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Schwann Cell–Secreted S100B Promotes Wound Healing via Paracrine Modulation

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Abstract

As the supply source for gingival grafts, the palatal tissue possesses marked regenerative ability after repeated wounding over the buccal attached gingiva and skin. However, the intrinsic mechanisms are poorly understood. Schwann cells reportedly participate in wound repair of many tissues. Here, we investigate whether Schwann cells play an essential role in the wound healing of palatal mucosa. We performed multiomics analysis in nonhuman primates, integrating scRNA-seq and proteomics analysis, and built wound-healing models in the palatal mucosa and buccal attached gingiva and skin to compare the regeneration among different sites and explore the paracrine role of Schwann cells in the healing of palatal mucosa. With regard to in vivo validation, GelMA hydrogels loaded with conditional medium or exogenous protein were applied in rat and monkey skin. We revealed greater distributions and a lower differentiation state of Schwann cells in the palatal mucosa at baseline. Moreover, S100B levels were significantly greater in the wound healing of palatal mucosa than in the buccal attached gingiva, and Schwann cell–secreted S100B can promote the healing-related capabilities of fibroblasts via paracrine modulation with receptor of advanced glycation end products (RAGE), which activates the crosstalk between NF-κB and Notch signaling, leading to expedited wound closure in vivo. Our work shows that Schwann cells play a crucial role in the wound healing of the palatal mucosa through the S100B/RAGE/NF-κB/Notch paracrine axis. In addition, our data provide novel insights into the therapeutic effects of S100B protein on wound healing.

Keywords: palatal mucosa, wounds, multiomics, glial cells, S100beta Protein, Receptor for Advanced Glycation End Products (RAGE)

Introduction

Wound healing is a widespread and complex process that occurs in various types of tissues and is initiated upon injury. Fibroblasts, the principal cells involved in wound repair, produce the extracellular matrix (ECM) to induce collagen deposition. In most tissues, skin in particular, wounds are repaired by a patch of cells (mainly fibroblasts) and a disorganized ECM called scar. Fibroblast dysfunction contributes to chronic wounds and excessive scar formation, which can impair the appearance, functional capabilities, and mental health of patients (Guo and Dipietro 2010; Eming et al. 2014). Therefore, effective treatments for promoting wound healing are necessary, especially for elderly and diabetic patients, who generally present with delayed and compromised healing (Jarbrink et al. 2017).

Unlike the scar-based healing model of skin, the oral mucosa heals by regeneration and shows less or no scar formation and accelerated healing after wounding (James et al. 1978). Variations in wound healing also exist inside the oral environment (Lari et al. 2011; Rojas et al. 2021; Ko et al. 2023). These differences may result from variations in the anatomy, histology, function, or periodontal phenotype (Squier and Kremer 2001; Nakasone et al. 2009; Karring et al. 2010; Barootchi et al. 2020). Palatal mucosa, a type of masticatory mucosa commonly considered as the supply source for gingival grafts, is generally thought to undergo rapid regeneration and remain scar free after wounding. Palatal mucosa showed higher healing scores in the early phase of wounding than the

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