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Review Article

Immunological mechanisms of scarring and their psychological impact on patients

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Abstract: A scar is a local symptom, which results from severe physical, biological and chemical damage to human skin and soft tissue. Scars can affect both skin appearance and function. The affected skin or soft tissue cannot be completely repaired normally by itself and is replaced by formed fibrous tissue. Patients with scars can develop physical pain and mental conditions, especially those with scars left after burns, scalds and severe traumas. The scar proliferation phase can be up to several years which could be almost unbearable for patients. Also, the atrophic period afterwards makes the patient's face unrecognizable and dysfunctional, causing great physical and mental impairment. Therefore, scar repair is of great clinical importance for patients, and understanding the immunological mechanisms of scar repair is an important prerequisite for the effective treatment of scars. This study is a systematic review of current research advances about the immunological mechanisms of scar repair, so as to provide a reference for the selection of regimens in clinical treatment.

Keywords: Immunological mechanism, scar, psychological impact

Introduction

Scars are pathological changes in skin tissues due to trauma, infection, and other factors, and are generally believed to be mainly due to the enhanced collagen synthesis capacity of fibroblasts in injured skin, resulting in an abnormal increase and excessive deposition of collagen in the extracellular matrix [1, 2]. Some studies have found that dark-skinned individuals are more likely to form scars than light-skinned individuals, and that there also is a dependency on genetical factors [3]. Scar formation is an important process of wound repair. However, the scars affect skin aesthetics and function as well as cause psychological burden and itching discomfort to patients. The mechanisms of scar formation and immunology have not been fully elucidated. So, there is a lack of reliable treatments to control wound healing in a gentle state and avoid scar formation [4, 5]. Scar tissue is higher in immunoglobulins, calcium, mucopolysaccharides, fibronectin and lactate dehydrogenase than normal skin tissue, and fibroblasts in scar tissue can produce large amounts of collagen [6]. These changes may be related to the immunological mechanisms of scar formation. Using gene microarray technology, Ma et al. investigated the changes in gene expression associated with proliferative scars in the early post-burn period and found that immunological mechanisms, apoptosis and cell signaling are involved in the development of proliferative scars [7]. The study by Zhang et al. found many lymphocyte clusters wrapped in collagen fibers in scar tissue except for those around the vascular cuff, which further suggests that immunological factors play an important role in the formation of scars [8]. The aim of this study was to investigate the role of immunological mechanisms in scar formation and the psychological impact of scars on patients.

Immunological mechanisms of scar formation

Immunomodulatory role of dendritic cells and Foxp3+ cells in scars

Dendritic cells (DCs) play a particularly important role in initiating the T cell immune response,

have a strong immune response induction capacity, and are the most functional antigen-presenting cells [9]. They can efficiently uptake, process, and deliver antigens. Immature DCs have a strong migratory capacity, while mature DCs (mDCs) can effectively activate the naïve T cells and are the key component for initiating, regulating, and maintaining the immune response. Most human DCs are in an immature state and express low levels of costimulatory and adhesion factors, showing a low ability to stimulate proliferative responses in homogeneous mixed lymphocytes *in vitro*. But immature DCs have an extremely strong capacity for antigen phagocytosis and can differentiate into mDCs upon uptake of antigens (including *in vitro* processing) or certain stimulations. MDCs express high levels of costimulatory and adhesion factors [10]. During maturation, DCs migrate from peripheral tissues exposed to antigens into secondary lymphoid organs, where they come into contact with T cells and stimulate immune response [11, 12]. Tai et al. examined the percentage of mDCs in peripheral blood by collecting peripheral blood from scarred patients and healthy subjects, respectively. The using surface molecules MHCII and CD83 as well as Treg cell-specific transcription factors, the Foxp3 cell ratios were detected, and the composition of mDC and Treg was observed, so as to delve into the immunological mechanisms of mDC and Treg in scar tissue. Their results found an immunomodulatory role between mDCs and Foxp3 cells in the peripheral blood of patients with scars. Moreover, they found an increase in the number of mDCs in peripheral blood and a decrease in the expression and function of Foxp3+ cells, which suggested that patients with scars may have diminished immunosuppressive function in the peripheral blood [13].

Aberrant expression of proteoglycan aggregates and hyaluronic acid in scars

A proteoglycan aggregate, as a member of the Lecticans family, is originally isolated from cartilage tissue with a core protein consisting of multiple structural domains and spliced with approximately 100 chondroitin sulfate chains [14]. A chondroitin sulfated proteoglycan expressed primarily in hyaline cartilage tissue. Current studies on proteoglycan aggregates have focused on their role in bone, cartilage development and central nervous system [15-17]. The main property of proteoglycan aggregates is to firmly bind the important extracellular matrix molecule hyaluronic acid with ligand proteins, resulting in the formation of macromolecular aggregates [18]. Previous studies have shown that expression of hyaluronic acid is significantly elevated in scar fibroblasts and epidermis. This may be related to the formation of macromolecular aggregates by aggregated proteoglycans [19, 20]. Shih et al. found that the expression of proteoglycan aggregates was significantly higher in the inner scar tissue than in the skin at its junction with normal tissues, which also confirmed that proteoglycan aggregates may be related to the proliferation of scars [21]. Zhao et al. used proteomic techniques to quantitatively label scar tissue proteins and found that proteoglycan aggregates were associated with the proliferation of scars. Study using quantitative labeling assay have found that the expression of proteoglycan aggregates is significantly upregulated in scars. Immunohistochemistry and protein blotting techniques were further used for verification and demonstrated that the expression of proteoglycan aggregates in scar tissue was significantly higher than that in normal controls [22]. It is suggested that proteoglycan aggregates have an important immunomodulatory role in the process of scar tissue formation.

Immune response mediated by immunoglobulins, complement and lymphocytes

Immunoglobulins are globular proteins that have antibody activity or chemical structure. They are similar to antibody molecules and can be classified as antibodies and membrane immunoglobulins. Antibodies are found primarily in serum, but also in other body fluids and exocrine fluids. Their primary function is to specifically bind antigens [23]. Membrane immunoglobulins are antigen receptors on B cell membranes that specifically recognize antigen molecules. Complement is a serum protein found in human, as well as vertebrate serum and tissue fluids. It is not heat resistant but is enzymatically active upon activation. Complement can mediate immune responses and inflammatory reactions and can be activated by antigen-antibody complexes or microorganisms, leading to lysis or phagocytosis of pathogenic microorganisms [24]. Lymphocytes

are a type of leukocyte and are the smallest white blood cells in size. They are produced by lymphoid organs and mainly found in the lymphatic fluid circulating in the lymphatic vessels. Lymphocytes are an important cellular component of the body's immune response, perform almost all the immune functions of the lymphatic system, function as the first-line "soldiers" against external infections, and monitor cellular mutations in the body [25]. In scar tissue, the deposition of immunoglobulins, complement and the degree of scar response correlate with lymphocyte infiltration at the trauma site [26, 27]. In scar tissue specimens, mast cells are scattered in the collagen bundles of the dermis, and they are activated by IgE to release cytoplasmic granules containing histamine, heparin and 5-hydroxytryptophan, which increase *in vivo* collagen formation *via* fibroblasts [28, 29]. Histamine is also a key component of the immune system. As a competitive inhibitor of lysine oxidase, histamine causes abnormal collagen association and increases the amount of soluble collagen in scar tissue by decreasing lysine oxidase activity [30]. This series of immune responses enhances scar formation. Wang et al. determined T lymphocytes and their subpopulations by flow cytometry in 6 keloid, 14 patients with hyperplastic scars and 10 peripheral blood lymphocytes from normal humans. They stimulated lymphocyte proliferation with cutin A in an *in vitro* lymphocyte culture. In addition, they measured lymphocyte proliferation activity by using the 3H-TdR doping method. The results showed that the proliferative activity of $CD4^+$, $CD4^+/CD8^+$ and lymphocyte were higher in the keloid and hyperplastic scar groups than in the normal control group, suggesting that abnormal T lymphocyte immune function may play an important role in scar proliferation [31].

Role of autoimmunity in scar formation

Normally, the body's immune system reacts only to antigens other than itself. But when the immune system fails to tolerate the immune active cells, an immune response to its own constituent components, namely an autoimmune reaction occurs, which can even lead to autoimmune diseases in severe cases [32]. Autoimmune disease is caused by initiating an inflammatory response that leads to tissue damage and a long-term inflammatory response eventually leads to tissue fibrosis, such as skin fibrosis due to scleroderma. The formation of scar tissue also has this close association with the inflammatory response similar to many autoimmune diseases. So, there may be an association between scarring and autoimmune response. Jiao et al. used direct immunofluorescence and immunohistochemistry, respectively to observe the deposition of immune complexes and immune cell infiltration within keloid tissues. They found that IgA, IgM, C3 and C1q deposits were seen within scar tissue, but no deposits of immune complexes were seen within normal skin. The number of Langerhans cells, B lymphocytes, macrophages, and T lymphocytes in the scar tissue was significantly higher than that in normal skin [33]. The results indicated that there was a large deposition of immune complexes and a large infiltration of immune cells, mainly $CD20^+$ B lymphocytes, in the scar tissue. It is suggested that the scars had pathological features associated with autoimmune diseases.

Psychological impact of scar formation on patients

Psychological health is a state in which all aspects of the psyche and its active processes are in a favorable or normal state. Ideally, mentally healthy refers to a state with intact character, normal intelligence, and correct cognition. It includes people showing generally appropriate emotions and behaviors, positive attitude and good adaptation [34, 35]. Negative psychological changes and emotions can develop in patients after traumas. Psychological abnormalities may occur, which include structural or functional disorders of the brain, distortions in the person's reflection of objective reality. These conditions can affect patients in social interpersonal relationships and lead to adjustment disorders in personal life [36].

Scar tissue is the inevitable product of trauma healing, which not only affects the appearance and function of the skin, but also affects patients' psychological condition [37]. Face is a relatively special and complex part of the human body, where gathers the five human senses, and is important in an aesthetics perspective. In daily life, due to trauma, burns, scalding and other accidental injuries to the face, scars are formed in the healing process,

resulting in deformity or dysfunction of the patient's five senses, affecting the appearance, bringing psychological burden to patients. Negative emotions such as anxiety and depression often exist in patients with facial scars, and these negative emotions can further affect the treatment and revision of scars, which is a vicious circle [38]. Therefore, improving the psychological conditions of patients with scars has an important role in the treatment of scars.

Scar tissue formation is a series of pathophysiological processes in which local tissues repair tissue defects through regeneration, repair and reconstruction. Essentially, the processes are an inherent defensive adaptive response of the body to tissue cell damage. The processes can be roughly divided into three stages: the inflammatory response phase, the granulation tissue formation phase and the tissue remodeling phase. Studies have confirmed that immunological mechanisms play an initiating and regulating role in scar formation [39]. The immune response has a dual role in scar tissue formation, both promoting regenerative repair and delaying healing of the wound. For example, during the inflammatory phase of scar formation, a large number of neutrophils, macrophages and T lymphocytes would accumulate, then participate in and initiate the local and systemic immune defense of the body. This mechanism can induce the production of a large number of cell growth factors and promote scar formation. The persistent immune response at the wound surface can also induce local tissue damage, resulting in delayed healing. In addition, scar formation can cause deformity or dysfunction of the five senses and affect appearance, especially facial scars, which can bring heavy psychological burden to patients [40]. An in-depth understanding of the immunological mechanisms of scar formation can allow us to study more aspects of the treatment plans and improve the treatment tools, so as to achieve better clinical efficacy and patient satisfaction. The improvement of patient satisfaction is also significantly related to the improvement of the negative emotions and psychological condition of patients.

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Disclosure of conflict of interest

None.

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