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Short Communication

# Pathogenetic and Diagnostic Role of Matrix Metalloproteinases as Biomarkers in the Study of Skin Scars

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## Introduction

A scar is a newly formed connective tissue that appeared at the site of deep skin defects accompanied by the destruction of the dermis due to ulceration, wounds, burns, cracks, and inflammatory processes [1-3]. The development of this tissue occurs in accordance with certain laws. Each stage corresponds to certain morphological changes: alterations and inflammation, fibroblast proliferation and granulation formation, defect epithelization, maturation and remodeling of scar tissue [4-6].

Scar tissue is formed as a result of healing of a wound defect, so to develop optimal methods for treating scar skin changes, it is necessary to understand the pathogenesis of the wound process, which is a complex set of biological reactions [1,4]. Despite the existing variety of approaches to the treatment of scarring skin changes, there is currently no standardized system for evaluating the effectiveness of various medical technologies for treatment, algorithms for selecting and applying certain areas of correction of scarring skin changes. There are practically no works of a fundamental plan that reveal approaches to the justification of a complex treatment system based on various etiopathogenetic mechanisms for the appearance of various types of scars.

To date, it has been established that matrix metalloproteinases (MMP), which are enzymes belonging to the endopeptidase family, also play an important role in scar formation. The active center of MMP includes zinc or calcium ion [7]. MMP plays an important role in both physiological processes and in the development of pathology, for example, in wound and infectious processes [7-9]. The main function of these proteins is to destroy the components of the extracellular matrix and remodel it. they also participate in the processes of proliferation, migration, and morphogenesis [8,9].

The aim of the study is to analyze the literature data on the role of matrix metalloproteinases in the mechanisms of development of scarring changes in the skin.

Currently, the primary diagnosis of scarring skin changes and evaluation of changes in the treatment process is carried out mainly on a few clinical signs. As a rule, they take into account the presence of subjective sensations (itching, tightening, etc.), the color of the scar, its size, shape and density. The disadvantage is that this assessment is always subjective, in addition, there is a long time interval between the two points (the beginning and end of treatment), but the detailed initial state of the scar is sometimes forgotten not only by the doctor, but also by the patient [10].

In addition to the complexity of objective assessment of the initial state of the scar, the development of methods and treatment algorithms is significantly hampered by the following groups of factors:

Slow response of connective tissue to therapy;

The ability of scar tissue to spontaneous regression, which often leads to «false-positive» conclusions about the effectiveness of a particular method;

Lack of objective control methods that characterize the growth and condition of scar tissue [2,11,12].

Currently, the area of special relevance is related to the development and implementation of skin research methods in vivo. Achievements in this area create prerequisites for a deeper understanding of the physiological mechanisms and etiopathogenesis of pathological conditions, which will allow us to successfully solve the problems of diagnosis, treatment and prevention of many skin diseases [12,13].

As is known, fibrogenesis - the formation of scar tissue at the site of skin injury-is carried out mainly with the participation of mast cells, lymphocytes, macrophages and fibroblasts [14]. The starting vasoactive moment is carried out with the help of mast cells, the biologically active substances they secrete help attract lymphocytes to the lesion [14,15]. Tissue breakdown products activate T-lymphocytes, involve macrophages in the fibroblastic process through the production of lymphokines, or directly stimulate macrophages with proteases [15-17]. Mononuclears not only stimulate the function of fibroblasts, but also inhibit them, acting as true regulators of fibrogenesis, isolating inflammatory mediators and other proteases [15,16].

Matrix metalloproteinases (MMP) are zinc-dependent endopeptidases involved in the degradation of the extracellular matrix. The participation of MMP in tissue restructuring and angiogenesis is shown [8,9]. Most MMP is secreted by cells in the form of inactive enzymes, while small amounts of them are found in tissues. Activation of these enzymes leads to proteolytic degradation of the proteins surrounding the cell. Increased MMP activity can lead to excessive tissue damage.

Although the main function of MMP is to destroy the extracellular matrix, MMP also cuts peptide chains and regulates the activity of a number of other extracellular biologically active substrates.

MMP are classified into 4 groups: collagenase, gelatinase was, stromelysin and membrane-type MMP. Collagenases include MMP-1, MMP-8 and MMP-13, which cleave type I and type III collagens, both of which are present in scar tissue [18,19]. MMP activity is regulated by tissue metalloproteinase inhibitors (TIMP), namely TIMP-1, TIMP-2, TIMP-3 and TIMP-4, which inhibit MMP [7].

MMP-1 (collagenase-1) is expressed in normal cells, such as fibroblasts, macrophages, endothelial and epithelial cells, as well as in various tumor cells [20].

Clinical associations of single-nucleotide polymorphisms in metalloproteinase genes with the development of a wide range of pathologies of various organs and systems, including diseases of the cardiovascular system, age-related maculodystrophy, cancer, and pathology of the female reproductive system are described [21,22].

A number of studies have examined the role of MMP in the formation of keloid and hypertrophic scars. It was found that MMP involved in scar formation is secreted directly by fibroblasts [22,23]. An imbalance in the expression of MMP and TIMP is a likely mechanism that contributes to changes in the synthesis and resorption of collagen, resulting in the formation of keloid and hypertrophic scars [24,25].

The activity of MMP-1 (collagenase), which initiates the degradation of collagen I, may be reduced in hypertrophied scars compared to normal skin [25]. At the same time, MMP-2 is more active in keloid and hypertrophic scars than in normal skin [26,27]. It was found that increased activity of MMP-2 due to the destruction of the extracellular matrix at the periphery of the keloid can contribute to the migration and invasion of keloid fibroblasts in the surrounding unchanged tissue [22]. This process leads to a gradual expansion of the keloid beyond the original damage [28].

The dose-dependent decrease in migration activity (and collagen levels) in the presence of the GM6001 broad-spectrum MMP inhibitor indicates the direct role of MMP in this process, and therefore the potential for therapeutic use of MMP inhibitors in the treatment of keloids

[28]. Based on the assumption that MMP can contribute to keloid expansion by destroying the extracellular matrix at the periphery of the keloid, it can be assumed that it is appropriate to conduct a study to assess these mechanisms in depth in order to justify and develop new methods for treating scarring skin changes.

It is possible that MMP activity may be reduced in the center (contributing to excessive collagen deposition and scar tissue formation) and increased along the edges of the keloid (thereby contributing to its expansion). G Uchida., *et al.* (2003) based on this hypothesis, we concluded that the variability of results in the study of collagenase activity may be due to the study of different regions of the keloid scar (center and periphery). The authors showed that the expression of MMP-1 and MMP-8 in human keloid fibroblasts is lower compared to normal fibroblasts, while MMP-13 is higher. The most active expression of MMP-13 was observed in marginal fibroblasts, while it was lower in Central fibroblasts [29].

MMP-9 (gelatinase) may also play a role in the formation of keloid and hypertrophic scars. This enzyme has been shown to be involved in early tissue repair and may be active in several key areas of wound healing [30].

In connection with the above, there is an assumption about the possible effectiveness of hepatocyte growth factor in the treatment of keloids due to the ability to enhance the expression of mRNA MMP-1 and MMP-3 of human keloid fibroblasts and increase the activity of MMP-2 in the intercellular matrix of the keloid [31,32]. During subcutaneous implantation of a mouse fragment of hypertrophic scar tissue, it was found that when exposed to fibroblast growth factor released in the first phase of the wound process, there is an increase in the expression of MMP-1 mRNA and the enzyme itself, which contributes to the degradation of collagen [19].

Other areas of scar treatment include monitoring the level of tissue growth factor (TFR)-β and the level of MMP. It has been shown that TFR-β reduces the production of MMP-1 in human keloid tissue, while the use of anti-TFR-β antibodies allows increasing the synthesis of MMP-1 [28]. The use of TFR-β as an MMP suppressor for the treatment of hypertrophic scars was evaluated in experiments on rabbits. It was shown that oleanolic acid (a natural triterpenoid) reduced the level of TFR, increased the level of MMP-1, which led to a decrease in the level of collagen I and III in the hypertrophic scar tissue [33].

Y Kuo., *et al*. (2005) it was found that treatment of keloid with a pulsed dye laser after biopsy resulted in a decrease in TFR-β expression and an increase in MMP-13 expression, which could contribute to scar regression [34].

Because immune system cells, including CD3 lymphocytes, Express fibrogenic factors (TFR-β) that suppress MMP-1, it was suggested that a decrease in the number of immune cells in the damaged tissue contributes to less pronounced scarring [35].

Several separate studies have been devoted to the study of the ability of MMP to influence fibroblast migration and keloid expansion. In particular, Uchida G., *et al.* (2003) found that tretinoin was able to reduce elevated levels of expression of MMP-13 and the corresponding mRNA, as well as elevated levels of MMP-1 and MMP-8. It was suggested that a decrease in MMP-1 and MMP-8 contributed to the accumulation of collagen I and III, while an increase in MMP-13 expression led to the remodeling of the peripheral matrix with subsequent keloid spread [29].

In other studies, the fixation of tissue inhibitor matrix proteinase (TIMP)-1 on the surface of dermal fibroblasts with glycosylphosphatidylinositol anchors led to a decrease in secretion of MMP-2 and MMP-9, reduced the migration and proliferation of fibroblasts, and reduced expression of profibrotic genes [36,37].

Tandara A and Mustoe T (2011) showed that compared with the monoculture of keratinocytes, mixed culture of human fibroblasts and keratinocytes shows an increase in the level and activity of MMP (including MMP-1) and a decrease in the content of collagen I [23]. Accordingly, it can be assumed that by changing the activity of MMP through paracrine interactions between keratinocytes and fibroblasts, it is possible to modulate the balance between synthesis and degradation of collagen, thus affecting the formation of the scar [38].

A number of studies have shown the ability of stratifin produced by keratinocytes (protein 14-3-3-σ) to increase the expression of MMP-1 and MMP-3 in human dermal fibroblasts, preventing the deposition of collagen I and III [38-40]. The stratifin released by keratinocytes can thus regulate the synthesis of collagen by fibroblasts during the remodeling phase. Stratifin therapy can be performed locally, by direct injection into the wound. In experiments, it was shown that wounds treated with carboxymethylcellulose gel containing stratifin take the form of flat Mature scars [39,40].

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