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Oxidative stress in wound healing – current knowledge

Role oxidativního stresu v hojení ran – současné poznatky

Abstract

Wound healing is a complex process based on a subtle coordination of biochemical and physiological interactions. Healing process itself and its quality are affected by numerous factors, both local (type, size, depth, and localization of the wound, bacterial contamination, microcirculation, oxygen supply, etc.) and systemic (age, comorbidities, smoking, nutritional status, etc.). Many studies, using various methodological approaches, focus on wound healing process at various levels. It is well known that reactive oxygen and nitrogen species play an important role in all phases of wound healing. Regardless increasing knowledge about the role of oxidative stress in wound healing process, the conclusions of research in this area are still rather contradictory. Therefore, aim of this paper is to summarize current knowledge about the role of oxidative stress in wound healing process.

Souhrn

Hojení ran je etapovitý proces probíhající na celulární i subcelulární úrovni jako souhra řady biochemických a fyziologických pochodů a interakcí. Rychlost a kvalita hojení jsou ovlivněny mnoha faktory, a to jak lokálními (typ, velikost, hloubka a lokalizace rány, bakteriální biofilm, stav mikrocirkulace, zásobení kyslíkem), tak systémovými (věk, komorbidity, kouření, stav nutrice, aj). I z tohoto důvodu je proces hojení předmětem zájmu řady studií a je zkoumán různými metodickými přístupy na mnoha úrovních. Je známo, že reaktivní formy kyslíku a dusíku hrají významnou roli ve všech fázích hojení ran. Navzdory rostoucí pozornosti, která je výzkumu role oxidativního stresu v procesu hojení ran věnována, jsou závěry aktuálních studií stále ještě rozporuplné. Cílem příspěvku je tedy poskytnout přehled o současných znalostech o úloze oxidativního stresu v procesu hojení ran.

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Klíčová slova

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Introduction

Wound healing is a complex process based on a subtle coordination of biochemical and physiological interactions. Healing process in the wound starts by a tissue damage and is finished when a functional scar is formed. Healing process itself and its quality are affected at various levels by numerous factors, both local and systemic. Local factors include type, size, depth, and locaization of the wound, then also bacterial contamination, microcirculation, oxygen supply, etc.

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Systemic factors are age, comorbidities, nutritional status, and others. Chronic and non-healing wounds (e.g. pressure ulcers, diabetic ulcerations) still represent a major concern not only for patient and his family, but also for public health system due to a steadily growing issue of socioeconomic cost. Specific group of patients at increased risk for development of pressure ulcers and other dermatological complications are those after spinal cord injury [1,2]. Therefore, any therapeutic approach potentiating or accelerating wound healing process at any level is considered beneficial. Several models have been used to evaluate wound healing process from macroscopic down to molecular level, using various experimental approaches from *in silico* (computational model to understand wound healing theoretically), *in vitro* (explaining pathogenesis of wound healing), *ex vivo* (providing 3D model of skin explant), and *in vivo* (using animal or human model) [3]. At present, one of the main topics in the theoretical research in wound healing is the role of oxidative stress in various phases of healing process. It is widely believed that the amount of oxygen/nitrogen radicals might be crucial for further direction of a healing process. However, number of systematic studies presenting detailed insight into reactive oxygen species (ROS) / nitrogen species (RNS) role in particular phases of wound healing is still limited. Aim of this article is to summarize in detail present knowledge about parameters of oxidative stress in particular phases of wound healing in order to provide an integrated, synthesized overview of the current knowledge.

Reactive oxygen and nitrogen species in wound healing – a general view

Wound healing is one of the most complex biological processes. It involves the spatial and temporal synchronization of a variety of cell types with distinct roles in the phases of haemostasis, inflammation, growth, re-epithelialization, and remodelling [4,5]. The first phase "haemostasis" prevents excessive blood loss; it triggers events that lead to local inflammation by neutrophils and then macrophages. The inflammation is followed by the performance of local tissue cells, keratinocytes and fibroblasts. The former cells first migrate into the injured area for the primary coverage and start to proliferate to recover the stratification. The latter transform to the myofibroblasts that are capable of producing extracellular matrix and of tissue contraction. Both cell migration of keratinocytes and fibroblasts-myofibroblasts conversion largely depend on the activity of a potent growth factor, transforming growth factor β (TGFβ), although a set of growth factors are believed to orchestrate the whole process of tissue repair [6]. Changes in the microenvironment, including alterations in mechanical forces, oxygen levels, chemokines, extracellular matrix, and growth factor synthesis directly affect cellular recruitment and activation, leading to impaired states of wound healing. Impaired wound healing, in turn, may lead to post-surgical complications frequently observed in elderly patients, chronic ulcers in diabetic patients, hindered and ineffective pain management, etc. [7]. The mechanism of delayed wound healing has multifactorial causes, including a prolonged inflammatory stage, postponed proliferation and remodelling stages. It has been reported that nuclear factor kappa B (NF-κB) regulates the gene expression of several cytokines, such as interleukin-1beta, interleukin-6, tumor necrosis factor-alpha, and interleukin-10; inducible nitric oxide synthase (iNOS); chemotactic and matrix proteins; immunological responses; and cell proliferation [8]. NF-κB can contribute to inflammation and fibroblast function, which are necessary components of incision and wound healing [9]. It has been shown that inhibition of these signal transduction pathways may provide novel strategies to prevent sepsis but may interfere with healing. The persistence of the inflammatory reaction is associated with oxidative stress, which is one of the most common reasons for the delayed wound healing [10]. The increased production of free radicals and decreased antioxidant activities of enzymes, such as superoxide dismutase, glutathione peroxidase, heme oxygenase-1, and heme oxygenase-2 may aggravate the situation leading to a delay in diabetic wound healing [11]. All these events indicate a pivotal role of ROS in the orchestration of the normal wound healing response. On the other hand, ROS act as secondary messengers to many immunocytes and non-lymphoid cells involved in the repair process and appear to be important in coordinating the recruitment of lymphoid cells to the wound site and effective tissue repair. ROS also possess the ability to regulate the formation of blood vessels (angiogenesis) at the wound site and the optimal perfusion of blood into the wound-healing area [8]. ROS act in the host's defence through phagocytes that induce a ROS burst onto the pathogens present in wounds, leading to their destruction. During this period, excessive ROS leakage into the surrounding environment exhibits further bacteriostatic effects. In light of these important roles of ROS in wound healing and the continued quest for therapeutic strategies to treat wounds, it is necessary to look for ways to manipulate with ROS as a promising avenue for improving wound-healing responses [12]. On the other hand, several applications of ROS in wound healing have been shown. Cold physical plasmas are particularly effective in promoting wound closure, irrespective of its aetiology. These partially ionized gases deliver a therapeutic cocktail of ROS and RNS safely at body temperature and without genotoxic side effects. Specifically, molecular switches governing redox-mediated tissue response, the activation of the nuclear E2-related factor signalling, together with antioxidative and immunomodulatory responses, and the stabilization of the scaffolding function and actin network in dermal fibroblasts are emphasized in the light of wound healing [13]. This example shows the inconsistency of published results and the need for further research in the role of ROS in wound healing.

Reactive oxygen species are closely connected with nitric oxide and other RNS. There is very close interplay between them – they can create common forms of free radicals; in addition, ROS and RNS are able to partake in the modification of thiol groups, suggesting that the final outcome will be dependent on the concentrations and locations of these molecules [14]. Nitric oxide itself is implicated in cellular and molecular events of wound healing, such as vasodilation, angiogenesis, inflammation, tissue fibrosis, or immune responses. Several studies suggested that NO synthesis is essential to the uncomplicated cutaneous wound healing. NO production is mediated by iNOS that is regulated independently of intracellular calcium elevations. Initial injury is followed by infiltration of inflammatory cells, that is, neutrophils and macrophages, fibroblast repopulation and its transformation to myofibroblast, and new vessel formation as well as keratinocyte migration and proliferation. The major source of TGFβ in a tissue under repairing process is macrophage. Recruitment of macrophage to an injured tissue is

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stimulated by NO. It is therefore hypothesized that NO might affect the healing process of cutaneous injury [15]. The process of wound healing is completed by action of other molecules. Growth factors such as epidermal growth factor, fibroblast growth factor, TGF-beta1, and vascular endothelial growth factor and several molecules including hypoxia-inducible factor-1alpha are involved in the healing process by stimulating and activating cell proliferation via activation of various reactions, such as angiogenesis, reepithelialisation, differentiation, and production of the extracellular matrix [16]. All above mentioned facts indicate often contradictory information about involvement of ROS and RNS in wound healing.

Conclusion

Reactive forms of oxygen and nitrogen – basic oxidative stress parameters – play an important role in all phases of wound healing. This "overview" of currently available scientific information offers a framework for the exploration of the role of oxidative stress during wound healing process. Despite of growing attention in the field of oxidative stress research, conclusions of contemporary studies are still contradictory, therefore further intense work is needed to fully understand its role in wound healing process. Based on the present knowledge, it can be concluded that balanced ROS response will debride and disinfect a tissue and stimulate healthy tissue turnover; suppressed ROS will result in infection and an elevation in ROS will destroy otherwise healthy stromal tissue. Understanding and anticipating the ROS function within a tissue will greatly enhance our possibilities to orchestrate the processes of wound healing.

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