reflecting real-time molecular changes within the oral environment, salivary exosomes may enable earlier detection of impaired healing responses and support personalized postoperative management. Although challenges related to biomarker validation, standardization of exosome isolation methods, and clinical implementation remain, continued advances in molecular diagnostics and regenerative dentistry are expected to improve their applicability. Future integration of salivary exosome profiling with artificial intelligence and digital health technologies may further enhance predictive accuracy and facilitate precision-based oral surgical care. Ultimately, exosome-based diagnostics hold significant potential to transform wound-healing assessment from reactive clinical observation to proactive, biomarker-guided intervention.

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