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Review Article

Stromal-cell-derived factor 1: Potentially an important promoter in healing of tooth extraction or dental implantation to stimulate the host healing mechanism?

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ABSTRACT

Wound healing after tooth extraction or dental implantation is an intricate process involving a series of biological events involving tissue repair and remodeling in response to injury. The healing process is greatly influenced by a variety of systemic and local factors. Wound failure remains a clinical problem that causes pain, dry socket, or other complications, and it can even affect dental implants and prosthodontic treatment. Numerous studies have demonstrated that stromal-cell-derived factor 1 (SDF-1) is an active chemokine for repair of injured blood vessels, and the SDF-1/CXCR4 signaling pathway might play an important role in repairing injured tissue by promoting host-cell recruitment and angiogenesis. In this article, the effectiveness of SDF-1 for enhancing wound healing is evaluated. It's hypothesized that increasing localized concentration of SDF-1 will contribute to the acceleration of wound healing after tooth extraction or dental implantation treatments, especially in diabetic and elderly patients.

1. Introduction

Wound healing is a complex physiological process by which the body facilitates the repair of injured tissues. Various intracellular and intercellular pathways are activated after an injury occurs. A variety of different cell types interact, including immune cells (neutrophils, monocytes, lymphocytes, and dendritic cells), endothelial cells, fibroblasts, progenitors, and stem cells, whose proliferation, differentiation, and migration are prerequisite to all stages of wound healing.[1] Oxygen and nutrients are also essential in the healing process.[2] However, many additional factors positively and

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negatively influence this process, such as age,[3] diabetes,[4] infection,[5] radiotherapy,[6] and steroids treatment.[7]

Clinically, the dislodgement of the blood clot is a common diagnosis of the failure of physiological healing of a tooth socket. The failure of the disturbed socket to heal is not limited to localized symptoms, but also jeopardizes the success of dental implantation and other procedures,[8] such as immediate dental implant treatment for replacing missing teeth immediately after extraction. The length of healing time for this procedure is partially related to the healing of the socket wound.

SDF-1, officially designated chemokine (C-X-C motif) ligand 12 (CXCL12), is a small cytokine belonging to the group of CXC chemokines. It has been well reported that the SDF-1/CXCR4 signaling pathway is of vital importance to organism development[9,10] and to various pathophysiological phenomena, such as tumor progression,[11,12] myocardial infarction,[13] ischemic cardiomyopathy,[14] and tissue injury.[15,16] Is SDF-1 also involved in cell recruitment and angiogenesis to promote wound healing after tooth extraction or immediate dental implantation? This question is still open.

2. Wound healing after tooth extraction

The classic model of wound healing divides the process into four overlapping but distinct phases[17]: hemostasis (not considered a phase by some doctors), inflammation, new tissue formation (proliferative phase), and remodeling. Hemostasis occurs within minutes of the initial injury, just before the initiation of the inflammatory phase. Thereafter, various soluble bioactive factors are released to attract cells that phagocytize debris, bacteria, and damaged tissue and release factors that initiate the proliferative phase of wound healing. Similarly, the first change after tooth extraction is the formation of a blood clot adjacent to the socket. All of the cells within the blood clot will degenerate and die. Within this same area, the fibroblasts and vascular endothelial cells that are actively proliferative migrate into the coagulum and form granulation tissue. Then, dense connective tissue and new bone regenerate.[8,18,19] Undoubtedly, blood clotting is essential for the phases of normal socket healing. In addition to becoming the scaffold for infiltrating cells, the blood clot must also release bioactive healing factors. However, the role of bioactive factors affecting the wound healing process after tooth extraction has not yet been fully clarified.

3. SDF-1 and cell recruitment in tissue repair

After injury, some soluble factors (including chemokines and cytokines) are released to attract cells that initiate the inflammation, proliferation, and remodeling.[1] Cells maintaining, generating, and replacing terminally differentiated cells within their own specific tissue are essential in the wound healing process.[20] Generation of new tissues can be initiated from surrounding existing tissues[21] or through recruitment of stem/progenitor cells through circulation (cell homing[14,22]) to the injured site.

Unlike other CXC chemokines, SDF-1 is known to be an effective chemotactic factor basally expressed in many tissues; its counterreceptor, CXCR4, is found in a variety of cell types.[23–26] Moreover, it has been demonstrated that the SDF-1/CXCR4 axis is a pivotal regulator in the body of the trafficking of various types of cells, especially stem cells.[12,27,28] As for wound healing, although the mechanism has not been fully explained, SDF-1 is believed to be involved in chemotaxis, migration, and homing of leukocytes, progenitors, and stem cells to the target site after injury has occurred.[15,16,23] Those cells are all essential in the different phases of wound healing. A more recent study also confirmed that increasing the level of the chemokine SDF-1 in the wound could increase stem cell recruitment to the wound, accelerating healing time in diabetic mice.[29]

On this basis, Schantz et al[30] proposed a new concept of 'cell guidance'. In this new cellular methodology for tissue engineering, SDF-1 mediates site-directed homing of mesenchymal stem cells. This research suggests that constant delivery of SDF-1 in vivo or in vitro can guide stem cells to the scaffold for the purpose of bone regeneration.

4. SDF-1 and angiogenesis after wound

Regeneration of blood vessels (neo-angiogenesis or vasculogenesis) that generate and feed new tissue is required in wounded tissue. Following injury, vessel deterioration results in local ischemia. Injured tissues release pro-angiogenic factors to recruit hematopoietic cells to promote the formation and stabilization of newly formed vessels.[31] Endothelial progenitor cells (EPCs) are the key cellular effectors of postnatal neovascularization and play a central role in wound healing.

Interestingly, SDF-1 is important to angiogenesis, recruiting EPCs from the bone marrow.[15] SDF-1–dependent recruitment of circulating progenitor cells might also contribute to angiogenesis in wound healing. The SDF-1 protein is detected primarily in smooth muscle cells (SMCs) of neointimal lesions and plays an instrumental role in neointimal formation after vascular injury.[32] Additionally, platelets can express and release SDF-1 upon activation, thereafter being functionally involved in the recruitment of EPCs to areas of vascular injury to effect vascular repair and angiogenesis.[14,31,33]

By contrast, in some pathological situations, angiogenic pathways involving SDF-1 also play a major role in aberrant neovascularization in proliferative diabetic retinopathy[34] or in tumor growth and metastasis.[11,35] Blocking SDF-1/CXCR4 interaction or inhibiting downstream intracellular signaling may facilitate the development of anti-angiogenic therapies or may prevent neovascularization.

5. The prospects of SDF-1 in dental treatment

Since there is a permanent demand for renewed cells and neoangiogenesis during the longstanding course of wound healing after tooth extraction, it's hypothesized that SDF-1, along with a multifactor mechanism, might be an important promoter in the process of socket healing. The possible