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Regeneration of Connective Tissue and Its Role in the Pathogenesis of Postoperative Ventral Hernia Development

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Abstract More than 200,000 operations for anterior abdominal wall hernias are performed annually in the Russian Federation, including approximately 50,000 procedures for postoperative ventral hernias (POVH), which emphasizes the socio-economic significance of this problem. This literature review summarizes current evidence on the pathogenesis of hernia formation with particular attention to postoperative wound healing, connective tissue remodeling, collagen metabolism, fibroblast activity, and extracellular matrix regulation. The review included 24 sources. The search was conducted in PubMed, the Cochrane Library, UpToDate, and eLIBRARY, as well as on the websites of reputable scientific journals and dissertation repositories. Publications from 1999 onward in Russian or English were considered. The article discusses the pathogenesis of anterior abdominal wall hernias on the basis of histological tissue characteristics and highlights the most reliable markers of hernia disease. Further research is needed to validate the principal histological markers that may allow assessment of the risk of postoperative ventral hernia formation and support the development of preventive strategies.

Keywords Postoperative ventral hernia, Collagen, Extracellular matrix, Fibroblasts, Wound healing, Hernia histology, Hernia disease, Incisional hernia, Recurrent hernia, Connective tissue abnormalities, Collagen metabolism, Abdominal wound closure techniques

1. Relevance

Abdominal wall hernias remain a pressing problem in modern surgery because of their high frequency and the complexity of treatment. Approximately 20 million abdominal wall hernia operations are performed annually worldwide. According to consolidated statistics, more than 200,000 hernia repairs are performed annually in Russia, of which approximately 50,000 are operations for postoperative ventral hernias [1,2,3]. These data confirm the socioeconomic importance of studying the mechanisms of hernia formation and improving the principles of treatment and prevention.

2. Study Objective

To review and summarize the literature on the current understanding of hernia pathogenesis based on studies of postoperative wound healing processes and the cellular factors that influence these processes.

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3. Materials and Methods

A review of scientific papers on hernia disease published over the past 27 years was conducted using PubMed, the Cochrane Library, UpToDate, and eLIBRARY, as well as websites of reputable scientific journals and dissertation repositories. The search criteria included publications from 1999 onward, Russian or English language, and relevance to postoperative wound healing, connective tissue remodeling, collagen metabolism, extracellular matrix regulation, fibroblast activity, and the pathogenesis of postoperative ventral hernias.

4. Results and Discussion

The initial search yielded 309 articles. After filtering, 121 publications remained. Sixty-three papers were selected for detailed analysis, and 24 publications were ultimately included in the literature review.

5. Literature Review

Abdominal wall hernias occur when the structure and function of load-bearing tissues, such as muscles, tendons, and the fascial layer, are disrupted [4]. The fundamental

biological mechanisms include primary pathological abnormalities of connective tissue and impaired surgical wound healing [5]. In both cases, abnormalities in extracellular matrix metabolism develop, leading to disturbances in collagen structure and composition. Altered collagen isoforms have been observed in patients with POVH [6]. Importantly, collagen abnormalities can be detected not only by histological examination of the surgical site or hernial tissue, but also by skin biopsy performed away from the hernia site, which confirms the systemic nature of hernia formation.

Secondary factors in hernia pathogenesis include processes that impair laparotomy wound healing, including replacement of the aponeurosis by scar tissue. The recurrence rate of POVH increases with each subsequent hernioplasty attempt [7]. Changes in fibroblasts and wound collagen are also observed in patients with POVH. Mechanical stress has been shown to cause secondary changes in fibroblast function [8]. Impaired postoperative wound healing and loss of the normal healing architecture lead to the formation of an abnormal fibroblast population, similar to that observed in wounds with chronic inflammation [9]. This process may result in the formation of abnormal structural collagen and contribute to hernia development [10].

On the basis of these data, a research direction has emerged that focuses on the predisposition to herniogenesis and on the development of methods for preventing POVH formation. This approach is based on the histological structure of connective tissue, especially the extracellular matrix and its functions [11], as well as systemic metabolic processes that influence its formation. The guidelines of the European Hernia Society (EHS) identify prevention of the formation and recurrence of anterior abdominal wall hernias as one of the priority areas [12]. Aseptic inflammation induces angiogenesis, which is manifested by the formation of multiple vessels in connective tissue. This is explained by the fact that microvascular damage of any origin stimulates regenerative processes accompanied by the formation of new vascular terminals [13].

Tissue fibroblasts play a central role in the metabolism of the extracellular matrix of the aponeurosis. Changes in fibroblast phenotypes indicate a possible mechanism underlying POVH formation. The identification of fibroblasts with a characteristic abnormal structure in tissues is therefore important for understanding the pathological process in connective tissue [14]. In POVH tissues, a change in nuclear morphology from linear to oval has been observed. Oval, spindle-shaped, and/or stellate cells with round or oval nuclei are active proliferative fibroblasts and reflect pathological changes in extracellular matrix function [15].

In another study comparing morphological changes in the skin, muscles, tissue adjacent to the hernial protrusion, and aponeurosis by electron microscopy, several pathological changes were identified. In the skin, the cytoplasm of spinous epidermal cells contained numerous vacuoles and lysosomes, and intercellular contacts were disrupted. Collagen fibers were swollen and disorganized; transverse striation in the papillary dermis disappeared; and erythrocytes and macrophages were found between the fibrils. Dystrophic changes, including vacuolization and a decreased number of ribosomes, were observed in the mitochondria and endoplasmic reticulum of fibroblasts.

A direct correlation was established between hernia size, hernia duration, and the severity of dystrophic changes. In aponeurosis tissue, the dense and parallel collagen bundles that form its basis lost their specific structure, undergoing uneven fibrillar swelling, disorientation, collagenolysis, and loss of characteristic transverse striation. These changes increased with the number of hernia recurrences. The authors therefore noted morphofunctional insufficiency of almost all abdominal wall tissues in patients with POVH on electron microscopy, which makes these tissues functionally and mechanically unsuitable for plastic repair using local tissues [16].

The reaction of connective tissue to implantation of a polypropylene endoprosthesis can be divided into stages analogous to the stages of wound healing. Microscopic studies show a stereotypical inflammatory response at 3, 7, and 14 days and at 1 and 3 months. On the third day after endoprosthesis implantation, an acute inflammatory phase develops in response to surgical intervention. A necrotic zone with accumulation of necrotic debris and a wide area of traumatic edema is observed at the margins of the surgical field. Circulatory disturbances appear as paretic dilation of microvascular vessels, partial thrombosis, and hemorrhage. Degenerative changes, some reaching the level of necrosis, are observed in the tissues surrounding the necrotic zone. Proliferative and reparative activity are absent. Isolated macrophages and numerous granulocytes are recruited into postoperative tissues three days after hernioplasty, corresponding to the injury phase.

By the seventh day, granulation tissue begins to form. Necrotic areas appear in the surgical wound zone and consist of leukocytes, lymphoid cells, and histioid elements. Arterioles and venules are congested, with stasis and sludge, while edema and hemorrhage are present around the vessels. Special staining methods reveal newly formed connective tissue as collagen layers located between vessels and muscle elements. These changes correspond to the injury stage and represent the starting point for repair through the formation of primitive connective tissue.

Beginning on day 14, the necrotic zone becomes limited and granulation tissue develops as a result of fibroplastic reactions. During this period, additional staining reveals a developing connective tissue network. Muscle fibers become surrounded by newly formed connective tissue. Proliferative activity increases in the perimysium; its structures enlarge and become hyperchromic.

After 30 days, fibrous tissue proliferates and is accompanied by active microvascular angiogenesis. Signs of this process include endothelial swelling, the appearance of angiomatous buds, and hypertrophy of the medial layer of the vascular wall. Inflammatory infiltration decreases and is concentrated mainly around the mesh prosthesis, where cells with a high

nucleation rate remain. Denser fibrous tissue forms in the extracellular space, marking completion of the reparative stage.

After three months, a clearly defined dense fibrous tissue is visible in the scar. Vessels with thickened walls are present. The final stage is characterized by disappearance of inflammatory signs and formation of mature connective tissue [17].

Thus, postoperative wound healing follows basic biological principles, including the foreign-body reaction during endoprosthesis implantation. To evaluate the activity of the wound healing process and the probability of adequate postoperative scar formation, it is necessary to assess the degree of inflammatory activity, including relevant inflammatory markers.

Wound healing is a dynamic and tightly regulated process involving cellular, molecular, and biophysical events. It begins immediately after injury and continues until tissue function is restored. Wound healing consists of three main stages: inflammation, proliferation, and remodeling. The extracellular matrix plays a key role in the last two stages [18].

The first stage, inflammation, lasts up to three days after injury and is mediated by platelets, macrophages, and neutrophils. It is characterized by clot formation, macrophage -mediated phagocytosis, neutrophil migration into damaged tissue, and activation of matrix metalloproteinases (MMPs). The cellular response develops during the first 24 hours with neutrophil activation and macrophage recruitment for phagocytosis, followed by cytokine release. These inflammatory cells are crucial for wound healing because they clear cellular debris and release lysosomal enzymes and reactive oxygen species. Based on gene expression, macrophages are classified as classically activated (M1, pro-inflammatory), alternatively activated (M2, anti-inflammatory), or proangiogenic. During the inflammatory phase, many pro-inflammatory cytokines are released, including interleukin-1 beta, tumor necrosis factor-alpha, and interferon-gamma. These cytokines mediate adhesion molecules required for cell migration by diapedesis. In addition, macrophages release platelet-derived growth factor and endothelial growth factor, which initiate angiogenesis and facilitate the transition to the second phase of wound healing [19].

The second stage, proliferation, begins 2-3 days after injury and lasts approximately 14 days. Molecular events associated with this phase reduce wound size through contraction and the formation of fibrous tissue, or fibroplasia, and the phase ends with wound closure. During this period, granulation tissue begins to form approximately four days after injury through fibroblast proliferation. Granulation tissue formation results from the synthesis and secretion of collagens and elastins and supports fibroplasia. The main component of granulation tissue that characterizes the proliferative phase is type III collagen secreted by fibroblasts. Angiogenesis, thrombolysis, epithelial cell proliferation, and wound contraction during the proliferative phase are provided mainly by myofibroblasts [20].

The third stage, remodeling, may last up to 12 months and restores tissue strength through degradation, reorganization, and resynthesis of the extracellular matrix. Granulation tissue is remodeled by matrix metalloproteinases, forming scar tissue that is less vascularized and contains fewer cellular elements. Type III collagen is then replaced by parallel matrices of thicker type I collagen, increasing tissue strength. Following these changes in the collagen phenotype, tissue functionality is restored and the tissue acquires a more mature structure. Collagen maturation is regulated by a wide range of growth factors, primarily transforming growth factor-beta (TGF-beta) and fibroblast growth factor. Approximately 70-80% of tissue strength is restored three months after injury [21].

The incidence of POVH after laparotomy ranges from 4.2% to 73%. Its impact on quality of life and the annual healthcare cost of 3.2 billion US dollars in the United States alone justify the implementation of preventive measures aimed at reducing the development of POVH [22]. One such measure is prophylactic placement of a mesh implant during laparotomy wound closure [23]. Prophylactic mesh reinforcement after midline laparotomy is of considerable clinical interest and has shown promising results in many randomized multicenter trials. However, comparison of these studies is limited by differences in mesh position, mesh type, suture material, and mesh fixation methods [24].

6. Conclusions

Understanding the pathogenesis of anterior abdominal wall hernias creates additional opportunities for improving the management of patients at risk of POVH. The available evidence indicates that connective tissue remodeling disorders, changes in the type I/type III collagen ratio, fibroblast dysfunction, matrix metalloproteinase activity, and systemic connective tissue abnormalities are important pathogenetic factors in hernia formation. Assessment of these markers may help predict the risk of hernia formation after surgery, identify patients who require individualized preventive measures, and justify reinforcement of the suture line with an endoprosthesis during laparotomy in high-risk patients.

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