Acute wound healing: the biology of acute wound failure

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Successful surgical therapy depends on predictable and reliable acute wound healing. Despite improvements in surgical techniques, acute wound healing failure remains a dreaded complication for all surgical disciplines. For the general surgeon, acute wound healing failure leads to fascial dehiscence, incisional hernias, gastrointestinal anastomotic leaks, fistulas, and vascular pseudoaneurysms. Each example of acute wound healing failure results in further morbidity and mortality for surgical patients.

Optimizing the management of acute wounds has been a major goal of surgical science over the past 100 years. Primary strategies have relied mainly on mechanical approaches to the problem of acute wound healing failure. Examples include varying the orientation of abdominal wall incisions, optimizing suture length–to–wound length ratios for abdominal wall fascial closures, and using stout prosthetic mesh materials to reinforce repairs \cite{1}. Purely mechanical approaches to the problem of acute wound healing failure ignore the important role the biologic response of injured tissue has in wound healing outcomes, however. The increasingly sophisticated understanding of the basic cellular and molecular mechanisms of acute tissue repair has yet to be translated into meaningful clinical applications.
Definitions

Acute wounds and acute wound healing

An acute wound is defined as the traumatic loss of normal structure and function to recently uninjured tissue after a noxious insult. 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 [2]. The integrated summation of each pathway along the continuum of this host response to injury results in acute wound healing (Fig. 1). Classically the phases of acute wound healing are described as hemostasis, inflammation, fibroproliferation (scar formation), and scar remodeling.

Acute wound failure

Acute wound healing failure occurs when there is an abnormality in the degree or duration of the sequential components of tissue repair. Inadequate hemostasis because of platelet dysfunction or poor technique can result in
hematoma formation with ensuing mechanical disruption of a provisional wound matrix. Delayed or deficient inflammatory responses can result in wound contamination or infection with abnormal signaling for progression into the fibroproliferative phase of acute tissue repair. A prolonged inflammatory response resulting from the presence of a foreign material or wound infection delays the progression of acute wound healing into the fibroproliferative phase, when rapid gains in breaking strength should occur. Delayed fibroblast responses impede the establishment of a provisional matrix and laying down of an early scar, prolonging the period that a wound is subjected to increasing mechanical loads and dependent entirely on suture material for strength. Ultimately the time required for the recovery of wound breaking strength determines the risk of acute wound failure.

The outcome of acute wound healing failure can be measured in many ways. Wound infections are a major concern for all practicing surgeons and are a form 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 also are forms of acute wound healing failure. Several studies now suggest abnormalities in hypertrophic scar fibroblast function [3]. 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, 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. Burst abdomens have long been associated with mortalities of almost 50% [4]. Less dramatic are incisural hernias, another example of acute fascial wound healing failure that is a large source of surgical morbidity. “Too little” acute repair occurring “too late” results in holes in celiotomy closures and leaks in intestinal and vascular anastomoses. In each case, the axial loads placed across the abdominal wall or the radial forces placed on an anastomosis exceed the resistive forces generated by the suture line and early scar.

**Magnitude of the problem**

Nearly 50 million operations are performed each year in the United States [5]. This number does not include the annual estimated 50 million
traumatic wounds [6]. Recovery from these procedures and injuries conservatively costs 250 million patient-days in lost productivity and billions of dollars in lost or supplemented earnings. Acute wound complications add to these numbers. Despite technical advances, the incidence of fascial dehiscence, incisional hernia formation, gastrointestinal anastomotic breakdown, pancreatic fistulas, and vascular pseudoaneurysms has not declined substantially in 75 years of modern surgery [6]. In 1997, the National Center for Health Statistics reported more than 100,000 operations annually for recurrent inguinal hernia, 110,000 incisional (ventral) hernia repairs, and an approximately 10% to 30% leak rate after pancreatic and colorectal operations [5]. These are just a few examples of acute wound healing failure.

**Mechanism of acute wound failure**

**Biologic components**

Acute wound healing failure occurs when the load placed across the wound exceeds the resistive capacity of the suture line and provisional matrix. Usually this situation occurs when there is abnormal progression through the integrated phases of acute tissue repair. Successful acute wound healing depends on timely, effective, and regulated hemostasis, inflammation, proliferation, and remodeling (Fig. 2). 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**

After formation of a stable clot, inflammatory cells marginate into the injured tissue, and an efflux of leukocytes and plasma proteins enters the wound site. Neutrophils arrive initially and sterilize and débride the wound but are not required for tissue repair in clean wounds. Monocytes and tissue macrophages predominate in the inflammatory infiltrate within 2 to 3 days. Macrophages phagocytose injured tissue and debris and secrete multiple growth factors. The macrophage orchestrates tissue repair and seems to be the only inflammatory cell type absolutely required [7].

Overall tissue strength of a wound is essentially zero during this inflammatory phase, and an excessive or prolonged inflammatory response, as is seen with incisional foreign bodies or infections, predisposes to wound failure. Steroids can reduce wound inflammation but also inhibit collagen synthesis and wound contraction synergistically, impeding tissue repair [8]. 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 [9]. Shah and colleagues [10] showed that
neutralization of transforming growth factor (TGF)-β decreases the inflammatory response and results in less scar formation in postnatal wounds, suggesting a central role of this growth hormone in the initial phase of fibroplastic tissue repair.

Fibroblasts

Much has been learned about fibroblast function during normal dermal repair. Fibroblasts migrate into acute wounds within 2 days, and they are the major cell type of granulation tissue by postinjury day 4. At first, fibroblasts populate the wound site through migration and increase in number by proliferation. Wound fibroblast migration and proliferation are influenced by soluble growth factors and inflammatory mediators [11]. The chemical and structural composition of the provisional matrix on which fibroblasts move is equally important. Receptor mediated interactions
between the wound extracellular matrix and activated repair fibroblasts is increasingly understood. Little is known, however, about defective fibroblast function during acute wound failure, and it is likely that defects in any or all of these repair pathways exist. Less is known regarding the behavior of repair fibroblasts in nondermal tissues. The mechanism for modulating the distribution of fascial repair fibroblast proliferative, growth, and synthetic activity is incompletely understood. Whether fascial wound failure reflects a defect in fascial fibroblast recruitment and function during incisional hernia formation or abnormal mechanical signals after fascial 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 fascial fibroblasts and acute wound failure.

Most cell-cycling studies in wound repair to date have focused on keratinocytes in models of reepithelialization. A defect was described in fibroblast cell-cycling activity in chronic pressure ulcers [12,13]. 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 (Fig. 3). 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 was 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

Cell Cycling in Wound Healing

Fig. 3. Abnormalities in the proportion of wound repair cells restricted to cell cycle quiescence, senescence, or even apoptotic pathways might explain delays in wound healing. Increased numbers of repair fibroblasts confined to G1 arrest have been measured in nonhealing ulcers and in a model of incisional hernia (thin arrows). Proliferating cell nuclear antigen (PCNA) is a classic marker of cells capable of DNA synthesis and cell cycle progression, whereas p21 is a cell cycle inhibitor. Increased numbers of arrested fibroblasts expressing p21 and reduced numbers expressing PCNA have been observed in nonhealing ulcers and in a model of fascial wound failure leading to incisional hernia formation. M, mitosis; S, synthesis; thick arrows, normal progress of the cell cycle.
recruitment of fascial fibroblasts into the cell cycle might contribute to delays in fascial repair and ultimately fascial 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 chronic ulcer studies, it was suggested that low wound growth factor levels might result in dermal fibroblast quiescence and senescence [14]. This situation also may be true in failing acute fascial wounds as an initially rapid rising growth factor signaling cascade became depleted. Relative fascial wound ischemia also might induce fibroblast cell cycle arrest. This ischemia would occur when a suture line is closed too tight or in a patient who is in shock and soft tissue perfusion is reduced. A relatively ischemic fascial repair might be deficient in the components and cofactors required for DNA and protein synthesis, resulting in repair fibroblast cell cycle arrest. Too little or too much tension across the fascial repair may disturb the optimal set-point of a normal mechanotransduction mechanism, resulting in premature fascial fibroblast cell cycle arrest.

The precise histologic origin of fascial fibroblast repair cells in healed versus herniated wounds is unknown. Differences may exist in the chemotactic response of ventral (anterior) myofascial versus mesothelial surface fibroblasts after midline incisions. It is known that peritoneal surface defects heal by simultaneously reepithelializing the entire wound surface as opposed to establishing an advancing epithelial edge as occurs in the skin [15,16]. 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 fascial repair in the abdominal wall. During fetal wound healing, amniotic fluid can accelerate the recovery of wound breaking strength and minimize the amount of scar formation [17].

Defects have been identified in the kinetic properties of fibroblasts cultured from fascial biopsy specimens obtained from a rat model of incisional hernias (MG Franz, personal communication, March, 2002). In these studies, it was observed that fibroblasts cultured from incisional hernias were significantly deficient in causing the contraction of fibroblast-populated collagen lattices. Normally healing fascial fibroblasts caused 80% lattice contraction over 5 days, whereas hernia fibroblasts caused only 50% lattice contraction. These same studies found no difference in the level of collagen gene expression between herniated and healed fascial wounds after 28 days. The results were interpreted to suggest that any difference in collagen gene expression is occurring earlier than postoperative day 28 of fascial repair in this model or that the defect in herniated fascial wounds is not one of collagen gene expression. Other possibilities included downstream abnormalities in collagen protein synthesis and assembly, early scar crystallization, and fibroblast kinetic activity.
Collagen

Abnormalities in collagen metabolism have been observed in several models of acute wound healing failure. Usually the problem results in either delayed or deficient 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 and an increased risk of acute mechanical wound failure [18,19]. Preliminary reports describing abnormalities in collagen metabolism have been described in small series of incisional hernias and direct inguinal hernias [20,21]. Abnormalities in the ratios of collagen isoform expression, decreased collagen cross-linking, and increased metalloproteinase activity have been described. A twofold increase in the amount of type III collagen has been reported in the skin fibroblasts of patients with inguinal hernias compared with controls [22]. A genetic predisposition to the formation of abdominal wall hernias also has been observed in large, controlled series of patients with abdominal aortic aneurysms, supporting the long-held impression of a common defect in vascular wall and abdominal wall collagen metabolism [23–27].

The mechanism by which an acute scar attaches to uninjured tissue at the wound border also is poorly understood. This conceptual deficiency is important because many acute wounds likely fail at the scar–to–normal tissue interface [28]. Animal models suggest that a provisional matrix and early scar mechanically fail within the scar matrix itself only during the first 3 to 5 days after injury. After that, mechanical failure is more likely to occur at the early scar–to–wound edge interface (Fig. 4). It also seems that differences in the rate of recovery of wound edge to scar breaking strengths exist between tissues. 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 [29,30]. Another way to describe this situation is by measuring the recovery in relative breaking strength in which 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, as in the case of dermis. Conversely, more “simply” arranged soft tissues, such as fascia with lower tissue collagen content but organized in a purely parallel manner along lines of tension, achieve uninjured breaking strength faster.

Growth factors

Tissue growth factors are an important class of tissue repair signaling peptides upregulated during the inflammatory phase of acute wound healing. Five to seven days are required, however, before peak levels of fibroproliferative growth factors such as TGF-β are reached within acute wounds [31–33]. It is unknown whether delays in the appearance of fibroproliferative growth factors contribute to the development of incisional
hernias. Acute wound therapy with exogenous proliferative growth factors accelerates the appearance of fibroblasts and collagen into the wound, shortening the natural inflammatory phase for gain in injured tissue tensile strength [34]. Several reports have shown the ability of TGF-β to accelerate the recovery of tensile strength in acute dermal and fascial incisions [32,35]. The effect of TGF-β or other fibroproliferative growth factors on the mesh-fascial interface is unknown.

Nutrition

Tissue repair is an anabolic process that requires energy and adequate nutritional building blocks. Patients who are malnourished or actively catabolic, such as patients with the systemic inflammatory response syndrome, show impaired healing [36]. 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, zinc, and copper cause syndromes associated with poor wound repair. Essential fatty acids are required for cell synthesis, particularly in areas of high cell turnover, such as healing wounds.

Host stress response

The normal host stress response to injury functions to reestablish homeostasis through complex endocrine, metabolic, and immunologic alterations. The initial response is proinflammatory followed by counter-regulatory anti-inflammatory processes that restore normal equilibrium.
Adverse physical conditioning of the host and significant physiologic injuries are known to affect the progress of acute wound healing. Advanced age, obesity, diabetes, and malnutrition have been shown in humans and animal models to result in delays in the recovery of tissue breaking strength after injury [4]. Similarly, noxious insults, such as grossly contaminated wounds or perioperative periods of hypotension and shock, are associated with increased wound dehiscence [37,38]. The physiologic condition of the host is known to affect the progress of acute wound healing. Perioperative periods of hypotension and shock have been shown in humans and animal models to result in profound delays in the recovery of tissue breaking strength after injury.

**Mechanical components**

Most studies designed to improve acute wound outcomes have focused on surgical technique and the mechanical properties of suture material [4,39,40]. 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 most often is due to suture pulling through adjacent tissue and not suture fracture or knot slippage [4,41]. Tissue failure occurs in the biochemically 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 [40]. This situation is especially true for gastrointestinal anastomoses, in which a fall in wound tensile strength has been measured during the first 3 days after repair [13,42–46]. The breakdown of the tissue matrix adjacent to the wound seems to be part of the mechanism for mobilizing the many cellular elements of acute tissue repair.

**Abdominal wall wound closure**

For secure abdominal wall closures, the reduced tissue integrity along the border of the acute wound led to development of the concept of an optimal suture length–to–wound length (SL-to-WL) ratio for the primary closure of midline celiotomies [47]. Well-done, large, prospective studies with the best follow-up found that a SL-to-WL ratio of approximately 4:1 minimized the incidence of fascial dehiscence and incisional hernia formation; this is where the surgical training dictum of 1-cm “bites” followed by 1 cm of progress originated. Theoretically the optimal SL-to-WL ratio affords adequate approximation and coaptation of abdominal wall tissues to maximize repair, while minimizing the effect of increased tension along the suture line.
Increased tension along the suture line results in failure at the suture–to–native tissue interface, as mentioned, and ischemia in the wound. It is well known that ischemia alone delays the recovery of tensile strength in incisional wounds [48,49]. The flexibility and extensibility provided by the 4:1 SL-to-WL ratio theoretically minimizes the tension placed along the suture line, although this is difficult to measure in vivo. Similar studies showed that mass abdominal wall closure was equally as effective for reducing the incidence of acute fascial wound failure as layered closures and that interrupted suturing offered no advantage.

More recent animal studies show that optimal mechanical signaling is important to the progress of acute wound healing. Mechanical signaling pathways are important for the regulation of acute tissue repair [29,50,51]. From this perspective, the midline fascia is behaving more like a ligament or tendon than skin. Classic surgical studies from the 1970s found that scars placed under mechanical loads ultimately behave more like tendons [52]. It also was observed that incisions placed under “low” loads organized scars with reduced tensile strengths [35]. The empirical observation that a SL-to-WL ratio of 4:1 results in the most reliable midline abdominal wall closure may reflect the technique resulting in establishing the optimal acute wound healing load set-point for the abdominal wall.

**Mesh**

Synthetic soft tissue prostheses were introduced to the management of acute wounds to replace soft tissue defects and to decrease the amount of tension (load) placed across suture lines in an effort to offset mechanical distractive forces and to promote optimal acute tissue repair. Despite its widespread use, the short-term and long-term biologic mechanism of mesh incorporation into the abdominal wall is poorly understood. Normal mesh incorporation involves a slightly prolonged cellular inflammatory phase and depends on fibroblast activation and “in-growth” of the mesh interstices to achieve functional tensile strength [53–55]. The detailed time course and mechanism of fascial fibroblast activation after mesh closure are unknown. It is not known whether repair fibroblast activation in the mesh/wound microenvironment differs from that of a primary fascial wound closure. It also is not known if the presence of mesh itself induces abnormal fascial repair fibroblast activation and contributes to the high incidence of recurrent incisional hernias even after mesh repairs [56].

The repair of ventral incisional hernias has suffered from the inadequacy of purely mechanical surgical approaches. The introduction of mesh incisional herniorrhaphy has improved outcomes after incisional hernia repair only modestly, with reported recurrences rates with mesh remaining 34% [56]. The benefit of mesh most likely is the result of reduced tension and ischemia along the suture line. It is unlikely that mesh will ever be used to secure primary abdominal wall closures because of the bulk of foreign material applied. The advantage of decreased tension provided by a mesh
prosthesis closure is balanced against the induction of prolonged and abnormal inflammatory and early proliferative responses. The effect of mesh on repair fibroblast function is unknown. The prolonged tissue inflammatory response induced by the foreign material hypothetically could delay progression of the acute wound healing trajectory into a normal fibroproliferative phase through the delay in the appearance of proliferative growth factors, such as TGF-β. A purely mechanical approach to acute fascial wound failure has not reduced significantly the incidence of this important surgical problem, and no biologic wound healing interventions exist.

**Biomechanical concept**

The abdominal wall fascia is a connective tissue likely dependent on mechanical signals to regulate fascial fibroblast homeostasis. Mechanotransduction pathways are beginning to be described in ligament and bone repair [28,50,51]. In connective tissues, mechanical signals can be transmitted to the structural cell through integrin receptors and subsequently affect 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 extracellular matrix by transmembrane integrin receptors located on the cell surface. In one proliferative pathway that is being described, subsequent activation of the focal adhesion kinase complex leads to cytoskeletal changes and the further activation of other downstream signaling tyrosine kinases, such as c-src and the Mitogen Activated Protein (MAP) kinase proliferation pathway. 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 [28,50,51].

The varying mechanical forces exerted across anatomically different celiotomy incisions, such as midline versus transverse, may affect repair fibroblast activation, provisional matrix assembly, collagen deposition, and ultimately the temporal recovery of fascial tensile strength. Surgical clinical experience has long held that transverse abdominal wall incisions oriented parallel to the predominant myofascial fibers regain unwounded tissue strength faster and to a greater extent, but a clear benefit on wound outcomes has never been proved [4,57].

Optimized acute wound healing depends on the normal assimilation of biologic and mechanical signals. Factors that interfere with either or both of these pathways result in delays or deficiencies in the early phases of acute wound healing. From the biologic perspective, these factors most commonly include infection, ischemia, malnutrition, and pharmacologic inhibitors. From the mechanical perspective, factors include the reinforcing cycle of wound failure with a loss in optimal strain loads and a downregulation of the mechanotransduction pathways normally activated to signal tissue...
repair. In one extreme, this downregulation is due to acute wound overload and overt mechanical failure, and in the other extreme, it may be due to acute wound under-load because of a poor suturing technique.

Preliminary observations found for the first time that an interactive biomechanical mechanism may be activated during acute fascial wound failure. In other words, “mechanical” failure alone might result in the abnormal function of repair cells. Fibroblasts isolated from rat and human hernias have been observed to be 50% to 75% less efficient in causing the contraction of a fibroblast-populated collagen lattice. 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. It is well known in tendon and ligament repair that mechanotransduction is an important pathway for setting fibroblast repair function [50,51]. From this perspective, an abdominal wall fascial wound behaves more like a ligament or tendon than skin during repair.

**Incisional hernias**

Each year in the United States, 4 million abdominal operations are performed [5]. Large, prospective, well-controlled series found that 11% to 20% of abdominal wall fascial closures fail, leading to ventral incisional hernia formation [56]. The true national incidence of ventral fascial wound failure is greater than 400,000 cases per year. These numbers suggest that more than 200,000 incisional hernias remain occult and go untreated. All general surgeons appreciate the frustration that is met with efforts to repair what otherwise presents as a simple abdominal wall defect. The recurrence rate of incisional hernias after repair is also high (24% to 58%), suggesting a biologic defect that predisposes to acute fascial wound failure [22,56].

Incisional hernias provide a useful paradigm to study acute wound healing failure. Biologic and mechanical components can contribute to fascial wound healing failure. Incisional hernias are dangerous because of the risk for bowel incarceration, obstruction, and strangulation. They never resolve spontaneously and usually increase in size over time.

The high incidence and recurrence rates for incisional hernias have not changed appreciably in 75 years [4]. Despite its clinical importance, the pathophysiology and time course of incisional hernia formation is poorly understood. Clinical experience suggests a biologic and mechanical component. From a biologic standpoint, it is generally accepted that certain patient characteristics increase the risk for incisional hernia formation. The most frequently reported biologic risk factors include deep wound infections, tissue hypoperfusion (shock), and malnutrition [22,56]. These observations point to a biologic defect in the activation and progression of the acute wound healing trajectory. Other well-described risk factors for incisional hernia formation point to mechanical components, including closure under tension, suture fracture, knot slippage, fascial tearing, and sub-optimal SL-to-SW ratio [4].
Most biomechanical failures occur early on the acute wound healing trajectory at a time when wound tensile strength is essentially zero and patients are recovering and increasing the loads placed across the abdominal wall [32,41]. A common feature of the mechanical risk factors for acute fascial wound healing failure is tissue ischemia along the suture line that is induced by the increased abdominal wall loads. The two most likely mechanisms for acute fascial wound failure leading to incisional hernia formation can be summarized as follows: A defect or delay in repair cell activation and provisional wound matrix crystallization during acute fascial repair leads to herniation (the biologic mechanism), or herniation resulting from mechanical failure leads to a delay or deficiency in the acute wound healing process (the mechanotransduction mechanism). It is also possible that both mechanisms are active in a reinforcing cycle of acute wound failure and herniation (Fig. 5).

**New approaches for preventing acute wound failure**

The goal of most acute wound healing research is to define better the combined biomechanical mechanism of acute wound healing failure at the tissue, cellular, and molecular levels. A major focus is fibroblast activation out of quiescence and cell cycle progression after surgical injury and how this correlates with the quality of early tissue repair. The recruitment of inflammatory cell mediators, fibroplasia, angiogenesis, and ultimately the recovery of wound breaking strength is measured. Specific attention also is being directed toward characterizing the biology of the mesh-fascial interface and how this wound healing microenvironment compares with primary fascial closure.

![Biological acute wound failure](image)

**Biological acute wound failure**

1. Impaired fibroblast function → Reduced acute wound breaking strength
2. Reduced mechanotransduction signal

**Mechanical acute wound failure**

Fig. 5. Acute fascial wound failure occurs if there is a defect or delay in repair cell activation and provisional wound matrix crystallization (the biologic mechanism) or if mechanical loads exceed the capacity of suture material, and the ensuing mechanical failure results in delayed or deficient mechanotransduction. When under way, a reinforcing cycle of biologic and mechanical acute wound failure pathways exists leading to herniation.
Acute wound healing trajectories

Time is perhaps the most important independent variable of acute wound healing. All of the repair pathways activated at the moment of injury, from hemostasis and early inflammation through fibroplasia and scar remodeling, require inherent periods of time. Theoretically, there is a biologic lower limit to the amount of time required to organize and mature an acute wound. Most graphic depictions of the progress of acute wound healing are sigmoid in shape with time plotted along the x-axis (see Fig. 2). The outcome measure expressed along the y-axis is typically wound breaking or tensile strengths. Given the limitations in measuring the progress of acute tissue repair in humans, most of this information is derived from animal studies. Expressed in this way, acute wound healing trajectories classically are described as beginning with a flat “lag phase” representing the activation of inflammatory and early matrix pathways. During this time, the risk of acute wound failure is greatest. The lag phase is followed by a steep rise in the slope of acute wound healing, representative of rapid fibroproliferation. The later flattening out of the acute wound healing trajectory represents a return to scar/wound homeostasis, when collagen turnover continues, but there is no further gain in wound collagen content. This period most often is defined as the remodeling phase.

When considered as a continuum, the progress of acute wound healing is more meaningful. Observing a single measurement of wound healing outcomes over time is subject to the huge variability in the quantification of acute tissue repair. A “normal” acute wound healing trajectory represents the mean over multiple observations. “Impaired” acute wound healing would occur when impediments to any or all of the acute wound healing pathways are active and result in a “shift to the right” of the acute wound healing trajectory. “Ideal” acute wound healing would be defined as the theoretical limit of any “shift to the left” of acute wound healing. This ideal healing would be achieved by accelerating any of the components of the acute tissue repair process.

Nothing yet proposed can alter the passage of time, but it may be possible to accelerate individual or all of the time-dependent components of the acute wound healing process closer to the biologic limit to achieve a protective wound breaking strength sooner. Some argue that any attempt to accelerate acute wound healing is futile, asserting that “normal” wound healing represents the biologic limit. A useful analogy is to consider the time required for an embryo to develop. There is a minimum time requirement for all of the complex cellular and molecular systems to operate, and any chance for accelerating embryonic development would be limited by this constant. There are major differences between embryonic tissue generation and acute tissue repair and regeneration after injury. In the case of a wound, the diploid cellular elements required for tissue repair are all in place before injury. In the case of surgical procedures, the moment of tissue injury is known. One strategy is to “preactivate” the cellular and molecular
components of acute tissue repair before injury. The emergence of cloned growth factors capable of pharmacologically initiating or propagating the acute wound healing cascade makes this idea feasible [10,32].

Delayed primary closure

The only surgical technique known to accelerate incisional healing is delayed primary closure of the dermis [58]. Using this approach, a dermal wound that is closed 3 to 5 days after developing a bed of granulation tissue develops breaking strength significantly faster over 10 days than an identical wound created and closed at the same time. The technique most often is applied to situations of gross wound contamination in an effort to reduce the wound bacteria counts and to bring the wound into bacterial balance before closure [17]. Wound bacterial contamination is not a requirement, however, for the phenomenon of accelerated acute tissue repair after delayed primary closure. The mechanism for accelerated repair after delayed primary closure undoubtedly involves the fact that the cellular and molecular elements of tissue repair are activated and recruited into place before wound closure. Delayed primary closure is impractical, however, for abdominal wall fascial closure, where evisceration would occur.

Priming of acute wound healing

The authors’ laboratory has been developing the concept that many acute fascial wound failures occur early in the postoperative period at a time when wound breaking strength is essentially zero at the same time abdominal wall loads are increasing. Clinical data are available pointing toward early postoperative wound failure as a predominant mechanism for the formation of incisional hernias [32,41]. The delay in recovery of fascial wound tensile strength occurs during the lag phase of acute tissue repair because of the time required to activate the complex cellular and molecular structural and signaling elements.

The observations made after delayed primary closure led the authors to develop the concept of therapeutic “priming” of potential fascial wound sites with peptide growth factors. Priming is defined here as infiltrating the wound site with a fibroproliferative growth factor before making the incision in an effort to preactivate the cellular elements of fascial repair. The theory is that the chemotactic and growth signaling properties of tissue growth factors, such as TGF-β, also would result in the recruitment of the cellular and molecular components of tissue repair into the site of an acute wound before injury [10,32,59,60]. Preliminary data in a rat model suggest this approach can reduce or eliminate the fascial wound failure and incisional hernia formation. Ongoing studies also are measuring the effect of growth factor priming on the incorporation of mesh materials into the fascial layer of the abdominal wall and the incidence of recurrent incisional hernias, the time course for the recovery of mesh scar tensile and breaking strengths, and recruitment and activation of repair fibroblasts.
Summary

Acute wound healing failure is an important source of morbidity and mortality for surgical patients. Many incisional hernias, gastrointestinal anastomotic leaks, and vascular pseudoaneurysms occur despite patient optimization and standardized surgical technique. Modern surgical experience suggests that biologic and mechanical pathways overlap during “normal” acute wound healing. The cellular and molecular processes activated to repair tissue from the moment of injury are under the control of biologic and mechanical signals. Successful acute wound healing occurs when a dynamic balance is met between the loads placed across a provisional matrix and the feedback and feed-forward responses of repair cells.

References


