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Kinins in the process of wound healing

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SUMMARY

Wound healing is a complex process with the inflammatory phase being one of its stages, followed by tissue re-shaping and remodeling. Kinins are active peptides released from their precursors, kininogens, by kallikreins. Their action is multidirectional and includes, e.g. modulation of inflammation severity and regulation of cell proliferation. They are local hormonal factors and act via the bradykinin receptors BR1 and BR2. Owing to the broad spectrum of action, kinins will probably enable treatment of various diseases in the future. Increased expression of type 1 bradykinin receptors is observed in chronic inflammation, whereas type 2 bradykinin receptors are activated in both physiological states and acute inflammation. An imbalance between the expression profiles of B1 and B2 receptors may be an indicator of chronic inflammation and of their role in cell proliferative activity. The transcriptional activity of genes encoding B1 and B2 kinin receptors may be a criterion in the prognosis of postoperative wound healing, thereby enabling its monitoring and individualization of treatment.
Key words: kinins, wound healing, inflammatory phase

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INTRODUCTION

Wound healing is a complex process involving multiple stages. As an evolutionarily conserved process, it requires coordinated action of keratinocytes, fibroblasts, macrophages, platelets, and other cells. All this is to ensure proper coagulation, inflammation, epithelialization, and the formation of granulation tissue and scar [1,2].

KININS IN THE PROCESS OF WOUND HEALING

The kinin-kallikrein system was discovered in 1908 by Abelous and Bardier, who demonstrated hypotensive effects of human urine-derived substances [3]. This system includes tissue serine proteases and plasma kallikreins, which liberate biologically active kinins from high- and low-molecular-weight kininogen (HK and LK) by proteolysis. In humans, the most explored kinins are bradykinin BK (nonapeptide) and kallidin KD (decapeptide) as well as their carboxy-terminal des-Arg metabolites. Kinins liberated from kininogen are BR2 agonists and must react with carboxypeptidases to form BR1 agonistic des-Arg 9-bradykinin and des-Arg 10-kallidin. Kinins act via BR2 and BR1 receptors present in, for instance, epithelial cells and peripheral blood mononuclear cells. Their broad spectrum of action in many physiological and pathological processes is linked with their ability to activate vasodilation, increase vascular permeability, release tissue-type plasminogen activator (t-PA), produce nitric oxide (NO), and mobilize the arachidonic acid cascade. Their activity is described as proinflammatory or protective, particularly with respect to the cardiovascular system, kidneys and hematopoietic system. Apart from plasma or tissue substances, kinin action is also regulated by metalloproteinases, serpins and multiple relationships with other metabolic pathways, such as the RAA, coagulation, or complement pathways [4,5], to stimulate phospholipase C followed by inositol phosphate production, or through Gi protein,

which triggers the arachidonic acid cascade in a phospholipase A-dependent mechanism. Increased expression of type 1 bradykinin receptors is observed mainly in the chronic inflammatory phase, whereas type 2 bradykinin receptors are activated in both physiological states and acute inflammation [6,7].

Kinin receptors are a future therapeutic target in many medical conditions (e.g. chronic inflammatory pain, asthma, edema, sepsis, cardiovascular diseases, renal diseases, diabetes mellitus, cancer and others). The relationship between the quantity of kinin molecules or their metabolites as well as the expression of genes encoding B1 and B2 kinin receptors in the skin is not exactly known, which makes it impossible to precisely define their role in postoperative wound healing [8].

Nowak studied 34 women with well healing wounds and 32 patients with poorly healing wounds after abdominal gynecological procedures. He compared the number of mRNA copies for B1 and B2 receptors in frozen skin sections obtained from the surgical cut line. The study revealed that patients with well healing wounds (by first intention, with no redness at the edges and when patients were discharged on day 4–6 after the procedure) had a lower mean quantity of BR1 copies compared with women with poorly healing wounds (redness at the edges, inflammatory discharge and dehiscence). The number of BR1 copies below 17,000 was associated with a 20-fold better chance for good wound healing. The mean value of BR1 to BR2 ratio in the well-healing group was significantly lower than in the poorly healing group. The BR1/BR2 ratio below 1.01 was linked with a 12.5-fold better chance for good wound healing. The transcriptional activity of genes encoding kinin receptors may be a significant marker characterizing the manner of wound healing. The expression of genes coding BR1 receptor in poorly healing wounds is considerably higher than the expression in well-healing wounds. An imbalance between the expression profiles of B1 and B2 kinin receptors may be an indicator of chronic inflammation and of their role in cell proliferative activity [9]. Desposito et al. showed on the mouse model that B1 agonist had no significant effect on wound healing. In contrast, BR2 stimulation impaired wound repair. Wound repair was improved by BR2 blockade [10].

Schremmer-Danninger et al. showed that bradykinin and B2 receptor are autocrine and paracrine mediators in fetal membranes and decidua. The mRNA expression of BR2 is higher than that of BR1 [11]. Wound healing in the developing fetus involves restoration of the normal epidermal and dermal architecture and extracellular matrix with preservation of all their properties. The difference in fetal wound healing lies in the course of the inflammatory response and cellular mediators, cytokines, growth factors, and extracellular matrix modulators engaged in it, as well as in the course of secondary messenger phosphorylation patterns and homeobox gene expression [12]. Animal studies have shown that this different wound healing pattern is observed during two first trimesters of pregnancy. The elucidation of these phenomena would probably enable broader usage of surgical techniques *in utero*, and utilization of these data in wound management in adults [13]. By activating the arachidonic acid cascade, kinins lead to the formation of PGE2 which induces inflammation and fibrosis. PGE2 largely decides about the final process of scar formation. Partial resistance of fetal fibroblasts to PGE2 is probably responsible for wound healing without scars. Re-epithelialization in the fetus is also more efficient [14].

Furthermore, keratinocyte differentiation, visualized as an increase of filaggrin, CK10 and involucrin, was caused by BR1 stimulation and tyrosine pathway activation as well as action on ErbB receptors [15]. Moreover, the outcome of wound healing is also dependent upon the environmental oxidative potential [16]. Kinins also exert their action though the Ca2+ pathway. Kinin receptors are an interesting target for new therapies in infections. *Staphylococcus aureus* causes an increase in BR1 expression, but also promotes carboxypeptidases CPM, and preserves the level of B1 receptor agonist des-Arg9-bradikinin [17].

The results of the study conducted by Pietrovski et al. indicate the presence of kinin receptors in the skin and their role in modulating a neurogenic inflammatory response [18]. Furthermore, experimental studies have shown the usefulness of selective B1 receptor antagonists in neuropathic pain management [19]. It is worth underlining that B1 receptor is a hypernociception mediator in the mechanism dependent on TNF-alpha and IL-1 beta which, in turn, can stimulate prostanoid and sympathetic amine production [20]. Experimental studies on rats have shown that 660 and 664 nm low-level laser therapy (LLLT) decreases mRNA expression for BR1 and BR2 receptors [21].

There is evidence suggesting the existence of endogenous/nuclear BR2 receptor population and intracrine signaling by BR2 receptor [22]. Disorders in the kinin signaling may reflect increased activation of circulating mononuclear cells, which are important participants of the atherosclerotic plaque formation and eventually rupture [23,24]. Activated monocytes are characterized by higher BR1 expression. In contrast, the activity of BR2 decreases. The presence of inflammation is confirmed by B1 receptor expression in the tunica intima of fragments of abdominal aorta aneurysms. Gene deletion of the kinin B1 receptor attenuates cardiac inflammation and fibrosis in experimental diabetic cardiomyopathy models [25].

In addition, BR2 overexpression has also been observed in head and neck squamous cell carcinoma [26]. Also, kinin receptor expression reflects the dynamics of vulvar cancer growth [27]. Moreover, it was noticed that the usage of B1 antagonists could disrupt the interaction between B1 receptor and EGF, thereby offering new possibilities for breast cancer therapy [28].

CONCLUSION

Kinins may serve as markers of the normal wound healing process and therefore be useful in wound healing prognosis, monitoring and individualization of treatment.

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