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Review Article

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Modern Methods of Treatment of Long-term Non-Healing Wounds and Prevention of Generalisation of Infection

B.Z. Khamdamov[1], B.Ya. Umarov[2]

ABSTRACT

The relevance of the problem of treating long-term non-healing wounds is due not only to medical significance but also to social and economic importance. Long-term non-healing wounds are a heavy burden for both patients and their family members. Due to the presence of pain, infection, loss of function in the affected area, as well as constant financial costs, not only does the quality of life decrease and the number of disabled people increase, but conditions are created for the generalisation of infection, the development of surgical sepsis and the death of the patient. A distinctive feature of the generalisation of infection in patients with long-term non-healing wounds is the presence of a focus on chronic inflammation caused by the infiltration of pro-inflammatory immune cells. Thus, the development of strategies based on the regulation of immune cell functions is a promising approach in regenerative medicine for the treatment of chronic wounds, including diabetic, vascular and pressure ulcers, on the one hand, and the prevention of generalisation of infection, on the other. We summarised different approaches to immunomodulation to improve wound healing and prevent generalised infection.

Keywords: long-term non-healing wounds, immunity modulation, vacuum wound therapy

The main types of prevention of generalisation of infection in long-term non-healing wounds according to the immunomodulation strategy are possible by polarisation of M_2 macrophages. Macrophage polarisation is carried out by the use of phosphatidylserine-containing liposomes, which have been used in experimental models of long-term non-healing wounds in young and middle-aged mice. The results showed that it was possible to prevent the generalisation of infection and the formation of new pressure ulcers. This method of treatment promotes wound healing and angiogenesis [20].

A possible variant of macrophage polarisation is the use of exosomes derived from M_2 macrophages. H. Kim et al. [6] applied this to experimental models of acute wounds, which led to the acceleration of primary as well

[1] Professor, Doctor of Medical Sciences, Head of the Department of Faculty and Hospital Surgery, Bukhara State Medical Institute, Bukhara, Uzbekistan. e-mail: dr.hamdamov@mail.ru

[2] ***Contact for correspondence:*** PhD, Director of the National Children's Medical Center of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan. E-mail: bakhtiyorumarov@mail.ru

as complete wound closure. Prevention of generalisation of infection was achieved by enhancing re-epithelialization and angiogenesis.

Modifying the macrophage phenotype could be a promising therapeutic approach to treating chronic skin inflammation. Phosphatidylserine-containing liposomes have been shown to induce macrophage polarisation towards the M_2 phenotype in mice with pressure ulcers. Thus, treatment with phosphatidylserine-containing liposomes accelerated wound healing, induced vascularisation, and inhibited pressure ulcer formation in mice with an ischemia-reperfusion model of pressure ulcers. Overexpression of the scavenger receptor gene CD163, a marker of the M_2 regenerative type, in M_1 macrophages contributed to more efficient wound healing, including by reducing the expression of monocytic chemoattractant protein-1 and the production of transforming growth factor-α [2].

M_2-derived exosomes induce complete reprogramming of classically activated M_1 macrophage cells into a healing-promoting phenotype, which promotes skin wound healing. In addition, M_2-derived exosomes secrete paracrine factors such as interleukin-4, CXCL12, and major fibroblast growth factors, which repair wounds by promoting collagen deposition and re-epithelialization. In addition, the expression of long non-coding RNA GAS5 is enhanced in diabetic wound cells and promotes macrophage differentiation towards the M_1 phenotype by increasing the regulation of the signalling transductor and transcriptional activator-1 [12].

Thus, GAS5 knockout promotes chronic wound repair by modulating macrophage phenotypes in chronic skin wounds.

Inhibition of mineralocorticoid receptor expression helps to accelerate the wound healing process in diabetic mice without affecting the wounds of healthy mice. This effect is due to a decrease in the production of LCN2, a ligand for mineralocorticoid receptors, which can contribute to macrophage polarisation, neovascularisation, and prevention of inflammation. NK-4 is another promising agent for antichronic wound therapy. NK-4 is a cyanine dye that has been shown to activate the differentiation of tumour macrophages into the pro-inflammatory M_1 phenotype and stimulate their phagocytic activity. Interestingly, when incubated, NK-4-treated M1 macrophages switched to the M_2 phenotype when incubated together with apoptotic Jurkat E6.1 (Apo-J) cells by suppressing tumour necrosis factor-α secretion and stimulating the production of interleukin-10. Finally, treating diabetic mice with docosahexaenoic acid significantly improved ulcer healing by stimulating macrophage polarisation towards the M_2 phenotype. In general, macrophage polarisation towards the anti-inflammatory type significantly improves delayed wound healing [4].

Thus, various approaches to modifying the macrophage phenotype can be used as therapies for the treatment of chronic wounds.

MiRs are important regulators of the immune system. Specifically, they control the response of macrophages, monocytes, dendritic cells, granulocytes, mast cells, T cells, and other immune cells by regulating the expression of multiple genes. On the other hand, some miR, such as miR-21, miR-424, miR-31, miR-221, and miR-222, are dysregulated in chronic wounds, resulting in an inadequate immune response compared to conventional wounds [13].

Thus, post-transcriptional modulation of immune cell gene expression by restoring normal miR expression by increasing and/or decreasing miR regulation can be considered as a rational complementary immunomodulatory therapy to improve chronic wound healing. This may involve delivering miRs embedded in viral vectors, liposomes, or biomaterials directly to the wound. MiR-146a is a potential target that promotes faster wound healing.

Suppression of miR-146a significantly slows down the regeneration of long-term non-healing wounds in mice with an experimental model of diabetes mellitus compared to similar models of the pathological process but without deleting the miR-146a gene by increasing the inflammatory response [1].

Thus, treatment with (2E,6E)-2,6-bis(2-(trifluoromethyl)benzylidene)cyclohexanone (C66) increased miR-146a secretion and suppressed NF-ϰB activity during the wound process in animals with an experimental model of diabetes mellitus, resulting in an anti-inflammatory response.

Moreover, recently, miR-146a was conjugated with cerium oxide nanoparticles and applied directly to a diabetic wound. Cerium oxide nanoparticles - miR146a accelerated the healing of chronic wounds by reducing inflammation and increasing angiogenesis [29].

It is known that miR-21 is involved in the regeneration of wounds that do not heal for a long time. The level of miR-21-3p was reduced in patients with diabetes mellitus compared to healthy patients, and treatment with the miR-21-3p agonist stimulated fibroblast activation by reducing SPRY1 [27].

Thus, the overproduction of microRNA-21-3p is another target for the treatment of wounds that do not heal

for a long time. Overall, microRNA expression modification is a novel target for the treatment of long-term non-healing wounds.

In addition to regulating the inflammatory phase of wound healing and eliminating it, new approaches based on stem cell transplantation and allogeneic skin grafts and substitutes emphasise the importance of immunomodulation for skin wound healing and preventing the generalisation of infection. Several immunomodulatory approaches have been used for tissue repair and regeneration, targeting both inflammatory factors such as tumour necrosis factor-α, interleukin-1, and NF-ϰB pathway, as well as anti-inflammatory factors such as interleukin-4, interleukin-10, and TGF-β [23].

Tumor necrosis factor-α, which is involved in the recruitment of neutrophils and macrophages, plays an early regulatory role in the inflammatory phase of wound healing. M. Ritsu and colleagues [26] reported early expression of tumour necrosis factor-α in full-length skin wounds in mice. In addition, the authors demonstrated delayed wound closure, a reduction in the number of inflammatory cells and fibroblasts in the wound bed when treated with tumour necrosis anti-factor-α mAb, and accelerated wound healing by delivering tumour necrosis factor-α. In addition, hyperglycemia can induce the production of tumour necrosis factor-α by M1 macrophages, and levels of this cytokine are increased in skin wounds in rats with an experimental model of diabetes mellitus. The use of neutralising antibodies of tumour necrosis factor-α and its antagonist increased the migratory capacity of keratinocytes and accelerated the healing of skin wounds in rats with diabetes mellitus, respectively.

The interleukin-1 family is another important therapeutic target for the regeneration of wounds that do not heal for a long time. According to D.P. Perrault and colleagues [11], interleukin-1β is an upward regulator of inflammasome activity in wound macrophages, which prevents their polarisation towards the anti-inflammatory phenotype. The use of an interleukin-1 receptor antagonist, in particular interleukin-1Ra, may have an immunomodulatory effect by stopping interleukin-1 signalling. Studies by D.P. Perrault have shown that anakinra, a recombinant interleukin-1R antagonist, accelerates the healing of diabetic wounds by reducing the infiltration of macrophages and neutrophils. In addition, J.L. Tan et al. [22] reported a delay in diabetic wound closure along the interleukin-1–interleukin-1R1 axis, which can be overcome by the engineered extracellular matrix-binding interleukin-1Ra. Inhibiting molecules that are excessively produced in long-term non-healing wounds and thus further complicate the healing process is another approach in immunological treatment. In particular, it has been proven that selective inhibition of matrix metalloproteinase-9, which is excessively secreted in diabetic ulcers by recruited neutrophils, with an inhibitor of (R)-ND-336, accelerates delayed wound healing, which makes matrix metalloproteinase-9 a potential target for therapeutic measures.

Delivery of exogenous growth factors can be applied to the treatment of long-term non-healing wounds due to their functions in enhancing granulation tissue formation, stimulating angiogenesis and immunomodulation. Growth factors whose levels were reduced in non-healing wounds, such as platelet growth factor, fibroblast growth factor, and epidermal growth factor, were the main candidates for delivery. For example, the platelet growth factor is a crucial factor in wound healing, which is involved in the chemotaxis of neutrophils, monocytes, and fibroblasts to the injury site in the early stages of wound healing and is involved in the contraction of collagen matrices at the proliferation stage [30].

Accordingly, Regranex® — a recombinant growth factor derived from human platelets-BB embedded in a gel — has been approved by the FDA and EMA for topical use in diabetic foot ulcers. Although Regranex® has demonstrated efficacy in the treatment of ulcers in placebo-controlled trials, the increased risk of adverse events identified during post-marketing surveillance led to the withdrawal of Regranex® from the European market [17].

In addition, the fibroblast growth factor family consists of several classes involved in wound healing, such as fibroblast growth factor-2, keratinocyte growth factor-2, fibroblast growth factor-7, and others. For example, fibroblast growth factor-2 (also called major fibroblast growth factor), which is part of hydrogel, cryogel, coacervate, and biofilm, can accelerate wound healing by increasing fibroblast proliferation, organising collagen deposition, promoting angiogenesis and keratinocyte migration, and reducing pro-inflammatory factors such as tumour necrosis factor-α and interleukin-6. Therefore, recombinant forms of the main growth factor of bovine and human fibroblasts, such as Fiblast Spray®, have been used to treat burns, choking, and diabetic foot ulcers. In another study, polysaccharide hemostasis microspheres were used to mediate the prolonged release of fibroblast growth factor-2 in a rat model of full-layer skin cutting [19].

The treatment reduced inflammation and accelerated wound healing, which was associated with greater

bioavailability and controlled release. Overall, the regulation of immune cells by modulating the expression of various cytokines and the delivery of growth factors is a promising strategy in the treatment of long-term non-healing wounds.

Therapies based on stem cell technologies are currently being actively researched in the field of regenerative medicine [8].

Experimental preclinical and clinical studies have shown a positive effect of the use of adult stem cells in the treatment of long-term non-healing wounds and the prevention of generalisation of infection. This beneficial effect is due to the unique properties of stem cells to suppress the immune response, repair damaged tissues, and maintain local cells through the secretion of trophic and paracrine factors [21].

Various in vivo studies have demonstrated a well-orchestrated interaction between stem cell secretomes and mediators found in the wound area, resulting in reduced scar size and reduced inflammation, as well as improved re-epithelialization of damaged tissue and no generalisation of infection [7].

Exosomes secreted by stem cells have the same biological activity as stem cells and are thus also a potential target for chronic wound treatment. The immunomodulatory properties of exosomes can be activated by an inflammatory environment. Exosomes derived from fat stem cells, when treated with pro-inflammatory cytokines such as interferon-γ and tumour necrosis factor α, enhance their immunosuppressive properties and switch macrophage polarisation towards the M2 phenotype [5].

Wound treatment with microvesicles derived from fat stem cells significantly increased the production of vascular endothelial growth factor, platelet growth factor-A, epidermal growth factor, and fibroblast growth factor-2, and thus enhanced epithelialisation, angiogenesis, and collagen deposition, ultimately leading to accelerated wound healing. Exosomes secreted by adipose tissue stem cells reduced ulcer size in diabetic mice by promoting angiogenesis, granular tissue formation, immunosuppression, and reduced proteins associated with oxidative stress [9].

In addition, exosomes from stem cells derived from human urine have been shown to overexpress proangiogenic factor DMBT1 and thus promote angiogenesis in mice with an experimental model of diabetes mellitus [3].

Stem cells derived from lipoma are another target in regenerative medicine. In vitro, studies have shown that lipoma-derived stem cell secretomes activate other cells, such as macrophages, and stimulate the overexpression of interleukin-10 while inhibiting the production of tumor necrosis factor [24].

Taken together, due to their immunosuppressive functions, stem cells and their secretions can serve as potential regenerative medicine tools for the treatment of long-term non-healing wounds. In addition to the delivery of biologics, physiotherapy approaches such as hyperbaric oxygen therapy, low-level laser therapy, and electrical stimulation have been attempted to accelerate the regeneration of long-lasting wounds [18].

Negative pressure wound therapy, also known as vacuum closure, is another approach to physical treatment that relies on differential suction or vacuuming wounds to improve fluid removal, reduce swelling, and alter the wound microenvironment [25].

Negative pressure wound therapy has demonstrated promising results in accelerating the regeneration of wounds that do not heal for a long time, including trophic ulcers of the lower extremities of vascular origin neurotrophic ulcers in diabetic foot syndrome.

A meta-analysis of randomised controlled trials conducted by S. Lui and colleagues evaluated the safety, cost-effectiveness, and therapeutic efficacy of negative pressure wound therapy in the treatment of diabetic foot ulcers [10]. An analysis of 11 studies concluded that negative pressure wound therapy has a higher rate of complete ulcer healing, faster wound healing, and a significant reduction in wound surface area compared to standard dressings without significantly affecting adverse events.

Another systematic review by M. Wynn and S. Freeman [28] also reported better clinical outcomes for negative pressure wound therapy compared to standard treatment for diabetic foot ulcers.

Although both reviews included limitations, such as methodological flaws in studies and conflicting protocols for negative pressure wound therapy, the available evidence supports the effectiveness of a vacuum closure approach as a non-invasive adjunctive treatment for long-term non-healing wounds and preventing generalisation of infection.

The exact molecular mechanisms that promote wound healing with negative pressure therapy are not fully understood. However, changes in cytokine expression and immune cell attraction are among the immunomodulatory effects exerted by negative pressure wound therapy. For example, negative pressure wound therapy has been shown to stop the increase in inflammatory stimuli of the

wound by preventing excessive production of nitric oxide-mediated by the inducible synthase of this compound. In addition, negative pressure wound therapy prevents NF-ϰB activation by inhibiting IkB-α and upregulating ATF-3, which subsequently reduces the expression of pro-inflammatory cytokines such as TNF-α and interleukin-6 and, in turn, reduces the risk of generalisation of infection [14].

T. Wang et al. reported [15] that negative pressure wound therapy reduces iNOS, interleukin-6, and tumour necrosis factor-α by regulating the MAPK pathway.

Local wound treatment using controlled negative pressure promotes the healing of full-layer skin defects in mice with diabetes mellitus by reducing the number of CD68+ macrophages, reducing the level of pro-inflammatory cytokines TNF-α, interleukin-6, interleukin-1β, and suppressing autophagy [16].

These observations emphasise the role of immunomodulatory effects in the therapeutic mechanism of accelerating the regeneration of wounds that do not heal for a long time when they are treated with negative pressure.

CONCLUSION

The presented basic information regarding the role and place of the immune system in wound regeneration confirms the high importance of both the innate and acquired components of this body system in the outcome of the pathology under study. Several studies have shown the critical role of immune cells in all four stages of tissue repair, including re-epithelialization and tissue remodelling. It has also been shown that dysregulation of their functions contributes to the formation of chronic wounds and fibrous scars.

However, from a clinical point of view, all of the above information will be widely used, provided that the results can be extrapolated into the practical system of medicine. For example, an attempt to modulate the immune system to improve wound healing has been successfully tested by many research groups.

The analysis of the literature data presented in this article allows us to identify several extremely important strategic positions regarding the possibilities of immunomodulatory strategies, namely macrophage polarisation, regulation of miR expression, inhibition of pro-inflammatory cytokines, and treatment with anti-inflammatory cytokines. These strategies are often used in conjunction with other methods to increase their effectiveness. In particular, bioactive substances can be incorporated into biomaterials such as nanoparticles and cryogens, which contributes to their protection and controlled release.

Despite the positive results obtained in preclinical studies, many issues need to be considered before translating the above-mentioned treatments into clinical trials. First of all, animal models on which treatment methods have been tested cannot fully reproduce the complexity of long-term non-healing human wounds. The possibility of conducting the study in conditions of long-term non-healing wounds and the possible development of generalisation of infection is reduced.

Thus, wound immunity, as well as the healing process in humans, is different from wound pathogenesis in mice, which is most commonly used to investigate skin lesions. Second, strategies that modulate the immune system must be evaluated very carefully from a safety perspective because they can trigger the wrong immune response. For example, these treatments can affect the immune response in places other than wounds and affect immune conditions present in patients, such as infections, allergies, and autoimmune diseases. Finally, the technical considerations of potential treatments, such as delivery methods and application techniques, as well as the timing of therapy, should be considered.

In general, although immunomodulatory therapy has shown promising results in preclinical studies, its transition to clinical trials may be difficult due to the complexity of long-term non-healing wounds in humans, and therefore, more research is needed. Moreover, a large aspect of the possibility of predicting and preventing the generalisation of infection in patients with long-term non-healing wounds remains not fully studied.

Conflict of interest – none

Study funding – not provided

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UZOQ MUDDATLI BITMAGAN YARALARNI DAVOLASHNING ZAMONAVIY USULLARI VA INFEKTSIYANING TARQALISHINI OLDINI OLISH

[1]B.Z. Xamdamov, [2]B.Ya. Umarov

[1]Buxoro davlat tibbiyot instituti

[2] O'zbekiston Respublikasi Sog'liqni saqlash vazirligi huzuridagi Milliy bolalar tibbiyot markazi

ABSTRAKT

Uzoq muddatli tuzalmagan jarohatlarni davolash muammosining dolzarbligi nafaqat tibbiy ahamiyatga, balki ijtimoiy-iqtisodiy ahamiyatga ham bog'liq. Uzoq muddatli tuzalmaydigan jarohatlar bemorlar uchun ham, ularning oila a'zolari uchun ham og'ir yukdir. Og'riq, infektsiya, zarar ko'rgan soxaning faoliyatini yo'qotish, shuningdek doimiy moliyaviy xarajatlar mavjudligi tufayli nafaqat hayot sifati pasayadi va nogironlar soni oshadi, balki infektsiyani sepsisga utishi, jarrohlik sepsisning rivojlanishi va bemorning o'limi uchun sharoitlar yaratiladi. Uzoq muddatli shifo topmaydigan jarohatlari bo'lgan bemorlarda infektsiyaning umumiy tarqalishining o'ziga xos xususiyati yallig'lanishga qarshi immunitet hujayralarining infiltratsiyasidan kelib chiqqan surunkali yallig'lanish markazining mavjudligidir. Shunday qilib, immun tizim faoliyatini tartibga solishga asoslangan strategiyalarni ishlab chiqish regenerativ tibbiyotda surunkali yaralarni, shu jumladan diabetik yaralar, qon tomir va yotoq yaralarini davolashda, boshqa tomondan infektsiyaning tarqashini oldini olish uchun istiqbolli yondashuvdir. Yaraning bitishini yaxshilash va umumiy infektsiyani oldini olish uchun immunomodulyatsiyaga turli yondashuvlar tug'risida ma'lumotlarni umumlashtirdik.

Kalit so'zlar: uzoq muddatli shifo topmagan yaralar, immunitet modulyatsiyasi, yarani vakuum terapiyasi.

СОВРЕМЕННЫЕ МЕТОДЫ ЛЕЧЕНИЯ ДЛИТЕЛЬНО НЕЗАЖИВАЮЩИХ РАН И ПРОФИЛАКТИКА ГЕНЕРАЛИЗАЦИИ ИНФЕКЦИИ

[1]Б.З. Хамдамов, [2]Б.Я. Умаров

[1]Бухарский государственный медицинский институт

[2] Национальный детский медицинский центр министерства здравоохранения Республики Узбекистан

АБСТРАКТ

Актуальность проблемы лечения длительно незаживающих ран обусловлена не только медицинской значимостью, но и социальной и экономической важностью. Длительно незаживающие раны – это тяжелое бремя как для пациентов, так и для членов их семьи. В связи с наличием болевого синдрома, инфицирования, потери функции зоны поражения, а также постоянных финансовых затрат не только снижается качество жизни и повышает количество инвалидов, но создаются условия для генерализации инфекции, развития хирургического сепсиса и смерти больного. Отличительной чертой генерализации инфекции у больных с длительно незаживающими ранами является наличие очага хронического воспаления, вызванное инфильтрацией провоспалительных иммунных клеток. Таким образом, разработка стратегий, основанных на регуляции функций иммунных клеток, является перспективным подходом в регенеративной медицине для лечения хронических ран, включая диабетические, сосудистые и пролежни, с одной стороны, и профилактика генерализации инфекции – с другой. Мы обобщили различные подходы к иммуномодуляции для улучшения заживления ран и профилактики генерализации инфекции.

Ключевые слова: длительно незаживающие раны, модуляция иммунитета, вакуумная терапия ране.