Hernia (2006) 10:462–471
DOI 10.1007/s10029-006-0144-9

REVIEW

The biology of hernias and the abdominal wall

Michael G. Franz

Published online: 28 September 2006

Abstract The fundamental mechanism for hernia formation is loss of the mechanical integrity of abdominal wall structural tissue that results in the inability to offset and contain intra-abdominal forces during valsalva and loading of the torso. There is evidence that genetic or systemic extracellular matrix disorders may predispose patients to hernia formation. There is also evidence that acute laparotomy wound failure leads to hernia formation and increases the risk of recurrent hernia disease. It may be that hernia formation is a heterogeneous disease, not unlike cancer, where one population of patients express an extracellular matrix defect leading to primary hernia disease, while other subsets of patients acquire a defective, chronic wound phenotype following failed laparotomy and hernia repairs. It is evident that an improved understanding of structural tissue matrix biology will lead to improved results following abdominal wall reconstructions.

Keywords Hernia · Wounds · Wound healing · Collagen · Fibroblast · Signal transduction

Introduction

Most hernias result when there is a loss of the mechanical integrity of abdominal wall structural tissue. The result is a defect in the ability of the abdominal wall muscles and tendons to contain viscera and to support the torso. Fundamentally, it is molecular and cellular matrix architecture that is injured or lost. Whether the subject is primary ventral hernias or secondary incisional hernias, biomechanical systems fail leading to structural soft tissue pathology. Abnormal collagen metabolism was one of the first biological mechanisms proposed for the development of primary and secondary hernias [1, 2]. The first suggested risk factors for hernia formation included cigarette smoking and strong family histories indicating a genetic predisposition [2]. Others measured abnormal collagen isoform and tissue metallo-protease expression in patients with inguinal and incisional hernias [3, 4]. It is not yet proven that a fundamental biological disorder like abnormal collagen metabolism is the most important mechanism for the majority of primary ventral hernias and direct inguinal hernias because a large population-based study does not yet exist of collagen expression in people who do not develop primary hernias. There is also evidence that mechanical strain, like coughing and weight lifting, can induce secondary changes in tissue fibroblast function within load-bearing tissues [5–7]. It is possible that chronic loading induces pathological changes in structural tissue cellular and molecular function, and not an a priori biological defect. Such selective changes in tendon fibroblast function within the load-bearing abdominal wall structures may also contribute to the long-standing difficulty in the surgical repair of ventral and inguinal hernias. It is therefore more likely that primary hernias are the result of a genetic predisposition in a subset of hernia patients. The remaining may acquire structural pathology as the result of mechanical strain with or without associated pre-disposing risk factors like cigarette smoking and no identifiable genetic tissue defect.

M. G. Franz (✉)
Department of Surgery, University of Michigan,
2922H Taubman Center, 1500 E Med Ctr Dr, Ann Arbor,
MI 48109-0331, USA
e-mail: mfranz@umich.edu

Secondary incisional hernias provide a useful paradigm for the study of hernia formation. The important difference is that a surgical incision and acute wound is identifiable as the inciting mechanical and biological event. Studies of scar tissue and skin from incisional hernia patients have demonstrated disorders in collagen metabolism and isoform expression [3, 8]. It is again difficult to prove that a fundamental disorder in collagen metabolism is the most important mechanism for incisional hernia formation since these studies were small and not completely controlled. Similar to inguinal hernias, there is also no available genetic information addressing collagen expression in the population that does not form incisional hernias. It has been proposed that acute laparotomy wound failure and the loss of a normal wound-healing environment induces the selection of an abnormal population of laparotomy wound repair fibroblasts [9, 10]. This may in turn result in the expression of abnormal structural collagen. One mechanism for this is the obvious loss of abdominal wall load force signaling as the incision mechanically fails. It has been long recognized in other tendon repair systems that load forces are important for maximum repair [11]. Wound ischemia also ensues during early acute wound failure, propagating deficient soft-tissue repair. The best studies of incisional hernia formation now show that *early* laparotomy wound failure is an important mechanism of incisional hernia formation [12]. Once again, it is possible that the early mechanical failure of the laparotomy wound induces pathological function of wound repair fibroblasts, and not the other way around. The majority of these incisional hernia patients do not demonstrate defects in any other type of wound healing. This hypothesis has now been tested in at least one animal model where intentional mechanical laparotomy wound failure lead to pathological wound fibroblast function in vivo and in vitro [10]. The concept of mechano-signaling during laparotomy wound repair challenges the 30-year-old dictum that tension-free is best during hernia repair. It now appears that in load-bearing systems, a "tension appropriate" or "tension equilibrium" point exists that maximizes repair signals to wound repair fibroblasts. Here again, it is possible that a subset of incisional hernia patients express a defect in collagen metabolism and or expression. It is hard to resolve this mechanism with the fact that the overwhelming majority of these patients have no history of a wound healing defect (making them surgical candidates) and also do not express a defect at the primary surgical site (GI tract, vascular system, solid organs, etc.). It is possible that mechanical failure is the major mechanism for incisional hernia formation and that the loss of mechanical load signaling or some other acute wound healing pathway induces defects in repair fibroblast biology. Since the tissue fibroblast is the major source for collagen synthesis and turnover, defects in fibroblast function are an important mechanism for subsequent tissue collagen disease.

The biology of incisional hernias and recurrent inguinal hernias provides a useful foundation for the study of the mechanism of hernia disease. If a fundamental, biological extracellular matrix or other tissue defect exists that predisposes to primary hernia formation, it is reasonable to assume that the same defect would express itself during wound healing following laparotomy or hernia repair. Furthermore, it is the problem of recurrent inguinal hernias that has plagued groin herniorrhaphists for centuries. Most evidence supports that the majority of recurrent inguinal hernias are due to surgical wound failure, as is the case with incisional hernias and recurrent incisional hernias. An inter-regulated series of time-dependent cellular and molecular events must be activated and modulated during the organization of a surgical wound matrix (Fig. 1). In addition to the natural delay in the activation of tissue repair, abnormal provisional and or final wound matrix structure may contribute to the mechanism of recurrent hernias. Ideally, normal aponeurotic, fascial, muscle or tendon structures would be regenerated following hernia repairs. Biological approaches for "normal" laparotomy wounds might be guided by information gained from identified genetic or epigenetic pathways associated with hernia formation like abnormal collagen matrix structure in Ehlers–Danlos syndrome or MMP/TIMP expression in abdominal aortic aneurysm (AAA) disease or in other chronic wounds.

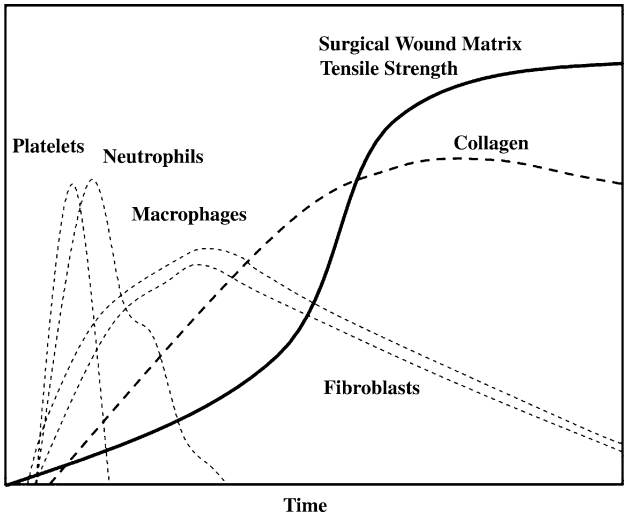

Fig. 1 Cellular and molecular wound healing elements must be activated and coordinated for successful laparotomy and hernia repairs

The fundamental mechanism of primary inguinal hernias is important to understand, and will certainly contribute to the success or failure of primary inguinal hernia repairs. How biological defects contribute to primary inguinal hernia formation will also likely contribute to the understanding of the mechanism of surgical wound healing. But, it is a better understanding of the mechanism of successful and failed hernia repairs that surgeons seek first today.

Growing evidence suggests that incisional hernias and recurrent hernias are most often the result of early surgical wound healing failure. Specifically, the majority of incisional hernias appear to develop following the mechanical disruption of laparotomy wounds occurring during the initial "lag phase" of the wound-healing trajectory (Fig. 2). Clinically evident laparotomy wound failure is a rare event, with reported dehiscence rates of 0.1% [13]. Prior wound healing literature therefore concluded that incisional hernias were the result of late laparotomy wound failure and scar breakdown [14]. This concept was challenged by clinical studies of incisional hernias that recorded high primary and secondary recurrence rates after short-term follow-up, typically only 2–4 years [15, 16]. One prospective study found that the total rate of laparotomy wound failure is closer to 11%, and that the majority of these (94%) go on to form incisional hernias during the first 3 years after abdominal operations [12] (Table 1). The real laparotomy wound failure rate is therefore 100 times, what most surgeons think it is. In simplest terms, most incisional hernias and recurrent hernias are therefore derived from clinically occult dehiscences. The overlying skin wound heals, concealing the underlying myofascial defect. This mechanism of early mechanical laparotomy wound failure is more consistent with modern acute wound healing science. There are no other models of acute wound healing suggesting that a successfully healed acute wound goes on to breakdown and mechanically fail at a later date.

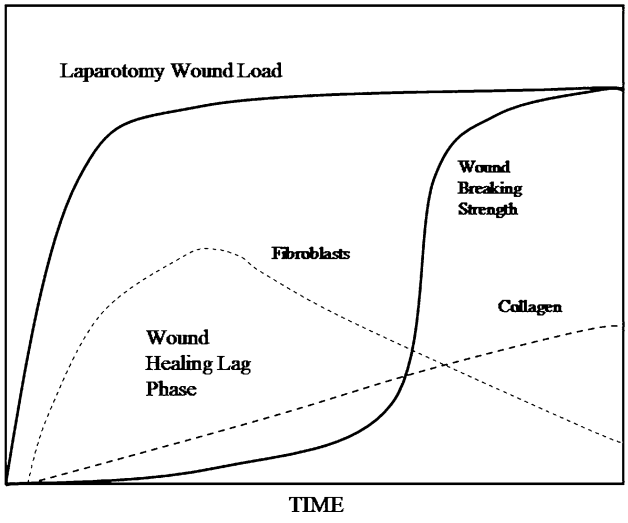

Fig. 2 Abdominal wall load forces rise well in advance of a durable wound matrix. It is during the initial "lag phase" of laparotomy wound repair that many incisional hernias develop

Table 1 Human laparotomy wound–edge gap on post-operative day 30

Laparotomy wound outcome at 43 months	Less than 12 mm	More than 12 mm
Healed (%)	95% (140/147)	6% (1/18)
Incisional hernia (%)	5% (7/140)	94% (17/18)

Numerous studies have now associated incisional hernias with impaired collagen and tissue protease metabolism. Tissue from incisional hernias expressed more soluble (immature) collagen, increased ratios of early wound matrix collagen isoforms (e.g., collagen III) and increased matrix metalloprotease levels [17, 18]. These studies were limited by small numbers of patients and no confirmatory animal model data exist. A decreased ratio of types I: type III collagen was detected in hernia ring and skin specimens obtained from patients with incisional hernia disease at both the mRNA and the protein level. Morphologic changes were present not only in the fascial tissue, but also in the hernia sac, skin specimens, and scar tissue surrounding explanted meshes of hernia patients; collectively, the changes indicate a generalized alteration of collagen metabolism. These studies were the most compelling for the presence of a genetic structural collagen defect in patients that develop incisional hernias.

Primary hernia formation may also be due to a biologic defect. MMP-2 overexpression was measured in fibroblasts of patients with direct inguinal hernia formation and MMP-13 overexpression was detected in specimens obtained from patients with recurrent inguinal hernias [3, 19]. Again, studies like these are only observations and it is not clear whether increased metalloprotease expression leads to direct inguinal hernia formation or whether direct inguinal hernia failure of the groin tissue in turn induces increase MMP levels. In most cases, recurrent inguinal hernias are likely a form of incisional hernia.

Acute wounds, acute wound healing and incisional hernia formation

Acute wounds are defined by the loss of normal tissue structure and function, usually as the result of a kinetic (traumatic) or metabolic injury. Acute wound healing

is the highly regulated process of cellular, humoral and molecular events activated at the time of acute injury and resulting in a time-dependent but predictable and orderly pattern of tissue repair [20]. It is the integrated summation of each pathway along the continuum of this host response to injury that results in acute wound healing. The phases of acute wound healing are described as hemostasis, inflammation, fibroproliferation (scar formation) and scar remodeling. A defect in any of these pathways activated during laparotomy and hernia repair may lead to hernia formation.

Hernia formation following laparotomy wound failure

Acute wound healing failure occurs when there is an abnormality in the quantity or quality of the sequential pathways of tissue repair. Inadequate hemostasis due to platelet dysfunction or poor technique can result in hematoma formation with ensuing mechanical disruption of a provisional wound matrix. A delayed or deficient inflammatory response can result in wound contamination or infection with abnormal signalling for progression into the fibro-proliferative phase of acute tissue repair. A prolonged inflammatory response due to the presence of a foreign material, like a mesh implant, or wound infection will delay the progression of acute wound healing into the fibroproliferative phase where rapid gains in breaking strength should occur. Delayed fibroblast responses in turn impede the synthesis of a provisional wound matrix, prolonging the period of time a surgical wound is subjected to increasing mechanical loads and dependent entirely on suture material for strength. Ultimately, it is the time required for the recovery of wound breaking strength that determines the risk of acute wound failure.

Acute wound healing failure can be measured in many ways. Wound infections, for example, remain a major concern for all practicing surgeons and are forms of acute wound healing failure. The risk of an acute wound infection is increased in the setting of an abnormal host inflammatory response. Overabundant scar formation, as occurs in burn hypertrophic scars and gastrointestinal strictures are also forms of acute wound healing failure. Several studies now suggest abnormalities in hypertrophic scar fibroblast function [21]. In essence, acute wound failure occurs when an acute wound fails to heal as expected.

Most often, acute wound healing failure is defined as an interruption in the timely recovery of the injured tissue's mechanical integrity. For practicing surgeons this is best measured as wound breaking strength. Wound breaking strength is a mechanical property of a healing wound and measures the ability of the early scar to resist distractive forces. Tensile strength normalizes breaking strength to the surface area of the wound edge, thereby measuring a physical property of the particular wound and scar (tensile strength = breaking strength/wound−edge surface area). Wound breaking strength is especially important for tissues placed under high loads. Burst abdomens, or acute fascial dehiscence with evisceration are one important extreme of acute wound failure. They have for a long time been associated with mortalities of 50% or greater [22]. Incisional hernias are an important example of acute abdominal wall wound healing failure that is a significant source of surgical morbidity.

The mechanism of acute wound failure leading to herniation

Biological components

Surgical wound healing failure occurs when the load placed across the wound exceeds the resistive capacity of the suture line and provisional matrix. Usually this occurs when there is abnormal progression through the integrated phases of acute tissue repair. Successful acute wound healing, therefore, depends on timely, effective and regulated hemostasis, inflammation, proliferation, and remodeling (Fig. 1). Acute wounds are totally dependent on suture until breaking strengths are achieved that are capable of off-setting the increased loads placed across an acute wound by a recovering patient.

Inflammation

Following formation of a stable clot, inflammatory cells marginate into the injured tissue and an efflux of leukocytes and plasma proteins enter the wound site. Neutrophils arrive initially and function to sterilize and debride the wound but are not required for tissue repair in clean wounds. Monocytes and tissue macrophages populate the inflammatory infiltrate within 2–3 days. Macrophages phagocytose injured tissue and debris as well as secrete multiple growth factors. The macrophage orchestrates tissue repair and appears to be the only inflammatory cell type absolutely required [23].

Overall, tissue strength of a wound is essentially zero during this inflammatory phase thus an excessive or prolonged inflammatory response as is seen with incisional foreign bodies, like suture or mesh material,

or infections predispose to wound failure. Steroids can reduce wound inflammation but also inhibit collagen synthesis and wound contraction synergistically impeding tissue repair [24]. Interestingly, there is minimal inflammatory cell infiltration seen in fetal wound repair during which the epidermis and dermis are restored to normal architecture without scar formation [25].

Fibroblasts

A great deal has been learned about fibroblast function during normal skin healing. Fibroblasts migrate into acute wounds within 2 days and they are the major cell type of granulation tissue by post-injury day 4. At first, fibroblasts populate the wound site through migration and increase in number by proliferation. Wound fibroblast migration and proliferation are both influenced by soluble growth factors and inflammatory mediators [26]. The chemical and structural composition of the provisional matrix on which fibroblasts move is equally important. Receptor mediated interactions are increasingly described between the wound extracellular matrix and activated repair fibroblasts. Very little, however, is known about defective fibroblast function during acute wound failure and it is likely that defects in any or all of these repair pathways exist. Even less is known regarding the behavior of repair fibroblasts in non-dermal tissues. The mechanism for modulating the distribution of fascial and tendon repair fibroblast proliferative, growth and synthetic activity, for example, is incompletely understood. Whether abdominal wall wound failure reflects a defect in tendon fibroblast recruitment and function during incisional hernia formation or whether abnormal mechanical signals following laparotomy wound failure subsequently results in impaired fibroblast function is not known. To date, no correlation has been made with the proliferative or cell-cycling response of abdominal wall fibroblasts and acute wound failure.

The majority of cell-cycling studies in wound repair to date have focused on keratinocytes in models of re-epithelialization. A defect was recently described in fibroblast cell-cycling activity in chronic pressure ulcers [27]. It was suggested that an abnormality in the proportion of wound repair cells restricted to cell-cycle quiescence, senescence or even apoptotic pathways might explain delays in wound healing. Fibroblasts confined to G1 arrest were measured by the expression of the cell cyclin inhibitor p21 and the proportion of fibroblasts capable of DNA synthesis were measured by the level of expression of the proliferating cell nuclear antigen (PCNA). How and when fascial fibroblasts are recruited out of the quiescence into a functional cell cycle is not known. It is possible that defects or delays in the recruitment of laparotomy wound fibroblasts into the cell cycle might contribute to delays in tendon repair and ultimately dehiscence and incisional hernia formation. The mechanism that controls the balance between uninjured fascial fibroblast quiescence; cell-cycle arrest or functional cell-cycle progression is unknown.

In the chronic ulcer studies, it was suggested that low wound growth factor levels might result in dermal fibroblast quiescence and even senescence. This may also be true in failing acute laparotomy and hernia wounds as an initially rapid rising growth factor signalling cascade became depleted. Relative fascial or tendon wound ischemia might also induce fibroblast cell-cycle arrest. This would occur, for example, when a suture line is closed too tight, or in a patient who is in shock and soft-tissue perfusion is reduced. An ischemic laparotomy repair might also be deficient in the components and co-factors required for DNA and protein synthesis, again resulting in repair fibroblast cell-cycle arrest. Finally, too little or too much tension across the laparotomy tendon repair may disturb the optimal set point of a normal mechanotransduction mechanism; again resulting in premature laparotomy wound fibroblast cell-cycle arrest.

The precise histological origin of abdominal wall fibroblast repair cells in healed versus herniated wounds is also unknown. Differences may exist in the chemotactic response of ventral (anterior) myofascial versus mesothelial surface fibroblasts following midline incisions. It is known, for example, that peritoneal surface defects heal by simultaneously re-epithelializing the entire wound surface as opposed to establishing an advancing epithelial edge as occurs in the skin [28]. Because epidermal to dermal communication is known to occur during the healing of skin, it is possible that a similar mechanism may be active on the peritoneal surfaces of abdominal wall (fascial) wounds. Peritoneal fluid itself may modulate acute repair in the abdominal wall. During fetal wound healing, amniotic fluid can act to accelerate the recovery of wound breaking strength in addition to minimizing the amount of scar formation.

Defects have been identified in the kinetic properties of fibroblasts cultured from laparotomy wound and hernia biopsies obtained from a rat model of incisional hernias [9, 10]. It was observed that fibroblasts cultured from incisional hernias expressed a defect in causing the contraction of fibroblast populated collagen lattices. Normally healing laparotomy wound fibroblasts caused 80% lattice contraction over 5 days while hernia fibroblasts caused only 50% lattice

contraction. The same studies found no difference in the level of collagen gene expression between herniated and healed laparotomy wounds after 28 days. The results suggested that any difference in collagen gene expression is occurring earlier than post-operative day 28 of laparotomy repair in this model, or that the defect in herniated wounds is not one of collagen gene expression. Other possibilities included down-stream abnormalities in collagen protein synthesis and assembly, early scar crystallization and or fibroblast remodeling activity.

Collagen

Collagen was an early target of investigations into the mechanism of hernia formation and recurrence. It is the predominant structural protein, especially of abdominal wall fascial layers, comprising 80% or more of structural tissue dry weight. The identified defects result in either delayed or abnormal collagen synthesis or increased wound protease activity leading to collagen degradation. The result is an imbalance in repair collagen homeostasis leading to a reduction in wound collagen levels, wound tensile strength and an increased risk of acute mechanical wound failure [29]. Lathyrism, a disorder of collagen cross-linking, and lathyrogens were shown to be associated with and to induce herniation, respectively. Reduced hydroxyproline and collagen levels were measured in structural tissues of patients with direct inguinal hernias. Isolated fibroblasts from these patients expressed a proliferative defect and a reduced ability to translocate hydroxyproline. Subsequent to that work, apparent abnormalities in the ratios of collagen isoform expression, decreased collagen cross-linking and increased collagen solubility was noted. A twofold increase in the amount of type III collagen has been reported in the skin fibroblasts of patients with inguinal hernias when compared to controls [3]. A genetic predisposition to the formation of abdominal wall hernias has also been suggested in large, controlled series of abdominal aortic aneurysm patients supporting the long held impression of a common extra-cellular matrix defect in both vascular wall and abdominal wall collagen metabolism [30].

The mechanism by which the collagen-rich early laparotomy wound matrix and ultimate scar attaches to uninjured tissue at the wound border is also poorly understood. This conceptual deficiency is important since acute laparotomy wounds that fail likely do so at the scar to normal tissue interface [31]. Animal modeling suggests that a provisional matrix and early scar will mechanically fail within the scar itself only during the first 3–5 days after injury. After that, mechanical failure is more likely to occur at the early scar to wound–edge interface (Fig. 3). It also appears that differences in the rate of recovery of wound–edge to scar breaking strengths exist between tissues as well. Native tissues with collagen bundles organized in a parallel orientation, as in fascia, ligament or tendon, regain breaking strength faster than tissue with a more complex, three dimensional fiber network, such as in the dermis. Another way to describe this is by measuring the recovery in relative breaking strength where wound progress is normalized to the uninjured tissue collagen content. The time required to achieve 50% unwounded breaking strength is greater in tissue with high collagen content, again, as in the case of dermis. Conversely, more "simply" arranged soft tissues like abdominal wall fascia, with lower tissue collagen content, but organized in a purely parallel manner along lines of tension, should achieve uninjured breaking strength faster.

Growth factors

Tissue growth factors are an important class of tissue repair signalling peptides up-regulated during the inflammatory phase of laparotomy wound healing. Five to 7 days are required, however, before peak levels of fibroproliferative growth factors like TGF-β are reached within acute wounds [32]. It is not known whether delays in the appearance of fibroproliferative growth factors contribute to the development of incisional hernias. Acute wound therapy with exogenous proliferative growth factors is known to accelerate the appearance of fibroblasts and collagen into the wound

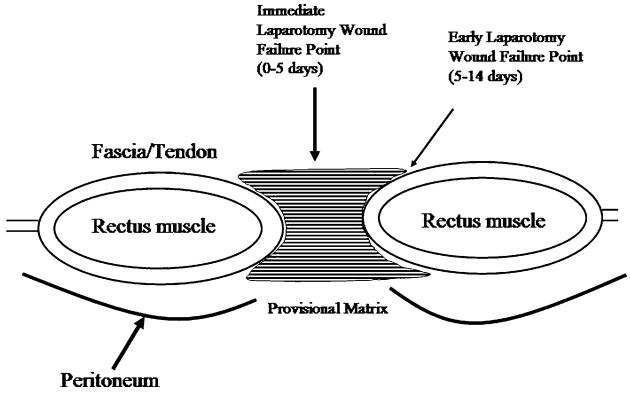

Fig. 3 Early incisional wound models found that a provisional wound matrix and early scar will mechanically fail within the scar itself only during the first 3–5 days after injury. Subsequently, mechanical failure is more likely to occur at the early scar to wound–edge interface

thereby shortening the natural inflammatory phase for gain in injured tissue tensile strength [33].

Nutrition

Tissue repair is an anabolic process that requires both energy and adequate nutritional building blocks. Patients who are malnourished or actively catabolic such as in the systemic inflammatory response syndrome demonstrate impaired healing. The National Surgery Quality Improvement Program sponsored by the Veterans Administration consistently measures low serum albumen as a risk factor for perioperative complications, including incisional hernia formation [34]. Inadequate nutrition also retards the immune response limiting opsonization of bacteria and sterilization of wounds. Several vitamin and mineral deficiencies also have been described that predispose to altered wound repair. Vitamins C, A, and B6 each are required for collagen synthesis and cross-linking. Deficiencies in Vitamins B1 and B2 as well as zinc and copper cause syndromes associated with poor wound repair. Finally, essential fatty acids are required for cell synthesis, particularly in areas of high cell turnover such as healing wounds.

Host stress response

Perioperative shock is a well-recognized risk factor for incisional hernia formation [35]. It is not clear whether the fundamental mechanism is tissue hypoperfusion, wound contamination or variability in surgical technique. The normal host stress response to injury functions to reestablish homeostasis via complex endocrine, metabolic, and immunologic alterations. The initial response is pro-inflammatory followed by counter-regulatory anti-inflammatory processes that restore normal equilibrium. Adverse physical conditioning of the host as well as significant physiologic injuries are known to affect the progress of acute wound healing. Advanced age, obesity, diabetes, and malnutrition have been shown both in humans and animal models to result in delays in the recovery of tissue breaking strength following injury [22]. Similarly, noxious insults such as grossly contaminated wounds or perioperative periods of hypotension and shock are associated with increased wound dehiscence. The physiological condition of the host is known to affect the progress of acute wound healing. Perioperative periods of hypotension and shock have been shown both in humans and animal models to result in profound delays in the recovery of tissue breaking strength following injury.

Mechanical components

Most studies designed to improve laparotomy and hernia wound outcomes have focused on surgical technique and the mechanical properties of suture material and mesh [36, 37]. During the evolution of inguinal hernia repairs, it was assumed that a strong, stout tissue such as the conjoined tendon rigidly sutured to a similarly stout structure such as Cooper's ligament would result in a reliable hernia repair with low recurrences. This and other essentially mechanical approaches to the problem of repairing a defect in the inguinal canal proved unreliable for most surgeons and recurrence rates remained unacceptably high.

Wound failure is most often due to suture pulling through adjacent tissue and not suture fracture or knot slippage [22]. Tissue failure occurs in the biochemical active zone adjacent to the acute wound edge where proteases activated during normal tissue repair result in a loss of native tissue integrity in the zone where sutures are placed. This is especially true for gastrointestinal anastamoses where a fall in wound tensile strength has been measured during the first 3 days following repair. The breakdown of the tissue matrix adjacent to the wound appears to be part of the mechanism for mobilizing the many cellular elements of acute tissue repair.

Bio-mechanical signalling pathways

Abdominal wall tendons and fascia are connective tissues placed under intrinsic and extrinsic loads that are likely dependent upon mechanical signals to regulate fibroblast homeostasis. Mechanotransduction pathways are being described in greater detail in ligament, tendon and bone repair [6, 7, 11]. It is becoming clear that in connective tissues, mechanical signals can be transmitted to the structural cell via integrin receptors, for example, and subsequently effect repair cell metabolism through the modulation of cytoskeleton anchoring proteins. In brief, a load imparted on a soft-tissue or bone is transmitted to structural cells through the extra-cellular matrix via transmembrane integrin receptors located on the cell surface. In one proliferative pathway that is being described, subsequent activation of the focal adhesion kinase (FAK) complex, leads to cytoskeletal changes, and the further activation of other downstream signalling tyrosine kinases like c-src and the MAP kinase proliferation pathway [38]. Ultimately, nuclear regulatory genes must be activated that are involved in the activation and regulation of tissue repair genes although detailed

mechanotransduction pathways for soft-tissue repair are not yet worked out.

The varying mechanical forces exerted across anatomically different celiotomy incisions such as midline versus transverse therefore may affect repair fibroblast activation, provisional matrix assembly and collagen deposition and ultimately the temporal recovery of laparotomy wound tensile strength. Surgical experience has long held that transverse abdominal wall incisions oriented parallel to the predominant myofascial fibers regain unwounded tissue strength faster, but a clear benefit on wound outcomes has never been proven [22].

Optimized laparotomy wound healing therefore depends on the normal assimilation of both biological and mechanical signals. Factors that interfere with either or both of these pathways will result in delays or defects in the early phases of acute wound healing. From the "biological" perspective this most commonly includes infection, ischemia, malnutrition and pharmacological inhibitors. From the "mechanical" perspective this involves the reinforcing cycle of wound failure with a loss in optimal strain loads and a down-regulation of the mechanotransduction pathways normally activated to signal tissue repair. In one extreme this is due to acute wound overload and overt mechanical failure and in the other extreme may be due to acute wound under load due to a poor suturing technique or even the placement of a bridging mesh implant.

Preliminary observations found for the first time that an interactive biomechanical mechanism may be activated during acute laparotomy wound failure. In other words, "mechanical" failure alone might result in the abnormal function of repair cells. Fibroblasts isolated from otherwise normal rat hernias were observed to cause 50–75% less contraction of a fibroblast populated collagen lattice (FPCL) than those fibroblasts isolated from a normally healing wound. One possible mechanism for this loss in repair fibroblast kinetic and proliferative activity may be the reduction in mechanical signals that occurs as a structural soft tissue fails. As already discussed, it is known in tendon and ligament repair, that mechanotransduction is an important pathway for setting fibroblast repair function. From this perspective, an abdominal wall laparotomy wound behaves more like a ligament or tendon than skin during repair.

Laparotomy wounds and incisional hernias injure the entire abdominal wall

Our laboratory develops models of incisional hernias in order to study the mechanism of acute wound healing during hernia formation and recurrence. As described above, well-controlled, prospective studies conclude that most laparotomy wound disruptions progressing to incisional hernias begin to form within 30 days of laparotomy wound closure [12]. In the hernia models, laparotomy wounds on the ventral abdominal wall of rats are temporarily repaired with rapidly absorbed suture. Laparotomy wound–edge separation occurs early, progressing to incisional hernia formation due to incompletely supported mechanical loads. The incisional hernias that develop have well-defined hernia rings, hernia sacs and visceral adhesions, all characteristic of the incisional hernias that develop in humans (Fig. 4). The function of intact abdominal wall structures during laparotomy repair can be measured, including distractive load-forces generated by the lateral oblique and midline rectus muscle and fascial components. We have observed not only the induction of wound healing defects within laparotomy wound fibroblasts during herniation, but pathological disuse atrophy, fibrosis and muscle fiber type changes in abdominal wall muscles during incisional herniation [39, 40]. The pathological changes in the lateral abdominal wall musculature support the important role load

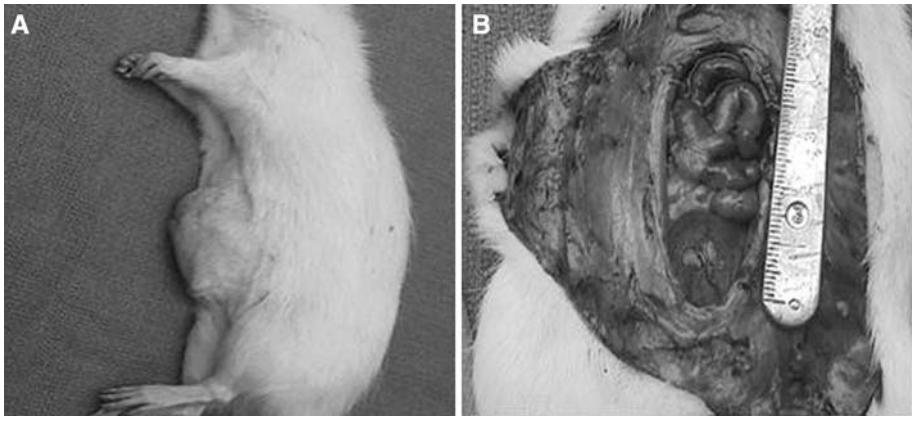

Fig. 4 **a** Early laparotomy wound failure will lead to incisional hernias in the rat model. **b** The abdominal wall defects form hernial rings, visceral adhesions, hernial sacs and lateral abdominal wall muscle shortening and fibrosis

signaling may play in abdominal wall wound repair. This is not surprising given the important function of the abdominal wall to support and animate the torso and to protect intra-abdominal organs. Surgically, it is equally likely that these pathological changes that result in reduced lateral abdominal wall compliance contribute to the difficulty in achieving durable ventral incisional hernia repairs.

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