



## Molecular and cellular aspects of the pathogenesis of incisional hernias

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### Abstract

The incisional hernias are one of the most common surgical pathologies worldwide. The achievements of medical science in recent decades have significantly improved the results of treatment of this disease, due to the justification and implementation of various methods of hemioplasty with implantation of synthetic endoprostheses. At the same time, the incidence rate of incisional hernias remains fairly high. For several years, research has been conducted to study the molecular and cellular mechanisms of incisional hernias formation. The key issue in the problem of tissue repair disorders after laparotomy is to understand the processes of extracellular matrix organization and fibroblast activation. The extracellular matrix appears to be a unique environment that promotes the proper structuring of collagen fibers, the acquisition of postoperative scar strength and timely wound cavity contraction. The regulation of extracellular matrix homeostasis depends on many factors that affect the timing and usefulness of tissue repair after surgical trauma. The main regenerative potential

consists of populations of fibroblasts responsible for the synthesis and degradation of collagen. Extracellular matrix and fibroblasts have a multifactorial effect on wound repair and imbalance of their interaction can contribute to the formation of incisional hernias. Molecular compounds synthesized by fibroblasts, which include matrix metalloproteinases, matrix metalloproteinase inhibitors, as well as actin and collagen proteins, play an important role both in the healing of surgical wounds and in the formation of hernias. Identification of critical points in the pathogenesis of incisional hernias at the molecular and cellular levels will make it possible to predict and prevent their formation. This opens up new opportunities for precision stratification of patients before abdominal wall hernia repair and the choice of personalized surgical tactics.

**Keywords:** incisional hernias, extracellular matrix, fibroblasts, collagen, molecular mechanisms of repair.

**Conflict of interest:** nothing to disclose.

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## Молекулярные и клеточные аспекты патогенеза послеоперационных вентральных грыж

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### Аннотация

Послеоперационные вентральные грыжи являются одними из самых распространенных хирургических патологий во всем мире. Достижения медицинской науки за последние десятилетия позволили значительно улучшить результаты лечения данного заболевания вследствие обоснования и внедрения различных способов герниопластики с имплантацией синтетических эндопротезов. В то же время частота возникновения послеоперационных вентральных грыж остается на достаточно высоком уровне. На протяжении нескольких лет проводятся исследования, направленные на изучение молекулярных и клеточных механизмов формирования послеоперационных грыж. Ключевым вопросом в проблеме нарушения репарации тканей после лапаротомии является понимание процессов организации внеклеточного матрикса и активизации фибробластов. Внеклеточный матрикс предстает той уникальной средой, способствующей правильной структуризации коллагеновых волокон, приобретению прочности послеоперационного рубца и своевременной контракции раневой полости. Регуляция гомеостаза внеклеточного матрикса находится в зависимости от многих факторов, влияющих на сроки и полноценность репарации тканей после операционной травмы.

Основной регенераторный потенциал составляют популяции фибробластов, ответственных за синтез и деградацию коллагена. Внеклеточный матрикс и фибробласты оказывают многофакторное влияние на репарацию раны, и нарушения баланса их взаимодействия может способствовать формированию послеоперационных вентральных грыж. Синтезируемые фибробластами молекулярные соединения, к которым относятся матричные металлопротеиназы, тканевые ингибиторы металлопротеиназ, а также актиновые и коллагеновые белки, играют важную роль как в заживлении операционной раны, так и в формировании грыж. Определение критических точек патогенеза послеоперационных вентральных грыж на молекулярном и клеточном уровнях позволит прогнозировать и профилактировать их образование. При этом открываются новые возможности для прецизионной стратификации пациентов перед оперативным лечением грыж и выбора персонализированной хирургической тактики.

**Ключевые слова:** послеоперационные вентральные грыжи, внеклеточный матрикс, фибробласты, коллаген, молекулярные механизмы репарации.

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**Список сокращений**

ПОВГ – послеоперационная вентральная грыжа; ВКМ – внеклеточный матрикс; ММП – матричная металлопротеиназа; ТИМП – тканевый ингибитор металлопротеиназы.

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## ■ INTRODUCTION

Anteroventral hernias remain some of the long-standing unresolved problems of surgical science. The history of the problem is decades old originating from the moment of formation of surgery as a medical science [1]. The most complicated and socially impactful are the hernias related to previous surgeries of the abdomen [2-5]. Recent data shows that the incisional ventral hernias (IVH) occur after 10-20% laparotomies; at the same time, in high-risk patients, the incidence may reach 70% [6]. Throughout XX century, experience and knowledge has been accumulated in the area of surgical treatment of IVH, in that way, many original and progressive methods have been created to restore the normal anatomy of the abdomen after herniotomy. From the time of advent and large-scale implementation of mesh endoprosthetics to reinforce the anterior abdominal wall in reparative surgeries of hernias, the outcomes of treatment of IVH patients improved significantly. At the same time, even with the development and improvement of surgical methods, significant reduction of IVH formation incidence and IVH recurrence is still a standing problem.

Surgical access during different operations of the abdomen has always been selected from the standpoint of comfortable visualization of the surgery area without regard to the common factors of tissue regulation of the wound repair and formation of the surgical scar. In order to understand the problem of IVH formation, it is important to know the specifics of not only the macroscopic but cellular composition of the structures of the anterior abdominal wall. The interaction between the cells and molecules involved in the tissue reparation and regeneration following the surgical wound becomes especially important. The re-conceptualization of the process of formation of the surgical scar, and discovery of new correlations of the formation and structurization of connective tissue may significantly improve both the outcomes of surgical treatment of IVH and reduce the incidence of IVH formation and recurrence [7, 8]. In the recent decades, the pathogenesis of IVH on various levels of biological organization has been the focus of many studies. Papers published by Russian and foreign authors show a distinct shift from the anatomical level of studies to histological and molecular. This is well justified by the necessity of search for pathogenic links of hernia formation on the initial level of cellular and subcellular organization [9, 10]. The study of molecular mechanisms of formation of IVH opens new horizons for the prediction, prevention and treatment of the pathology [11, 12].

*The goal of this review is to update the latest achievements in the studies of molecular and cellular mechanisms of IVH formation, to give a critical view of specific pathogenic processes of reparation of surgical wound tissues, and to look for new diagnostic and treatment targets of antero-ventral hernias.*

*Method of search for sources.* The search for literature was performed in the RSCI and PubMed databases using the following keywords: incisional hernias, molecular mechanisms of hernia formation, cellular mechanisms of hernia pathogenesis, extracellular matrix, the importance of fibroblasts in the formation of incisional hernias. Only the papers published in the past 20 years were selected. For the purposes of our review, we selected the systematic reviews and meta-analyses, randomized controlled studies, international recommendations and literature reviews. We also reviewed references of the selected papers. Subsequently, we chose the papers based on the analysis of the full text, abstract, level of validity and statistical significance of presented results. The search for sources for this review produced 65 articles to be included.

## ■ HOMEOSTASIS OF THE EXTRACELLULAR MATRIX IN THE REPARATION OF THE LAPAROTOMY WOUND

The incision of the anterior abdominal wall to provide surgical access is a serious injury that is accompanied with a classic inflammatory reaction that progresses in aseptic conditions. The reparative processes after laparotomies are aimed not only on the closure of the wound and the isolation of the abdomen, but on the reinforcement of the injured area by excessive synthesis of connective tissue. In the early post-surgery period, the strength of the incision line is secured with sutures on the layers of the anterior abdominal cavity thus creating conditions for a favorable progression of the wound process. The complete reparation of the tissues after the laparotomy occurs 100 days after the surgery, and the strength of the scar is up to 90% from that of the physiologically normal tissue of the anterior abdominal wall [13]. The highest importance in the process of healing of the tissues of the abdominal wall, aponeurosis in the first place, is attached to the structure and the composition of the extracellular matrix (ECM). In response to the alternation and the inflammation, thrombocytes, neutrophils, macrophage and lymphocytes migrate from the systemic blood flow to the wound area. These cells form a spatial structure without a distinct organization, or the temporary ECM [14]. Multiple proinflammatory cytokines responsible

for cellular adhesion are produced, viz. interleukin-1 beta (IL-1 $\beta$ ), tumor necrosis factor alpha (TNF- $\alpha$ ) and gamma interferon (IFN- $\gamma$ ) [15, 16]. The mechanical strength of the temporary ECM is low and depends on the thrombocytes and fibrin. At this initial stage of tissue reparation, integrity of the temporary ECM until formation of the collagen matrix is especially important. The insufficient intraoperative hemostasis results in the formation of a hematoma; at the same time, the temporary ECM is disorganized and the time of wound healing increases [17, 18]. This phenomenon contributes to the formation of IVH and recurrent of hernias after hernioplasty.

The study of properties of intracellular interactions in the spatial model produced the notion of the matrisome, a complete set of all proteins and genes encoding them that form the ECM. The view of the ECM as a dynamically changing cytological platform opens a new view of the processes of reparation of connective tissue and formation of hernias. The changes of the matrisome and the loss of mechanical strength of the ECM are associated with the proliferation of an abnormal population of fibroblasts. Some studies showed an increase of atypical fibroblasts responsible for the disruption of normal synthesis of collagen in early incontinence of the laparotomy wound [19, 20]. The analysis of the matrisome provides an opportunity of identification of the leading cascades of molecular reactions and cellular interactions responsible for the mechanotransduction of tissues [21-23]. The study of the matrisome may enable identification of genetic determinants and predictors of formation of hernias of the anterior abdominal wall.

Thus, various components of the ECM may influence the processes of reparation of the laparotomy wound and participate in the formation of IVH. The complex analysis of the composition of the ECM in the formation of IVH will identify the pathogenic targets in order to address the disorders of tissue homeostasis in advance.

### ■ REGULATION OF COLLAGEN METABOLISM AND ITS ROLE IN THE PATHOGENESIS OF IVH

The primary granulation tissue of the wound surface after the laparotomy predominantly consists of elastin and type III collagen. As healing progresses and phases of regeneration change, there occurs a significant reorganization of the ECM and its elements. The formation of a strong scar stems from the replacement of cellular and molecular components in the place of the surgical wound. The restructuring of the ECM is related to the loss of type III collagen by the granulation tissue, its replacement with type I collagen, contraction of the wound due to fibroplasia and mechanotransduction of myofibroblasts [24, 25]. These key processes underlie the acquisition of mechanical strength and decrease of the size of the wound, processes, whose disruption is of highest importance for the formation of IVH. At the same time, the significance of other types of collagen is also studied; type IV collagen involved in the formation of the basal membrane of cells, and type V collagen regulating the processes of fibrillogenesis, are in the focus

of scientific interest. The work of N. Henriksen *et al.* (2015) demonstrated the changes in the quantities of type IV collagen in patients with and IVH and patients without hernias. Thus, the IHV group showed a greater activity in the processes of denaturation and resynthesis of this protein [26]. L. Lorentzen *et al.* (2018) also demonstrated higher metabolic activity with respect to type V collagen in patients with IVH [27].

The processes of physiological remodeling of the ECM are mediated by the activity of matrix metal proteinases (MMP). The MMP family includes 23 proteins with a wide variety of biological substrata and respective functions. The major role of all proteins in this family is involvement in the ECM homeostasis in the healing of wounds. Some studies demonstrated their activation by numerous proinflammatory cytokines, hormonal substances and growth factors, most important of which are the IL-1 $\beta$ , TNF- $\alpha$  and tissue inhibitors of metal proteinases (TIMP) [28-31]. The TIMP are zinc-mediated endopeptidases capable of breaking down all types of ECM proteins. There are four types of these enzymes, viz. TIMP-1, TIMP-2, TIMP-3 and TIMP-4 [32]. In physiological conditions, the distribution of MMP and TIMP is 1:1, which ensures the continuity of protein composition of the tissue and the ECM. The change in the MMP to TIMP ratio may influence the metabolism of collagen, which was seen in patients with IVH. In their work, J. Guillen-Marti *et al.* (2009) demonstrated a correlation between MMP and TIMP in the tissues of IVH patients. The authors noted the decrease of RNA TIMP-3 transcripts in the aponeurosis and TIMP-4 in the skeletal muscles, as well as TIMP-3 in the tissues of hernia defect in IVH patients [33].

Exposed to MMP proteins, type III collagen denaturates, and the fibroblasts receive the signal for the synthesis of type I collagen, whereupon gradual replacement of protein in the tissue occurs [34]. The process progresses in a dynamic equilibrium, which ensures a balance between the synthesis of collagen and its breakdown, and the ECM and the forming scar acquire the necessary mechanical strength. What is interesting is that the regulation of the ECM homeostasis is highly variable and depends not only on the synthesis of collagen forms but on its degradation as well, which may directly influence the formation of IVH. Some studies demonstrated a correlation between the disorganization of the ECM and increased activity of MMP-1, MMP-2, MMP-9 and MMP-13, and a correlation with the formation of hernias of the anterior abdominal wall [35, 36]. The proven role of changes in the type I collagen to type III collagen ratio in the regulation of the ECM homeostasis allowed for a detailed study of the molecular mechanism of IVH formation. At the same time, the regulation of processes of collagen degradation may have no lesser meaning than that of its synthesis. The work of R. Rosch *et al.* (2006) studies the influence of MMP on the formation of IVH. The authors reported elevated expression of MMP-2 in the connective scar tissue of IVH patients [37]. At the same time, the work of J. Salameh *et al.* (2007) also demonstrated high expression of MMP-2 in IVH; however, the analysis involved the tissues remote from the hernia defect [38]. This phenomenon shows the

systemic pathology of the metabolism of connective tissue involving MMP, not the local dysregulations.

The products of collagen breakdown in the course of the ECM remodeling or its abnormal synthesis go to the systemic blood and may be detected as serum biomarkers. The level of markers of collagen breakdown circulating in the bloodstream characterizes its homeostasis on the organismic level, since this protein and its forms are seen in various organs and systems [39]. Some studies were performed that demonstrate the correlation between the indicators of collagen breakdown and status of IVH [40]. H. Kayashima et al. (2015) studied serum levels of fragments of type IV collagen in IVH patients. They found that the level of serum N-terminal propeptide of the 7S domain of type IV collagen (P4NP-7S) was elevated in patients with IVH and was related to the development of ventral hernias [41]. It is not out of the question that there are other serum markers of collagen degradation influencing its metabolism and the fibroblast function. These circulating oligopeptides may serve as valuable tools for IVH prediction.

The analysis of collagen-mediated molecular reactions in the process of wound reparation is vital to the understanding of IVH pathogenesis. Elevated synthesis of type I collagen on the tissue level may preclude formation of IVH after any kind of laparotomy, since this protein is the main component of the ECM that determines the strength and integrity of the scar. On the other hand, suppression of type I collagen degradation has a positive effect on its metabolism and functional activity. In recent years, there were some breakthroughs in the identification of points of impact on collagen exchange regulation in order to prevent IVH and plan the treatment thereof.

## ■ FIBROBLAST POPULATIONS AND THEIR SIGNIFICANCE IN IVH FORMATION

Laparotomy induces a fibroproliferative response mediated by endogenous inflammatory factors. Fibroblasts are major participants of regenerative processes in the wound that synthesize collagen and form the ECM structure. Under physiological repair conditions, fibroblasts migrate into the injury site starting from day two and participate in granulation tissue formation over a four-day period. In response to the inflammation mediators, the intercellular interactions stimulate fibroblasts to synthesize collagen, the main 'construction' protein [42]. The accumulation of collagen ensures strength of the ECM, which regulates its normal functioning and supports its homeostasis [43]. The disruption of collagen metabolism in the formation of the ECM is a known factor of IVH development. Predominance of type III collagen over type I reduces the mechanical strength of ECM and alters its architecture [44]. Of particular interest are the causes of abnormal collagen synthesis during tissue repair, which are associated with the functional activity and phenotype of fibroblasts, which constitute the main regenerative cell pool of the ECM [45].

Migration, proliferation and activation of collagen synthesis by fibroblasts are regulated by cytokines, platelet-derived (PDGF) and vascular endothelial (VEGF) growth

factors [46]. Molecular mechanisms of tissue repair directly depend on synthetic activity of fibroblasts. The key feature of fibroblasts as participants of IVH pathogenesis is the change of their functional activity and synthesis of type III collagen instead of type I collagen. Other processes of biological tissue repair demonstrate decrease or cessation of synthetic activity of fibroblasts, e.g. process of healing of trophic and ulcerous defects of various tissues [47]. The analysis of morphological characteristics of tendon and fascial elements of the anterior abdominal wall in IVH revealed significant specific features of their cellular composition and structure. The histological analysis of sections of IVH tissue showed deficiency of the ECM, decreased quantity of fibroblasts and immune cells. The cytological analysis of fibroblasts from the IVH tissue showed their significant deficiency: spindle morphology, vacuolated cytoplasm, swollen mitochondria and elevated expression of vimentin. Another important feature of fibroblasts from IVH is their increased apoptotic activity and propensity for autophagy [48]. Differentiation of fibroblasts is highly important in the processes of tissue repair after laparotomy. Selection of cell populations occurs due to unfavorable conditions of wound healing (suppurative inflammation, eventration, hematoma), which promotes degradation of the ECM, synthesis of type III collagen and mediates the formation of IVH.

In the structure of the ECM cells, there is a population of fibroblasts that is a component of connective tissue before the onset of the surgical wound. This cellular pool is referred to as resident fibroblasts that stay at rest without any endogenous stimulation. As compared to dermal fibroblasts, the resident fibroblasts have a greater plastic potential with respect to collagen. The greatest amount of resident fibroblasts was found in the fascial structures of the anterior abdominal wall. Laparotomy stimulates proliferation and migration of fascial fibroblasts, which fosters proper organization of the ECM. Recent data shows that the functional activity of fascial fibroblasts and dermal fibroblasts is different [49]. The special feature of resident fibroblasts is the synthesis of various components of the matrisome including proteoglycans, fibronectin and hyaluronic acid [50]. At the same time, resident fibroblasts are not only sources of collagen but also of enzymes involved in its breakdown. These cells synthesize MMP-1, MMP-2, MMP-9, MMP-19, and TIMP-1, TIMP-2, TIMP-3 [51]. This fact provides a completely new view of fibroblasts in the tissue repair process after laparotomy, including in the process of IVH formation. The regulation of synthetic activity of fibroblasts allows for changes in the strength of the connective-tissue scar on various stages of its organization. It would be logical to suggest, therefore, that such regulation is mediated both by exogenous stimuli and by the endogenous stimuli, including genetically determined ones.

Another important feature of fibroblasts is their differentiation to myofibroblasts, a contractile phenotype synthesizing the smooth muscle alpha-actin ( $\alpha$ -SMA). Myofibroblasts are unique cells of connective tissue that are capable of mechanotransduction. The contraction of actin proteins causes contraction of the ECM and alignment of the edges of the wound cavity [52]. The stress

in the intercellular interaction of the ECM fibroblasts triggers a cascade of specific reactions resulting in the activation of mechano-sensitive genes of the matrisome. Mechanotransduction of the ECM also initiates the differentiation of fibroblasts to myofibroblasts. In the process of wound repair, the latter act as additional markers of scarring and fibrosis [53, 54]. Myofibroblasts are also involved in the remodeling of the ECM at later stages of repair and ensure wound contraction by stress fibers and formation of  $\alpha$ -SMA. As repair processes come to an end, the number of myofibroblasts decreases due to their apoptosis [55]. The main source of myofibroblasts is in the connective tissue: the resident pool of fibroblasts [56]. When the tissues of the anterior abdominal wall are damaged by laparotomy, the reserve of myofibroblasts is replenished from the populations of dermal and fascial fibroblasts [57]. Another important source of myofibroblasts is the fibrocytes. These cells circulate in the bloodstream and are able to migrate to any tissues of the body, performing various functions. Fibrocytes attain a special significance in the tissue repair after laparotomy; they are capable of impacting the IVH formation, being involved in the regulation of the ECM remodeling and wound contraction. Fibrocytes can synthesize different subtypes of collagen, vimentin and fibronectin, which are the substrate of the ECM and which mediate activity of fibroblasts [58]. At the same time, due to inflammatory endogenous stimulation, fibrocytes can differentiate to myofibroblasts thereby increasing the contraction of the ECM and its strength. Fibrocytes also trigger the inflammatory reactions in the surgical wound and increase synthesis of structural components of the ECM involving the signaling pathway of the beta-1 transforming growth factor (TGF- $\beta$ 1) [59]. Myofibroblasts are unique participants of the repair process greatly involved in the repair of the defect of the anterior abdominal wall after the surgical injury. The regulation of differentiation and apoptosis of fibroblasts occurs by mechanotransduction of the ECM and the TGF-  $\beta$ 1 signaling pathway [60]. TGF- $\beta$ 1 is a regulatory cytokine peptide involved in numerous physiological cellular processes. In the first place, the synthesis and the activation of this peptide ensures the differentiation, proliferation, migration, adhesion and apoptosis of various cells in the body. In the ECM, the TGF- $\beta$ 1 is linked to its prodomain, the latency-associated peptide (LAP). The TGF- $\beta$ 1–LAP complex dissociates during tissue repair, including under the influence of myofibroblasts and the integrin  $\alpha$ V synthesized by the [61]. Thus, a positive feedback loop is observed between the processes of proliferation, differentiation of myofibroblasts, and contraction during post-laparotomy wound repair.

Fibroblasts are instrumental in reparative processes after laparotomies. They are vital for the formation of a strong post-operative scar. These cells regulate the synthesis of collagen, its breakdown, they ensure the homeostasis of the ECM, trigger the myofibroblasts and differentiate into them contributing to the wound contracture. The detailed study of fibroblast populations, their genetic and epigenetic characteristics, as well as the means of regulation of their

synthesis function, will enable control and programming of regeneration of connective tissue in the location of the surgical wound. At the same time, the functional and morphological features of specific populations of fibroblasts influences the formation of IVH via collagen metabolism and degradation of the ECM. Studying the characteristics of fibroblasts in the anterior abdominal wall of patients with IVH will enable the modulation of wound healing processes after the hernioplasty, the selection of a synthetic mesh implantation technique, and the prediction of recurrences.

## ■ ROLE OF INFLAMMATION AND HYPOXIA IN THE IVH PATHOGENESIS

Laparotomy-induced surgical wound of the anterior abdominal wall is an alteration of tissue and the first phase of the regenerative process. The specific feature of surgical wounds is that they are sterile, therefore, the inflammatory reactions occur in aseptic conditions. The aseptic inflammatory process differs from the infectious one by the lack of exogenous mediators of inflammation (infectious agents). The activation of aseptic inflammation occurs under the influence of the damage-associated molecular pattern (DAMP). The DAMP comprises different protein molecules within the nucleus of the cell and in the intracellular liquid of the tissues of the body that trigger immune processes due to sterile alteration and inflammatory reaction [31]. One of the main component of the DAMP is a protein from the group of nuclear non-histone proteins (high-mobility group protein B1 - HMGB-1). This molecule is one of the earliest to react to the damage and stimulates the immune system to trigger to inflammatory cascade [62]. The HMGB-1 ensures cell migration to the aseptic focus of inflammation and chemotaxis, and triggers immune-mediated cellular reactions and cytokine production [63]. Following the laparotomy, the HMGB-1 is involved in the MMP overexpression by triggering the TNF- $\alpha$ , IL-1 $\beta$ , IL-1 $\alpha$ , IL-2, IL-8, IL-18 and type I IFN I, which results in the degradation of type I collagen and its replacement with type III [31].

Another aspect of the surgical wound is the hypoxic stress of the tissues in the area of the wound. Deficit of oxygen inhibits processes of angiogenesis and repair in the laparotomy area [21]. Hypoxia also precludes differentiation of fibroblasts into myofibroblasts, reduces expression of type I collagen and  $\alpha$ -SMA [64]. One of the principal molecular responses to hypoxia is the increased expression of the hypoxia-induced 1-alpha factor (HIF-1 $\alpha$ ). The activation of this protein triggers processes of neoangiogenesis in the area of the surgical wound, leading to revascularization and faster repair of tissues. Enhanced tissue trophism directly influences fibroblast activity and their synthetic capacity, leading to increased synthesis of type I collagen and improved ECM strength [65].

Investigating the expression of DAMPs and HIF-1 $\alpha$  may allow for predicting the occurrence of IVH after primary laparotomies. Studying the activity of these compounds will help optimize surgical strategies for the operative treatment of IVH and recurrent hernias by

mitigating the impact of inflammation and hypoxia in the intra- and postoperative periods.

## CONCLUSION

Over several decades, regenerative processes have attracted active scientific interest. This area of studies attained special significance in the investigation of mechanisms of IVH formation. The analysis of molecular and cellular processes of healing of the surgical wound may allow for a more detailed insight in the reasons of formation of secondary abdominal hernias. The mechanisms of repair of connective tissue after laparotomy differ greatly

from other types of injuries and damage to the anterior abdominal wall. The specifics of formation and structure of ECM, collagen, fibroblasts, myofibroblasts, and the tissue response to aseptic inflammation and hypoxia allow for a completely new view of the process of IVH formation. Biochemical reactions and intercellular interactions are no less important for tissue healing than proper laparotomy wound closure technique. It is now becoming evident that understanding critical disturbances in physiological repair processes opens up opportunities for the improvement of early diagnosis, refinement of surgical correction, and development of methods for recurrence prevention. ■

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<b>Statement of originality.</b> No previously published material (text, images, or data) was used in this work.	<b>Оригинальность.</b> При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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