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Review Article

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The Role and Place of Innate and Acquired Immunity in the Regeneration of Long-term Non-healing Wounds Against the Background of Diabetes Mellitus

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ABSTRACT

The physiological process of wound healing includes four stages: hemostasis, inflammation, proliferation, and maturation. The correct and coordinated work ensures a strict staged regenerative process. However, when wounds do not go through this organised process, their healing is delayed, and this eventually leads to chronic or long-lasting wounds. Common signs of non-healing wounds are exudation, reinfection, tissue necrosis, defective re-epithelialization, decreased angiogenesis, and excess production of reactive oxygen species. In general, chronic wounds can be divided into three main categories: diabetic foot ulcers, vascular ulcers, and pressure ulcers. They are usually observed in elderly people suffering from pathological conditions such as diabetes mellitus, vascular diseases and obesity. This review article is devoted to the features of the reaction of innate and acquired immunity in the course of long-term non-healing wounds.

Keywords: Long-term non-healing wounds, innate immunity, acquired immunity.

Diabetes mellitus affects all four stages of skin damage repair. Diabetic ulcers are associated with a high pro-inflammatory profile caused by overexpression of inflammatory cytokines such as TNF-α and decreased production of mediators that promote healing, including IL-10 and TGF-β. This leads to macrophage polarisation towards the M1 phenotype, activation and degranulation of CD8+ T cells, which leads to tissue necrosis [10].

Chronic wounds are characterised by the long-term presence of populations of myeloid cells, such as macrophages, neutrophils, and monocytes, at a late stage of inflammation. In contrast, the percentage of Langerhans cells, dermal dendritic cells, and eosinophils decreases throughout the process. Mast cells are also involved in the development of long-term non-healing wounds. Skin mast cells are degranulated in diabetic ulcers, and suppression of their activity accelerates wound healing [13].

T cells are involved in maintaining the pro-inflammatory profile of long-term non-healing wounds. The ligand

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for CXCR3, which is found in Th1 cells, is highly expressed in chronic inflammation. In addition, patients with diabetic ulcers have increased levels of inflammatory T cell subtypes, such as Th1, Th17, and Th22 [17].

Immune cells actively interact with non-blood-forming cells, such as keratinocytes, through the secretion of various signalling molecules. Keratinocytes make a significant contribution to the formation of long-term non-healing wounds, but the exact mechanism of their action is not fully understood. Dysregulation of some miR cells, such as miR-34a/c, miR-203, miR-19a/b, and miR-20a, in keratinocytes is known to affect immune functions and lead to delayed healing of soft tissue wounds [14].

Thus, inhibiting the expression of miR-19a/b and miR-20a slowed wound healing and induced a stronger inflammatory response in mice by activating the NF-κB pathway, leading to overexpression of pro-inflammatory cytokines and chemokines in keratinocytes.

The process of long-term non-healing wound formation is also epigenetically regulated by miR, which controls inflammatory responses through the modulation of signalling pathways. Wnt/β-catenin, NF-κB, PI3K/Akt/mTOR, TGF-β/Smad, and vascular endothelial growth factor growth factor pathways are regulated by miR during the regeneration of long-term non-healing wounds. Immune and structural cells actively express and regulate cytokines, chemokines, and growth factors during the wound-healing process. For example, increased levels of INF-γ, vascular endothelial growth factor, and soluble vascular cell adhesion molecule-1 observed in patients with diabetic foot ulcers promote ulcer healing [9].

However, in wounds that do not heal for a long time, the dysregulation of certain factors is disrupted, which is partly responsible for the pathogenesis of the injury. Mice deficient in the IL-36 receptor antagonist showed delayed wound healing due to overproduction of IL-36γ, TGF-β, and CXCL1, excessive neutrophil and macrophage infiltration, and excessive granulation tissue formation. In addition, the chemokine receptor CCR4 negatively affects long-term non-healing wounds caused by diabetes mellitus. Diabetic mice depleted of CCR4 showed reduced expression of cytokines that promote wound healing, such as IL-6, IL-12, IL-1β, TNF-α, and IL-10 [16].

In a study by A.P. Sawaya et al. [3], Dysregulation of transcription factors FOXM1 and transcription transducer and activator-3 in patients with diabetic foot ulcers was revealed. FOXM1 and the signalling transducer and transcriptional activator-3 are responsible for the proliferation of macrophages and neutrophils and their recruitment into the microenvironment of the diabetic wound. Thus, inhibition of transcription factors FOXM1 and transcription-3 signal transducer and activator in patients with diabetic foot stimulates the mechanisms of disease progression due to a defective set of immune cells.

In the scientific works of a group of scientists led by J. Dissemond [4], the presence of another factor that contributes to the delay in wound healing was proven. This factor is known as matrix metalloproteinases. During normal wound healing, cells in the injured area, such as fibroblasts, keratinocytes, and immune cells, are induced by local mediators to secrete matrix metalloproteinases. These mediators include various cytokines and growth factors involved in wound healing, such as TGF-β, vascular endothelial growth factor, epidermal growth factor, interleukins, and interferons.

Matrix metalloproteinases are usually required in small amounts and are responsible for proper epithelialisation and proliferation. However, their dysregulation leads to impaired epithelialisation and is closely related to difficult-to-heal wounds. In general, increased expression of matrix metalloproteinases-9 by activated neutrophils is associated with delayed ulcer healing in patients with diabetes mellitus. In addition, high glucose levels can stimulate the overexpression of matrix metalloproteinases-9 through activation of the ERK/AP1 signalling pathway [6].

Thus, the development of a long-term non-healing wound occurs when the immune system is unable to continue the normal repair process, resulting in a prolonged presence of neutrophils and pro-inflammatory macrophages in the damaged skin, which contributes to inflammation, tissue fibrosis, and poor vascularisation.

Neutrophils are the most common inflammatory cells that invade a new wound and function primarily to remove debris and prevent infection. Their influx is mediated by several chemical signals, including IL-8 or CXCL8, as mentioned above, and neutrophils have more than 30 different receptors that mitigate their migratory and activation responses. Neutrophils are indeed involved in the removal of dead cells in the early stages of wound healing, but their persistence, as will be discussed in detail below, is associated with delayed wound healing and wounds that do not heal for a long time. Moreover, experimental results from wound healing simulations have shown that in ageless models without impaired neutrophil intake, it does not negatively affect wound healing as profoundly as macrophage deletion. In models with impaired wound healing, such as diabetes mellitus,

where the risk of infection is higher, neutrophils were needed [24].

K. Pittman and P. Kubes [15] believe that DAMPs isolated from necrotic cells are the first signals for neutrophil recruitment to the wound bed. These dangerous signalling molecules can activate neutrophils directly by binding to various neutrophil surface receptors, in addition to signalling cells in the tissue to produce neutrophil chemoattractants.

One of the most well-described chemoattractants produced by tissue macrophages and fibroblasts is CXCL8 (IL-8). CXCL8 binds to and stimulates the surface neutrophil receptors CXCR1 and CXCR2, resulting in an overactive recruitment of neutrophils to the site of tissue injury. Interestingly, after neutrophils migrate to the wound, they can also release CXCL8, creating a pro-inflammatory feedback loop [5].

CXCL8 also increases vascular endothelial permeability, which further stimulates the influx of inflammatory cells into the wound. Other chemokines of the CXCL8 family, such as CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, and CXCL7, have also been shown to play a role in neutrophil chemotaxis [21].

By binding glycosaminoglycans on tissue cell walls and in the extracellular matrix, these chemokines, including CXCL8, create a signalling gradient that allows a clear, directional migration of neutrophils to injury. Additional cellular byproducts induced by DAMP, such as hydrogen peroxide and leukotriene-B4, also form gradients to stimulate targeted neutrophil migration [22].

Although neutrophils are not considered an important cell type for wound healing without impairment, they perform various functions that support this process. First of all, neutrophils protect against wound infection by phagocytosing pathogens and then killing them by releasing reactive oxygen species, proteases, or antimicrobial proteins. During degranulation, antimicrobial proteins can also be released into the environment to kill extracellular organisms [2].

Neutrophils also show increased expression of cytokines that promote angiogenesis [e.g., vascular endothelial growth factor (VEGF), CXCL3, and MCP-1], fibroblast and keratinocyte proliferation (IL-8, IL-1 β, and MCP-1), keratinocyte adhesion to the dermal layer (laminin five β-3), and tissue remodelling [urokinase-type plasminogen activator (uPA)] [1].

Macrophages are crucial during wound healing. However, their prolonged presence in the damaged environment or dysregulation during recovery leads to impaired wound healing and tissue fibrosis.

The inability of macrophages to polarise from pro-inflammatory M1 to a healing reparative M2 phenotype is closely associated with long-term non-healing wounds. This failure is due to overexpression of pro-inflammatory cytokines in the wound microenvironment and impaired clearance of apoptotic neutrophils by macrophages. Treatment of natural killer-4 THP-1 macrophage cells induced morphological features characteristic of classically activated M1 macrophages, an inflammatory cytokine profile, and increased expression of CD38 and CD86 molecules associated with M1 macrophages. Interestingly, natural killer-4 increased the production of TNF-α by THP-1 macrophages in combination with LPS, Pam3CSK4, or poly(I: C). In addition, treatment of natural killer-4 enhanced the phagocytosis of THP-1 macrophages in latex granules. These results indicate that natural killer-4 stimulates macrophage polarisation towards an inflammatory M1-like phenotype with increased phagocytic activity. Efferocytosis is an important event to resolve the inflammatory phase in wound healing. Treated natural killer-4 THP-1 macrophages cultured with Jurkat E6.1 (Apo-J) apoptotic cells switched from the M1-like phenotype to the M2-like phenotype, as seen by the inverse TNF-α to IL-10 ratio produced in response to LPS. The authors have identified two separate mechanisms that are involved in this phenotypic switching. First, the recognition of phosphatidylserine molecules on Apo-J cells by THP-1 macrophages inhibits the production of TNF-α. Second, phagocytosis of Apo-J cells by THP-1 macrophages and activation of the PI3K/Akt signalling pathway enhances the production of IL-10 [8].

A study that compared macrophages derived from the wounds of healthy people with patients with diabetes mellitus revealed a distinctive expression of Setdb2 methyltransferase, the production of which in wound macrophages is controlled by INF-β. In patients with diabetes mellitus, impaired INF-β–Setdb2 interaction leads to the inability to switch from the M1 to M2 phenotype, which leads to the accumulation of pro-inflammatory macrophages in long-term non-healing wounds. In addition, it was found that M1 macrophages in the diabetic wound microenvironment overexpressed miR-21, which led to increased secretion of inflammatory mediators such as IL-1α, TNF-α, iNOS, IL-6, and IL-8, and further polarisation of macrophages towards the M1 phenotype [18].

In general, regulating the M1-M2 polarisation is critical for proper wound healing. Any changes in this balance lead to consequences such as the development of

long-term non-healing wounds or increased tissue fibrosis.

Congenital lymphoid cells are cells of lymphoid origin and morphology that do not possess antigen-specific receptors and markers of T and B cells but can be activated by innate immune signals.

The three lines of innate lymphoid cells perform different effector functions depending on their transcription factor and cytokine expression profile. Natural killer cells, which belong to group 1 innate lymphoid cells, can produce INF-γ, granzymes, and perforins to kill virus-infected cells and cancer cells, distinguishing natural killer cells from helper innate lymphoid cells. As a major factor in the production of INF-γ, natural killer cells are involved in the inflammatory phase of the wound healing process, having a largely negative impact on tissue repair. INF-γ derived from natural killer cells polarises macrophages into the pro-inflammatory M1 phenotype and enhances the infiltration of immune cells into the wound area of IL-1β, IL-6, IL-12, IL-23 and the expression of TNF-α by macrophages. INF-γ, primarily secreted by CD4+ T cells, a natural killer T cell, has been reported to prevent prolonged neutrophil infiltration in the inflammatory phase and enhance fibrosis in the proliferative phase of the wound healing process.

The level of innate lymphoid cells-2 is also increased in chronic skin inflammation. Alarmin cytokines such as IL-33, thymic stromal lymphopoietin, and IL-25, as well as pathogen-associated molecular patterns, can attract innate lymphoid cells to the injured site. In turn, it was reported that innate lymphoid cells-2 express IL-5, M2 macrophage, polarising IL-13 and IL-4, as well as amphiregulin, a mitogen of keratinocytes, which also enhances Treg homing to the injury site. In addition, innate lymphoid cell-2 is involved in stimulating Treg expansion and polarisation of Th2 cells. In addition, innate lymphoid cells-3 also show a positive effect on skin wound healing. At the signal of epidermal Notch-1, TNF-α and chemokine recruitment of innate lymphoid cells-3, ligand-20 of motif C-C and CXCL13 are expressed to recruit innate lymphoid cells-3 into the wounded dermis. Innate lymphoid cells-3 can attract macrophages to the wound bed as a key source of IL-17F and the C-C-motif-3 ligand and enhance epidermal proliferation through the expression of the important keratinocyte growth factor IL-22 [23].

Consequently, congenital lymphoid cell-3 deficiency has been reported to lead to reduced macrophage infiltration and epidermal proliferation, as well as delayed skin wound healing in mice [11].

According to previous findings, the role of innate lymphoid cells in wound healing is pleiotropic, depending on their subsets. Innate lymphoid cells-3 and natural killer cells are involved in increasing inflammatory responses, while innate lymphoid cells-2 can exert anti-inflammatory effects by enhancing macrophage M2 polarisation and expanding and homing Tregs.

The role and place of acquired immunity in the regeneration of wounds that do not heal for a long time has not been widely studied. T cells in long-term non-healing wounds are present in a defective and unresponsive state, which is manifested in their inability to secrete factors that they produce in a normal state [7].

T cells are involved in maintaining the pro-inflammatory profile of non-healing soft tissue injuries. The ligand for CXCR3, which is found in Th1 cells, is highly expressed in chronic inflammation. In addition, patients with diabetic ulcers have increased levels of inflammatory T cell subtypes such as Th1, Th17, and Th22 [20].

Even though the central regulators of the immune response play a balancing role in inflammation by suppressing the immune response, some studies have shown that an increased number of central regulators of the immune response at sites of chronic soft tissue inflammation is not only unable to eliminate the injury but even contributes to the pathogenesis of the disease itself. In addition, soft tissue commensals help improve the regeneration of long-term non-healing wounds by inducing the activation of T cells with immunoregulatory and tissue repair functions through a non-classical immune response [12].

Skin-resident B cells are involved in the local production of antibodies, the formation of ectopic lymphoid tissue, and other effector functions associated with the cutaneous antigen-specific immune response. However, the exact role of B cell subpopulations in chronic wound healing is still unclear. Early suggestions about the therapeutic effects of B cells on chronic skin wounds were made by R.F. Sîrbulescu and colleagues [19], who reported accelerated healing of both acute and chronic wounds, significant mitigation of apoptosis, and improved fibroblast proliferation after topical application of purified mature naïve B cells to the cutaneous wound bed in mouse models. As a result, 43% of diabetic wounds were completely closed, compared to 5% in the control group, with no therapeutic effect from an equivalent

number of destroyed B cells, hematopoietic stem cells, and T cells.

CONCLUSION

The process of full regeneration of long-term non-healing wounds does not occur when the immune system is unable to continue the normal recovery process, resulting in the prolonged presence of neutrophils and pro-inflammatory macrophages in the damaged skin, which contributes to inflammation, tissue fibrosis, and poor vascularisation. Research in this direction continues, however, today, it is necessary to clarify the causes of the development of generalisation of the inflammatory process when using well-known methods of treating long-term non-healing wounds and to determine the role of changes in the immune status. This would make it possible to develop effective methods of immunodiagnostics, as well as to predict and prevent the generalisation of infection, which ultimately, in our opinion, can improve the results of treatment of patients with long-term non-healing wounds.

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QANDLI DIABETDA UZOQ MUDDAT SURUNKALI YARALARNI REGERATSIYADA TUG'MA VA ORTTIRILGAN IMMUNITETNING O'RNI VA AXAMIYATI

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ABSTRAKT

Yarani davolashning fiziologik jarayoni to'rt bosqichni o'z ichiga oladi: gemostaz, yallig'lanish, proliferatsiya va chandiqlanish, to'g'ri va muvofiqlashtirilgan ishi qat'iy bosqichma-bosqich rejenerativ jarayonni ta'minlaydi. Biroq, jarohatlar ushbu jarayondan o'tmasa, ularning shifo topishi kechikadi va bu oxir-oqibat surunkali yoki uzoq davom etadigan jarohatlarga olib keladi. Surunkali jarohatlarning umumiy belgilari ekssudatsiya, qayta infektsiya, to'qimalarning nekrozi, nuqsonli qayta epiteliyalizatsiya, angiogenezning pasayishi va reaktiv kislorod turlarining ortiqcha ishlab chiqarilishidir. Umuman olganda, surunkali jarohatlarni uch asosiy toifaga bo'lish mumkin: diabetik oyoq yarasi, qon tomir yarasi va yotoq yaralari. Ular odatda qandli diabet, qon tomir kasalliklari va semirib ketish kabi patologik kasalliklardan aziyat chekayotgan keksa odamlarda kuzatiladi. Ushbu maqolada uzoq muddatli surunkali jarohatlar regeneratsiya davrida tug'ma va orttirilgan immunitetning xususiyatlariga bag'ishlangan.

Kalit so'zlar: uzoq muddatli surunkali jarohatlar, tug'ma immunitet, ortirilgan immunitet.

РОЛЬ И МЕСТО ВРОЖДЕННОГО И ПРИОБРЕТЕННОГО ИММУНИТЕТА ПРИ РЕГЕНЕРАЦИИ ДЛИТЕЛЬНО НЕЗАЖИВАЮЩИХ РАН НА ФОНЕ САХАРНОГО ДИАБЕТА

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АБСТРАКТ

Физиологический процесс заживления ран включает в себя четыре этапа: гемостаз, воспаление, пролиферацию и созревание, правильная и слаженная работа которых обеспечивает строгий этапный регенеративный процесс. Однако, когда раны не проходят через этот организованный процесс, заживление их задерживается, и это в конечном итоге приводит к хроническим или длительно не заживающим ранам. Общими признаками незаживающих ран являются экссудация, повторная инфекция, некроз тканей, дефектная реэпителизация, снижение ангиогенеза и избыточная продукция активных форм кислорода. В целом, хронические раны можно разделить на три основные категории: диабетические язвы стопы, сосудистые язвы и пролежни. Обычно они наблюдаются у пожилых людей, страдающих такими патологическими состояниями, как сахарный диабет, сосудистые заболевания и ожирение. Данная обзорная статья посвящена особенностям реакции врожденного и приобретенного иммунитета при течении длительно незаживающих ран.

Ключевые слова: длительно незаживающие раны, врожденный иммунитет, приобретенный иммунитет.