Published in final edited form as:

Expert Rev Clin Immunol. 2019 July ; 15(7): 791–800. doi:10.1080/1744666X.2019.1608822.

Novel understanding of high mobility group box-1 in the immunopathogenesis of incisional hernias

Nicholas K. Larsen¹, Matthew J. Reilly¹, Finosh G. Thankam^{1,2}, Robert J. Fitzgibbons^{1,2}, and Devendra K. Agrawal^{1,*}

¹Departments of Clinical and Translational Science, Creighton University School of Medicine, Omaha NE 68178, USA

²Departments of Surgery, Creighton University School of Medicine, Omaha NE 68178, USA

Abstract

Introduction: Incisional hernias (IH) arise as a complication of patients undergoing a laparotomy. Current literature has assessed the role of extracellular matrix (ECM) disorganization, alterations in type I and type III collagen, matrix metalloproteinases, and tissue inhibitors of metalloproteinases on IH. However, there is limited information on the underlying molecular mechanisms that lead to ECM disorganization.

Areas covered: We critically reviewed the literature surrounding IH and ECM disorganization and offer a novel pathway that may be the underlying mechanism resulting in ECM disorganization and the immunopathogenesis of IH.

Expert opinion: High mobility group box-1 (HMGB-1), a damage-associated molecular pattern, plays an important role in the sterile inflammatory pathway and has been linked to ECM disorganization and the triggering of the NLRP3 inflammasome. Further research to investigate the role of HMGB-1 in the molecular pathogenesis of IH would be critical in identifying novel therapeutic targets in the management of IH formation.

Keywords

Incisional hernia; Pathogenesis; ECM disorganization; HMGB-1; Sterile inflammation

1. Introduction

A hernia is defined as a defect in a body wall which allows for protrusion of an organ(s) through the body wall that typically contains it. Hernias of the abdominal wall are called

*Corresponding author: Devendra K. Agrawal, Ph.D. (Biochem), Ph.D. (Med. Sciences), MBA, MS (ITM), FAAAAI, FAHA, FAPS, FIACS, Professor and Chairman, Department of Clinical & Translational Science, The Peekie Nash Carpenter Endowed Chair in Medicine, Creighton University School of Medicine, CRISS II Room 510, 2500 California Plaza, Omaha, NE, 68178, USA, Tel: (402) 280-2938; Fax: (402) 280-1421, dkagr@creighton.edu.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ventral hernias and include umbilical, epigastric, incisional and others. An incisional hernia (IH), the focus of this manuscript, develops as a complication of abdominal surgery and subsequent wound healing impairment. The incidence of the development of an incisional hernia after a laparotomy, a surgical incision into the abdominal cavity, is variously estimated, but on average is between 10–20%, but can be as high as 65% depending upon the patient population being studied, the type of surgery, and length and method of the follow-up¹. This is because pathological processes such as diverticulitis and abdominal aortic aneurysms are highly prone to form an incisional hernia when they require surgical repair^{2,3}. It is estimated that 100,000 to 150,000 ventral incisional hernia repairs are performed in the United States each year^{4,5}. Further complicating the issue is the fact that after surgical repair, patients have an even greater risk of developing another incisional hernia, referred to as a recurrent incisional hernia, when compared to the incidence after the initial laparotomy⁶.

Why is the incidence of an incisional hernia after a laparotomy so high? And why is it even higher after repair of a recurrent hernia? The cause is undoubtedly multifactorial. Technical factors at the initial operation and patient related factors including morbid obesity, cigarette smoking, diabetes mellitus, and other preexisting comorbid conditions have also been incriminated. Many of these factors can be manipulated clinically to produce better outcomes such as pristine surgical technique, cessation of smoking, nutritional improvement etc., but these efforts have had only a limited role in decreasing the incidence of IH. Although many risk factors have been correlated with the development of IH, few studies have evaluated the underlying molecular mechanism. Most of the research on IH has been devoted to understand the disorganization of the ECM, focusing primarily on type I and type III collagen (COL1 and COL3), matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs)^{7–12}. However, few studies have investigated the pathophysiology and etiology of this ECM disorganization in patients with IH, but sterile inflammation mediated by high mobility group box 1 (HMGB-1) has been predicted to play a role. This article critically reviews the current literature regarding ECM disorganization in patients with IH and offers a novel, sterile inflammatory pathway triggered by HMGB-1. The HMGB-1-mediated sterile inflammatory pathway is based on well-studied molecular mechanisms that effect ECM biology and may be a causative link in the etiology of IH.

2. Physiological Wound Healing Responses

Connective tissue consists of many components which form a supportive network of fibrous components to anchor cells and proteins. Recent evidence has shown that the network can bind growth factors and cytokines to regulate cell function and wound repair¹³. The extracellular matrix (ECM) and connective tissue play an important role in the pathological and physiological components of wound healing. Wound healing is a dynamic and tightly regulated process that associates cellular, molecular, biochemical, and physiological events together, which start immediately after wounding and continues until the complete healing and restitution of the tissue functionality¹⁴. The wound healing process consists of three phases: inflammatory, proliferative, and remodeling (Figure 1). The ECM has a major role in the latter two. The ECM has classically been considered to be the architectural foundation for cellular support, but current evidence suggests that it also plays a large role in many

important cellular functions including: proliferation, migration, protein degradation, and apoptosis¹⁴.

The inflammatory phase lasts up to three days after the initial wound and is mediated by platelets, neutrophils, and macrophages. This phase is characterized by clot formation, macrophage and neutrophil mediated phagocytosis of debris, migration of neutrophils into the tissue, and the activation of MMPs. A cellular response is established within the first 24 hours as with the activation of neutrophils which in turn recruit macrophages for phagocytosis and to elicit the production of cytokines¹⁵. These inflammatory cells are crucial to wound healing by facilitating clearance of cellular debris, release of lysosomal enzymes, and reactive oxygen species (ROS)¹⁶. Macrophages can be classified as classically activated, M1 pro-inflammatory, or alternatively activated, M2 anti-inflammatory and pro-angiogenic, based on their gene expression¹⁷. During the inflammatory phase, many pro-inflammatory cytokines are released, which include interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interferon gamma (IFN- γ) that promote adhesion molecules essential for cellular migration via diapedesis¹⁸. In addition, macrophages release platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) which trigger angiogenesis and accelerate the transition into the 2nd phase of wound healing, the proliferative phase¹⁹.

The second phase of wound healing begins 2–3 days after the initial wound and continues for 14 days and is known as the proliferative phase²⁰. The molecular events associated with the proliferative phase decrease the size of the wound via contraction and the formation of fibrous tissue (fibroplasia) resulting in wound closure¹⁵. In this phase, granulation tissue starts to form around 4 days after the wounding due to the proliferation of fibroblasts^{15,21}. Granulation tissue formation results from the synthesis and secretion of collagens and elastins, and also cause fibroplasia¹⁵. The main component of the granulation tissue that characterizes the proliferative phase is type III collagen (COL3) secreted from fibroblasts. Gonzalez et al. reported that angiogenesis, thrombolysis, epithelial cell proliferation, and wound contracture via myofibroblasts occur during the proliferative phase¹⁵.

The last phase of wound healing is remodeling which lasts up to twelve months after the initial wounding to restore tensile strength through degradation, reorganization, and re-synthesis of the ECM¹⁵. The granulation tissue is remodeled via matrix metalloproteinases (MMPs) creating scar tissue that is hypovascular and less cellular. COL3 is replaced by parallel arrays of the thicker type I collagen (COL1) to increase tensile strength of the tissue. Following this change in collagen phenotype, tissue functionality returns, and the wounded area regains a healthy appearance. A wide range of growth factors controls this collagen turnover, mainly tumor growth factor β (TGF- β) and fibroblast growth factor (FGF). Three months after the initial lesion, 70–80% of the tensile strength is regained²².

The ECM is dynamic and plays an important role in tissue repair through the interaction between its structural and cellular components^{23,24}. IH is the result of abnormal wound healing due to the disorganization of the ECM. It is important to note that many exogenous and endogenous factors modulate and affect the wound healing process, thus resulting in IH. This article evaluates what is currently known about the potential pathogenic mechanism of

IH and how sterile inflammation via HMGB-1 may influence the wound healing process causing IH. Understanding the role of the ECM in wound healing and the underlying pathological mechanism that causes ECM damage may lead to novel therapeutic targets.

3. Incisional Hernias – Disruption of extracellular matrix homeostasis

Incisional hernias (IH) by definition are the result of a wound that is created when the abdomen is entered surgically or traumatically. The incidence is high, in the range of 10–20% and is even higher in certain subsets of patients such as those whose operative procedure is for diverticulitis or an abdominal aortic aneurysm^{1,3,4}. Studies have suggested that an unidentified connective tissue abnormality is common to both the primary disease process and the subsequent development of an incisional hernia³. In addition, there is an increased risk of incisional hernia after sigmoid colectomy for diverticulitis compared with colon cancer²⁵. Abdominal aortic aneurysm and abdominal wall hernia are manifestations of a connective tissue disorder. Recurrence of an incisional hernia after an initial incisional hernia repair is common especially when tissue repairs are done. A tissue repair is one in which only the patient's own tissue is used without any prosthetic material. Even when prosthetic material is used, the recurrence rate remains unacceptably high. Many studies have reported on underlying chronic conditions that are associated with a higher incidence of IH such as morbid obesity, cigarette smoking, pulmonary disease, debilitation from cancer, immunosuppression (chemotherapy), the use of steroids, cachexia, hypoalbuminemia, diabetes mellitus, and other preexisting comorbid conditions²⁶. However, the basic mechanism by which these conditions result in a higher incidence of IH is not well studied. Does collagen, matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs (TIMPs) play a role in the disruption of extracellular matrix (ECM) homeostasis, resulting in abnormal wound healing, and the development of IH (Figure 2)?

3.1 Collagen

Collagen is the principle component of the ECM and is responsible for the tensile strength and stability of the abdominal cavity²⁷. Type 1 collagen (COL1) has been regarded as the strong, fibrous, and stable protein which is found throughout the body and is a major component of the ECM. On the other hand, type 3 collagen (COL3) is thinner, globular, and significantly weaker than COL1. COL3 is found primarily during the proliferative phase of wound healing and is subsequently degraded by MMPs and replaced by COL1²⁸. Under physiological conditions, there exists a dynamic balance between the synthesis of collagen and its degradation by MMPs.

MMPs are a family of 23 proteins with a wide variety of substrates and functions, especially the rearrangement of the ECM. MMPs are secreted by macrophages, neutrophils, fibroblasts, and chondrocytes during normal tissue turnover as well as during disease. MMP expression is influenced by numerous cytokines, hormones, growth factors and inhibitors such as IL-1 β , TNF- α , and TIMPs^{29–31}. The interaction between collagen and MMPs is crucial for continual degradation and regeneration of healthy ECM. However, in chronic conditions and IH patients there is a disorganization of the ECM leading to tissue damage and persistence of inflammation.

Although the conversion of COL3 to COL1 is a normal wound healing process, several studies have investigated the role of this turnover in patients with IH. Based on various findings, there appears to be a consensus that levels of COL3 are increased in patients with IH and ventral hernias^{7–12,32}. This increase in COL3 leads to ECM disorganization and fluidity, potentially contributing to the formation of a weak fibrous scar and a reduction in tissue integrity³³. Currently, the interplay between COL1 and COL3 levels leading to ECM disorganization have been established in IH, but it is not clear whether it is a result of altered collagen synthesis or degradation via MMPs.

Type 4 collagen (COL4) which composes the basement membrane of cells, and type 5 collagen (COL5), which aids in the control of fibrillogenesis, are two minor components of the ECM and are poorly understood in the formation of IH. However, there is evidence that the COL4 synthesis and breakdown ratio was significantly increased compared to the control for IH³⁴. Levels of COL5 in IH patients were shown to have a higher turnover rate after hernia repair, however, postoperative turnover levels showed no difference from controls³⁵.

3.2 Matrix Metalloproteinases

The alteration of COL1/COL3, COL4, and COL5 ratios in ECM disorganization leading to IH are not fully understood, but recent studies have implicated matrix metalloproteinases (MMPs) as key regulators of these collagen homeostasis. Elevated levels of MMPs have been identified in numerous chronic inflammatory conditions including: rheumatoid arthritis, osteoarthritis, chronic cutaneous ulcerations, cancer progression and recently, hernia formation^{33,36–39}. Bellon *et al.* were first to show an overexpression of MMPs associated with any hernia formation⁴⁰. Over the last two decades, numerous studies have begun to focus on the role of MMPs in the pathophysiology and etiology of the different types of hernias. Current evidence supports a role for gelatinases (MMP-2 and MMP-9) and collagenases (MMP-1, MMP-8 and MMP-13) in the etiology of IH^{8,11,29,41–44}.

In the ECM, MMP-2 functions as a cleavage enzyme for COL1 through COL5 and COL9, suggesting its role in the formation of direct inguinal hernias. Rosch *et al* demonstrated the increased level and activity of MMP-2 in scar fibroblasts from patients with IH⁴². These scar fibroblasts were cultured *ex vivo*, which may have deprived them of potent signaling mediators known to influence fibroblast functions^{42,45}. Salameh *et al* reported the increased levels of MMP-2 at remote sites from incisions in patients with IH¹². This potentially suggest that elevated MMP-2 is a predisposing factor to the development of incisional hernias, however, further research is warranted to define the exact role of MMP-2 in IH²⁹.

MMP-1 and MMP-13 are another set of enzymes that are involved in the pathogenesis of IH. MMP-1 functions in cleavage of COL1 and MMP-13 aids in rearrangement of the basement membrane. Interestingly, MMP-1 has shown little effect in the development of primary inguinal hernias, direct or indirect^{9,10,40,43}. However, recent studies have demonstrated MMP-1 expression was elevated in patients with recurrent inguinal hernias and IH at protein and mRNA levels^{11,44}. Contrastingly, Klinge *et al* reported that detectable amount of MMP-1 was absent in IH subjects which warrants further optimization of tissue level MMP-1⁸. On the other hand, MMP-13 is an elusive enzyme with numerous studies showing difficulty in analyzing its expression in the skin, fascia, or peritoneum of hernia

patients^{8–10,43}. Zheng *et al* quantified an elevated expression of MMP-13 mRNA transcripts in patients with recurrent inguinal hernias, but there is currently little evidence of MMP-13 expression in patients with IH⁴⁴. MMP-9 is another enzyme that has been implicated as a pathogenic factor in hernia formation; but few studies have investigated its role in IH. In addition to the degradation of the basal lamina around cells, elevated levels of MMP-9 have a role in the development of varicocele, inguinal hernia and chronic venous disorders⁴⁶. Also, Antoniou *et al* reported that elevated levels of MMP-9 have been identified in the tissue of inguinal hernia patients⁴¹. Conversely, Bellon *et al.* were not able to quantify any levels of MMP-9 in the transversalis fascia of inguinal hernia patients⁴⁷.

3.3 Tissue inhibitors of metalloproteases (TIMPs)

Tissue inhibitors of metalloproteases (TIMPs) function to turn off active MMPs. There are four endogenous TIMPs: TIMP-1, TIMP-2, TIMP-3, and TIMP-4, and evidence has shown that an altered ratio between MMPs and TIMPs may affect collagen turnover in patients with IH⁴⁸. Typically, TIMPs regulate MMPs in a 1:1 manner and alteration of this ratio has been seen in numerous pathologies such as cancer, rheumatoid arthritis, and periodontitis. Marti *et al.* established a relationship between the ratio of MMPs:TIMPs and IH formation⁴⁹. They found an elevated MMP:TIMP ratio which would favor ECM breakdown. Specifically, it was shown that RNA transcripts for TIMP3 in the aponeurosis and TIMP4 in skeletal muscle were reduced as well as active TIMP3 in IH patients⁴⁹. Henriksen *et al.* found no difference in TIMP-1 serum levels in patients with and without IH⁵⁰. Though this does not exclude a potential pathological process for TIMP-1, further study is needed in IH patient peritoneal and fascia tissues.

IH is associated with a complex pathology of the ECM, where evidence has shown the involvement of many collagen phenotypes and various types of MMPs and TIMPs (Table 1). The available data have shown a consensus that during the wound healing process, there is an alteration of collagen levels that may be due to the elevated synthesis of MMPs or inhibition of TIMPs. However, it is not well understood how or why MMP signaling is increased, but due to the time between incision and hernia development, it has been proposed that IH formation is a chronic condition with inflammation as an underlying risk factor.

4. The Role of Inflammation in IH

Tissue trauma induced by surgery causes a systemic immune response that has yet to be investigated as a potential pathogenic mechanism for ECM disorganization in IH patients. This tissue trauma triggers sterile inflammatory responses as there is no involvement of any foreign microbe or pathogen. Sterile inflammation is mostly triggered by endogenous damage-associated molecular pattern (DAMP). DAMPs act in a similar fashion as a pathogen-associated molecular pattern (PAMP) but activate immune pathways when the host has a non-infectious inflammatory insult (i.e. trauma or surgery). DAMPs are released from necrotic, damaged, or stressed cells and interact with components of the innate immune system via pattern recognition receptors (PRR). Few studies have reported on the effects of DAMPs in relation to pathophysiology of IH.

An important DAMP associated with sterile inflammation is high-mobility group box-1 (HMGB-1), which responds early to events caused by hypoxia or necrosis. Due to its bivalent nature of pro-inflammation and enhancing tissue repair, HMGB-1 has become a protein of interest in many inflammatory conditions⁵¹. HMGB-1 is an intra-nuclear, non-histone DNA binding protein. Once released from the nucleus of a stressed or damaged cell, HMGB-1 stimulates the innate immune system and triggers inflammation⁵². HMGB-1 facilitates cell migration and chemotaxis, activates immune and non-immune cells, and induces cytokine production⁵³. HMGB-1 interacts with many surface molecules and receptors, specifically toll-like receptors 2 and 4 (TLR2 and TLR4), triggering receptors expressed on myeloid cells-1 (TREM-1), and receptor for advanced glycation end products (RAGE)⁵⁴. Upon binding to these receptors, a signaling cascade is triggered that leads to an inflammatory response via NF- κ B, ELK1, c-fos, and AP-1 (Figure 3). These interactions may result in HMGB-1 being the driver of the sterile immune response, which can result in collateral tissue damage. Table 2 shows the downstream effect of HMGB-1 interacting with each of its receptors. In addition, HMGB-1 stimulates classic modulators of inflammation, including TNF- α , IL-1 β , IL-1 α , IL-8, IL-18 and others⁵⁵. HMGB-1 has been studied in cancer and many inflammatory diseases, however no studies have reported on the status of HMGB-1 in patients with IH⁵⁶.

4.1 HMGB-1/TLR2 and TLR4 Interaction

TLR2 and TLR4 play a fundamental role in the innate immune systems and are localized to the cell surface where they interact with HMGB-1⁵⁷. TLR signaling is mainly divided into two pathways, the MyD88 or TRIF dependent pathways. Both TLR2 and TLR4 utilize the MyD88 pathway, but TLR4 can utilize the TRIF pathway as well. MyD88 is recruited to the cell surface and has downstream signals that activate NF- κ B and MAPKs/API⁵⁸. On the other hand, the TRIF pathway elicits downstream effects on IRF3. Together these mediators upregulate type I interferon and inflammatory cytokine genes^{59,60}. In addition, the binding of a ligand to TLR2 and TLR4 triggers the activation and nuclear translocation of NF- κ B and subsequently enhance the expression of the mediators associated with NLRP3 inflammasome.

4.2 HMGB-1/TREM-1 Axis

Triggering receptors expressed on myeloid cells-1 (TREM-1) have been associated with various PAMPs and DAMPs, especially HMGB-1 and heat shock protein 70 (HSP70)⁶¹. This PRR acts in a similar way to TLRs and lipopolysaccharide (LPS) and control inflammation through cytokine, chemokine and receptor upregulation^{62,63}. TREM-1 activation in macrophages and neutrophils stimulates the secretion of MMPs that degrade components of the ECM, including gelatin (MMP-2 and MMP-9), collagen (MMP-1, MMP-8 and MMP-13), elastin (MMP-12) and fibrin (MMP3 and MMP-10)⁶⁴.

TREM-1 interacts with a diverse array of ligands, but the mechanism underlying these interactions remains unknown. Once TREM-1 binds a ligand, in this case HMGB-1, it phosphorylates ITAM and DAP12, which triggers the downstream pathway. Ultimately, this pathway activates signaling molecules of PI3K, PLC- γ , ERK1/2, and MAP kinases that regulate inflammatory genes and NF- κ B⁶⁵. In addition to cytokine release, TREM-1

mediates degranulation and ROS production that contribute to the inflammatory response⁶⁶. Although the exact interaction is unknown, it is believed that there is cross talk between TREM-1 and TLRs^{67–70}. Activation of TREM-1 results in the increased production of IL-8, TNF- α , and IL-2. Evidence has shown an increase of MMP-1 and MMP-9 and decreased expression of collagen genes COL1A1 and COL3A1 in carotid plaques of symptomatic patients with carotid stenosis⁶⁴. Further research is warranted for the better understanding of the interaction between HMGB-1 and TREM-1 and its role in ECM disorganization of patients with IH.

4.3 HMGB-1/RAGE Axis

Receptor for advanced glycation end products (RAGE) has multiple binding partners that lack sequence similarities. One of these binding partners is HMGB-1, along with several members of the calcium-binding S100 family of proteins, some species of AGEs, and β -sheet fibrillar material such as amyloid- β , serum amyloid A, immunoglobulin light chains, transthyretin, and prions⁷¹. Even with multiple binding partners, RAGE can be considered a PRR that binds endogenous molecules that result from cellular stress⁷¹. When activated, RAGE is linked to an array of signaling pathways, including NF- κ B^{72–74}, MAPKs^{74–76}, PI3K/Akt⁷⁷, Rho GTPases⁷⁸, JAK/STAT⁷⁹, and Src family kinases⁸⁰. Significantly, NF- κ B pathway releases pro-inflammatory cytokines that upregulate the expression of RAGE, and potentially cause a receptor-dependent auto inflammatory loop⁷¹. In addition, HMGB-1-RAGE interactions activate the ERK-MAP kinase pathway, which is important for the invasion and expression of MMPs, tumor proliferation, and cell migration⁸¹. The binding of HMGB-1 to RAGE triggers angiogenesis and inflammatory cell migration leading to the recruitment of more mediators and inflammatory cells⁵³. However, the exact mechanism for the interaction of HMGB-1 and RAGE in relation to sterile inflammation in the fascial tissue of IH patients remains unknown.

4.4 HMGB-1 Role in the NLRP3 Inflammasome

Inflammasomes are multi-protein assemblies, common to the pathophysiology of many diseases that elicit a large inflammatory response through the release of cytokines⁵⁴. The Nucleotide-binding domain, Leucine-rich Repeat containing Protein-3 (NLRP3) inflammasome releases the pro-inflammatory cytokines of IL-1 β and IL-18⁸². Ultimately, the NLRP3 inflammasome is responsible for the proteolytic cleavage of pro-caspase-1 to caspase-1 via the recruitment of apoptosis-associated Speck-like protein containing a CARD (ASC), the adapter protein⁵⁴. Caspase-1 matures and stabilizes IL-1 β and IL-18 and initiates pyroptosis⁸³. The signal for NLRP3 inflammasome activation is induced from the binding of a ligand to TLR2 and TLR4. The binding of a PAMP or DAMP to the TLRs triggers the release of NF- κ B and enhances the expression of the NLRP3 inflammasome in damaged cells. HMGB-1 is a ligand for TLR2, TLR4, and RAGE, thus amplifies NLRP3 mediated inflammation^{83,84}. One of the end products for the NLRP3 inflammasome pathway, IL-1 β , can mediate collagen degradation by the activation of MMPs in connective tissue^{85,86}. To date there is no evidence of the existence, assembly, and activation of NLRP3 inflammasome-mediated inflammation in patients with IH. Studies are needed to investigate if elevated levels of HMGB-1 are present in patients with IH and if HMGB-1 is associated with the activation of NLRP3 inflammasome pathway in IH fascial tissue.

4.5 A Potential Inflammatory Mechanism for IH

Acting as a DAMP in sterile inflammation, HMGB-1 acts on many pathways that lead to an exaggerated inflammatory response and the overexpression of MMPs leading to ECM disorganization. HMGB-1 binds to TLR2, TLR4, TREM-1, and RAGE which all release NF- κ B to increase inflammatory cytokine gene expression. In addition, these interactions may contribute to the formation of the NLRP3 inflammasome. Together, these pathways release a milieu of cytokines including TNF- α , IL-1 β , IL-1 α , IL-2, IL-8, IL-18, and type I interferon^{55,59,60,82}. Many of these cytokines are linked to overexpression of MMPs that lead to COL1 and COL3 degradation. Thus, one molecule of HMGB-1 binding to a receptor can amplify the inflammatory response and cause ECM damage. This ECM damage results in the weakening of the transversalis fascia and the abdominal wall leading to increased susceptibility of IH. This perpetuating cycle of tissue damage, ECM disorganization, and exaggerated inflammatory response is the result of MMP hyperactivity. Further investigation is needed to elucidate the role of HMGB-1 and ECM disorganization on MMP hyperactivity in patients with IH.

5. Conclusion

Patients with IH undergo long, strenuous surgical procedures due to a continual disruption in the wound healing process. The current understanding of IH focuses on the varying levels of expression of ECM components, mainly collagen, MMPs, and TIMPs (Table 1). However, few studies have demonstrated the etiology and potential pathogenic factors that lead to the disorganization of the ECM. In this article, we have critically reviewed pathways, signaling cascades, and immunobiochemical events that may lead to IH. HMGB-1 has been linked to cancer and various inflammatory diseases, but few reports have investigated the role of HMGB-1 in patients with IH. Furthermore, elevated levels of HMGB-1 have been reported in animal models for some patient related factors including: morbid obesity, diabetes mellitus, and smoking, that have been associated with abnormal wound healing and higher incidence of IH^{87,88}. Further investigation is warranted to elucidate the role of HMGB-1 in exacerbating the sterile inflammatory response that leads to ECM degradation and higher susceptibility to IH.

If HMGB-1 and the resulting receptor interactions, TLR2, TLR4, TREM-1, and RAGE, are identified in patients with IH, further study is needed to examine the role of HMGB-1 on ECM disorganization, specifically looking at the activation of the NLRP3 inflammasome, overexpressed MMPs, and an altered COL1 to COL3 ratio. Further study is needed to elucidate this HMGB-1 triggered pathway in animal and human IH fascial tissue. Positive findings may suggest several novel therapeutic modalities to inhibit NLRP3 assembly in patients with IH and prevent ECM disorganization.

6. Expert Opinion

The current clinical management of IH consists of monitoring the size and symptoms of the hernia. If the size becomes too large or symptoms begin to impair the patient, surgical intervention is warranted. Current repair methods for incisional hernias (IH) include primary closure, which has the highest recurrence rate, though is rarely used now in favor of a

prosthetic mesh repair. The principle behind the prosthetic mesh repair is to reinforce inadequate native tissue with a strong barrier which can be incorporated into the repair. A wide variety of prosthetic material have been developed which can be placed either laparoscopically or with an open laparotomy technique. However, even after surgical repair, the patients have a greater risk of developing another incisional hernia, a recurrent incisional hernia, when compared to the incidence after the initial laparotomy, thus complicating the clinical management of IH. Today, clinical management is focused on treating the underlying condition and relieving symptoms.

The etiology of IH is multifactorial with initial operation and patient related factors playing a large role. These patient related factors include obesity, cigarette smoking, diabetes mellitus, hypertension, history of abdominal aortic aneurysm or diverticulitis, and other preexisting conditions. Many of these factors can be manipulated clinically to produce better outcomes such as pristine surgical technique, cessation of smoking, nutritional improvement etc., however these efforts have had only a limited role in decreasing the incidence of IH. Although many risk factors have been correlated with the development of IH, few studies have evaluated the underlying molecular mechanism.

Due to the multifactorial etiology, patient-related factors must be taken into account and held constant when possible, however due to clinical manipulation, further research is needed to identify an underlying pathological mechanism that leads to IH. Our current area of interest is sterile inflammation which has been shown to play roles in many disease processes and results in impaired wound healing. IH has been characterized as ECM disorganization that leads to impaired wound healing.

Within the next five years, clinical management may remain the same for patients with IH. However, high risk patients will be able to be identified based on an algorithm of patient related factors. These high-risk patients would be encouraged to comply with lifestyle modification guidelines to achieve better surgical outcomes and reduce the risk of IH and/or recurrent IH. Furthermore, greater emphasis will be given to the underlying mechanism that leads to impaired wound healing, and thus, IH. Many sterile inflammatory pathways have potential sites for suppression, inhibition, or stimulation of receptors that work upstream of the signaling molecules that lead to ECM disorganization. The next generation of research on IH may focus on the molecular pathogenesis aiming to find potential therapeutic targets of intervention to prevent the risk of IH formation following the laparotomy.

Funding

The research work of DK Agrawal is supported by research grants R01 HL120659, and R01 HL144125 from the National Institutes of Health, USA. The content of this review article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Article Highlights

- Incisional hernias (IH) are a complication of patients undergoing a laparotomy and many risk factors have been correlated with the development of IH, technical factors at the initial operation and patient related factors, but few studies have evaluated the underlying molecular mechanism.
- Current literature has evaluated the roles extracellular matrix (ECM) disorganization, alterations in type I and type III collagen, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) on IH. However, few studies have investigated the underlying molecular mechanism leading to ECM disorganization. In this review, we offer a novel pathway that may lead to the development of IH.
- HMGB-1 is an important damage associated molecular pattern that is associated with sterile inflammation and responds to events caused by hypoxia and necrosis. HMGB-1 interacts with many surface molecules and receptors, specifically toll-like receptors 2 and 4 (TLR2 and TLR4), triggering receptors expressed on myeloid cells-1 (TREM-1), and receptor for advanced glycation end products (RAGE) and this binding results in a signaling cascade that leads to an inflammatory response via NF- κ B, ELK1, c-fos, and AP-1.
- In addition to interacting with these receptors, HMGB-1 can aid in the assembly and activation of the NLRP3 inflammasome, which releases the pro-inflammatory cytokines of IL-1 β and IL-18 that lead to ECM disorganization.
- If HMGB-1 and the resulting receptor interactions are identified in patients with IH, further study is warranted to examine the role of HMGB-1 on ECM disorganization and to elucidate this pathway in animal and human IH tissue. The findings may suggest several novel therapeutic modalities to inhibit NLRP3 assembly in patients with IH and prevent ECM disorganization.

Figure 1:
Sequential phases of normal wound healing process

Figure 2:
Potential locations on wound healing timeline for ECM disorganization and development of IH

Figure 3:

Inflammatory response due to the signaling cascade when HMGB-1 interacts with surface receptors TLR2/TLR4, TREM1, and RAGE. Upon interacting with TLR2/4, HMGB-1 activates the MyD88, or TRIF only for TLR4 and results in the upregulation of NF- κ B, c-fos, and AP-1, which are inflammatory cytokines. When HMGB-1 interacts with TREM1, the DAP12 or ITAM pathway is triggered and results in the activation of inflammatory cytokines, c-fos, ELK1, and NF- κ B, and it results in the inhibition of apoptosis. Finally, when HMGB-1 interacts with RAGE the m-Di9-1 pathway is activated. This results in NF- κ B and AP-1 upregulation and enhancing the inflammatory response. Ultimately, the

synergistic interactions of HMGB-1 and these surface receptors results in the increase of the inflammatory response and causes ECM disorganization.

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Table 1:

ECM components that have been implicated in IH

ECM component	Function	Role in RIH
COL1	Major ECM component; fibrous and supportive; provides tensile strength after lesion;	Reduced expression; reduces tensile strength of tissue
COL3	Globular and thinner collagen; important for early stages of wound healing; weak and not supportive if not replaced by COL1	Overexpression and creates a dynamic and fluid ECM that is weaker and more susceptible to injury
COL4	Formation of basement membrane of epithelial cells	Evidence has been inconclusive about the role of COL4 in IH
COL5	Aid in fibrillogenesis of collagens	Evidence has been inconclusive about the role of COL5 in IH
MMP-1	Collagenase responsible for the cleavage of COL1, COL2, and COL3	Overexpression causes an increased degradation of ECM collagen, weakening the overall framework
MMP-2	Gelatinase responsible for the cleavage of COL1, COL5, and COL9	Overexpression causes an increased degradation of ECM collagen, weakening the overall framework
MMP-9	Gelatinase responsible for the cleavage of COL4 and laminin	Overexpression causes an increased degradation of basement membrane between cells, loosening connections
MMP-13	Collagenase responsible for the cleavage of COL1, COL2, and COL3	Evidence has been inconclusive about the role of MMP-13 in IH
TIMP-3	Inhibits various MMPs and TNF- α	Under expression allows MMPs to degrade collagens
TIMP-4	Inhibits a broad spectrum MMP	Under expression allows MMPs to degrade collagens

Table 2:

The downstream effects of HMGB-1 interacting with the surface receptors of TLR2, TLR4, TREM-1, and RAGE

Surface Receptor	Effects on wound healing and IH
TLR2/TLR4	Play a fundamental role in the innate immune system as cell surface receptors
	Both activate the nuclear translocation of NF- κ B and MAPKs/AP1 via the MyD88 pathway
	TLR4 can utilize the TRIF pathway to activate IRF3
	These mediators upregulate type I interferon and inflammatory cytokine genes
	Enhance the expression of the mediators associated with NLRP3 inflammasome
TREM-1	Stimulates the secretion of MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-10, MMP-12, and MMP-13
	Activates PI3K, PLC- γ , ERK1/2, and MAP kinases that regulate inflammatory genes and NF- κ B
	Mediates degranulation and ROS production that contribute to the inflammatory response
	Increased production of IL-8, TNF- α , and IL-2
RAGE	Linked to signaling pathways of NF- κ B, MAPKs, PI3/Akt, Rho GTPases, JAK/STAT, and Src family kinases
	ERK-MAP kinase pathway is important for the invasion and expression of various MMPs
	NF- κ B pathway releases pro-inflammatory cytokines that upregulate the expression of RAGE
	Triggers angiogenesis and inflammatory cell migration
NLRP3 Inflammasome	ASC cleaves pro-caspase-1 to caspase-1
	Caspase-1 matures and stabilizes IL-1 β and IL-18
	IL-1 β mediates collagen degradation by the activation of MMPs in connective tissue