Letter to Editor

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The Immunoregulatory Role of Programmed Death-Ligand 1 in Wound Healing Dynamics

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DEAR EDITOR

The burden of chronic wounds on the healthcare system is rising annually due to the increasing prevalence of diabetic patients, an aging population, and lifestyle changes. Wound healing is a dynamic process comprising four overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling (1). In chronic diabetic wounds, normal healing is impaired due to persistent inflammation, which arises from dysregulated immune responses.

Immune responses play a pivotal role in normal cutaneous wound healing by contributing to extracellular matrix (ECM) reconstruction, clearance of damaged tissue, and prevention of infection (2). However, dysfunction in immune cells, such as prolonged presence of neutrophils, impaired macrophage polarization, upregulation of pro-inflammatory cytokines, downregulation of anti-inflammatory cytokines, and reduced levels of growth factors, disrupts the wound microenvironment and leads to delayed wound healing (3).

Programmed cell death 1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1) are key proteins involved in maintaining the balance between immune activation and suppression (4). PD-1 is a receptor expressed on the surface of immune cells, including activated T cells, B cells, macrophages, monocytes, and natural killer (NK) cells. PD-L1 also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1), is a transmembrane protein typically expressed by immune cells, tumor cells, and epithelial cells. Under inflammatory conditions, PD-L1 is also expressed by fibroblasts and keratinocytes. As a ligand for PD-1, PD-L1 inhibits cytokine production and T cells proliferation, ultimately suppressing immune responses (5). The PD-1/PD-L1 pathway is critical for preventing excessive immune activation and maintaining immune

homeostasis (6). However, the precise role of PD-1/PD-L1 signaling in chronic wound inflammation is not completely understood.

Research on PD-L1 in wound healing represents a paradigm shift, as it identifies an immune checkpoint molecule, previously studied primarily in cancer, as a key regulator of tissue repair. PD-L1 uniquely connects immune modulation with direct effects on fibroblasts and keratinocytes, opening therapeutic possibilities beyond conventional inflammation-focused treatments. Studies indicate that PD-L1 expression in fibroblasts can influence macrophage polarization, thereby modulating inflammation and promoting the wound healing process. For example, a study by Wang et al. demonstrated that fibroblast-like cells derived from wound tissues express PD-L1 during the inflammatory phase, with its expression correlating with M2 macrophage polarization and improved wound healing (7). In contrast, PD-L1 knockout mice exhibited delayed healing, characterized by excessive inflammation and a predominance of M1 macrophage. These findings indicate that PD-L1 expression in fibroblasts plays a crucial role in regulating the inflammatory phase and promoting healing in chronic wounds.

Another important study by Kuai et al. highlighted the potential role of PD-L1 in diabetic wound healing (8). The researchers found that diabetic ulcers exhibited reduced PD-L1 expression compared to normal wounds, and treatment with exogenous PD-L1 improved healing by promoting keratinocyte proliferation and migration, reducing inflammation, and enhancing tissue repair (9). The study further identified IRS4 as a key mediator of PD-L1's effects: PD-L1 overexpression decreased IRS4 levels, reduced pro-inflammatory cytokines, and enhanced keratinocyte function. These findings suggest that PD-L1 not only modulates immune responses but also facilitates the

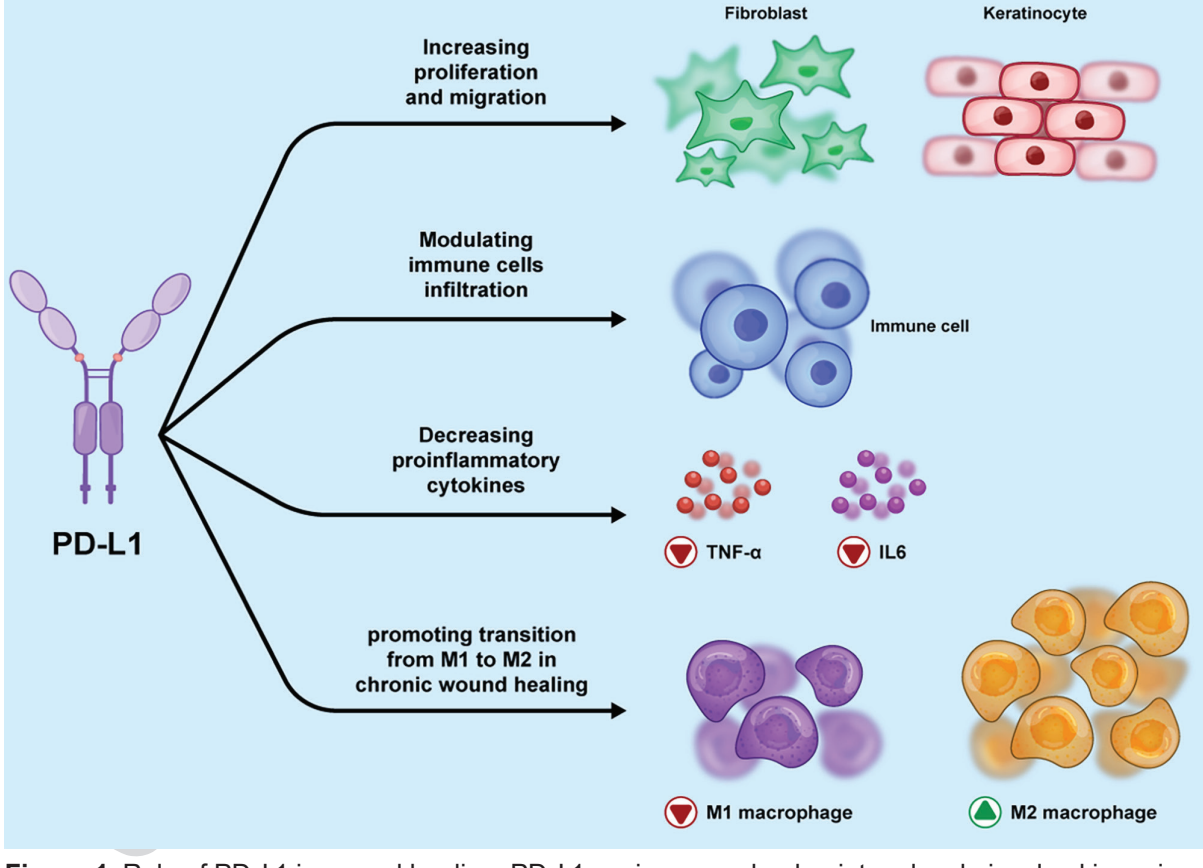

Figure 1. Role of PD-L1 in wound healing. PD-L1, an immune checkpoint molecule involved in various aspects of the wound healing process, including epithelialization, dermal restoration, immune cell regulation, modulation of inflammation, and macrophage polarization.

transition from the inflammation to the proliferative phase of wound healing (Figure 1).

Moreover, the use of PD-L1 in its exosomal form has shown promising results in accelerating wound healing. Researchers demonstrated that exosomal PD-L1 derived from melanoma cells stimulated the migration of keratinocytes and fibroblasts, comparable to the effects of basic fibroblast growth factor (bFGF). Exosomal PD-L1 treatment reduced inflammation and immune cell infiltration, offering an effective approach for promoting healing in chronic wounds. However, it is important to note that, while PD-L1 can mitigate chronic inflammation, its immunosuppressive effects must be carefully considered, as excessive immune suppression could potentially impair microbial clearance at the wound site and increase a risk of infection (10).

Recently, strategies have been developed to incorporate exogenous PD-L1 into polymeric wound dressings. This approach improves protein stability, enables controlled and sustained release, and, when combined with other therapeutic agents such as growth factors, may synergistically enhance wound healing (11).

In conclusion, persistent inflammation impairs wound healing by disrupting tissue repair mechanisms. Immune checkpoint molecules such as PD-L1 can mitigate inflammation and promote regeneration, primarily by influencing macrophage polarization and facilitating the transition from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, thereby aiding resolution of inflammation. This regulation involves activation of signaling pathways, including PI3K/AKT/mTOR and p38/ERK, which enhance PD-L1 expression in fibroblast-like cells. Additionally, PD-L1 affects keratinocyte proliferation and migration through the eIF3I/IRS4 axis, further supporting tissue repair. However, the precise molecular interactions and downstream effectors of PD-L1 in wound healing remain to be fully elucidated. While immune checkpoint modulation shows therapeutic potential, its application in normal wound healing is complex, as immune responses are critical for eliminating microbial infections and clearing debris at the wound site. A related concern is the potential risk of compromised clearance of bacteria, both locally and systemically. For example, treatment with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) Ig has been reported to reduce the severity of dermatitis and tissue necrosis, but it may prolong wound healing compared to the control group. Necrotic and apoptotic cells release damage-associated molecular patterns (DAMPs), including ECM cleavage products and reducing necrosis through immune checkpoint therapy may delay or attenuate the inflammatory response. Nonetheless, integrating PD-L1 into advanced wound dressings and combined therapeutic approaches represents a promising strategy to improve outcomes in chronic wound management.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

This article does not include any studies involving human participants or animals conducted by the authors.

DATA AVAILABILITY

No datasets were generated or analyzed in this study.

AUTHORS' CONTRIBUTION

MH. S: Conceptualization, Writing – original draft and supervision; H. KN, S. N: Writing and editing.

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