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The biology of adhesion formation in the peritoneal cavity

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ABSTRACT

Intraperitoneal adhesions are frequently encountered and present significant challenges to the practicing surgeon, including increased operating time, bowel obstruction, pelvic pain, and infertility. Until recently, however, our knowledge of the biology of adhesion formation within the peritoneal cavity has been limited, which in turn limits prevention and treatment strategies for surgical patients. Extensive research has now led to an increased understanding of adhesion formation, with hypoxia playing a central role. Hypoxia stimulates a cascade that leads to oxidative stress, anaerobic metabolism, formation of free radicals, and ultimately the adhesion phenotype. By understanding the precipitants to adhesion development, we may begin to develop prevention and treatment therapies that will provide clinically significant improvement over the currently available approaches to limit postoperative adhesions.

Introduction

Adhesions, defined as abnormal fibrous connections joining tissue surfaces at non-anatomic locations, are generated between adjacent tissues and organs that are injured during surgery and are a sequel of the healing process.[1,2] They are encountered frequently and present many challenges for the practicing surgeon. Occurring in up to 55–100% of women who underwent second-look laparoscopies after gynecologic procedures, this rate is similar in men and women who undergo general surgical procedures.[3–5] It is now clear that adhesions occur after all types of intra-abdominal procedures, regardless of surgical approach (laparotomy versus laparoscopy), and the likelihood of adhesion reformation is high, with sites such as the ovary after laparotomy or laparoscopy recurring as frequently as 65–80%.[1,6] The clinical consequences of adhesions are significant; these include bowel obstruction, infertility, pelvic pain, increased operating time due to extensive adhesiolysis, and increased morbidity. In addition, the economic burden of adhesions (calculated as hospital cost plus surgeon fees for all adhesion-related admissions) in the United States, as reported by Ray et al.[7] in 1998, was estimated at 1437.1 million per year, but this figure does not include the additional burden of outpatient expenditures and loss of work.

Adhesions can generate de-novo (the development of adhesions at sites that initially did not undergo adhesiolysis), or they can re-form (the redevelopment of adhesions at sites after adhesiolysis).[3,8] They can be quantified intra-operatively by adhesion scoring systems, which takes into account the type, extent, and anatomic location of the adhesions.[1] Although adhesion scoring systems provide a basis by which physicians can describe adhesions and correlate management and outcomes, agreement does not always exist. In a study reviewing 13 gynecologic surgical procedures by 11 experienced laparoscopic surgeons, there was only a 64% positive correlation between scoring physicians using the AFS system, but this increased to 89% positive correlation using a more complex scoring system.[9] Agreement is also lacking in the extent to which adhesions cause pain as well as management of these adhesions. In a survey of 13 gynecologic surgeons regarding the likelihood of an adhesion to cause pain at a particular location, surgeons tended to associate more dense adhesions with pain; however, the maximum percentage of patients thought to have pain related to adhesions was 60–70%; thus demonstrating that some patients with dense adhesions have been found to be pain free.[10] Need for lysis of adhesions was also thought to be proportional to the extent of adhesive disease, with 83% of surgeons recommending surgery for sites 80% involved in adhesions. The site of adhesions was also felt to be important with all surgeons recommending surgery for adhesions involving 50% of adnexal structures.[10]

As a means for evaluating adhesions at the time of second-look laparoscopies in gynecologic patients, Diamond and Nezhat developed a classification system for postoperative adhesion development, which recognizes an understanding of adhesion formation and reformation. Adhesions were divided into Type I, de novo adhesions, or Type 2, adhesion reformation. The two types were further divided into two subgroups based on whether surgical procedures were conducted at each site. The likelihood of postoperative adhesion development appeared to be highest at sites

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with adhesiolysis and surgical treatment of pathology (such as treatment of an ovarian endometrioma in an ovary adhered to the pelvic sidewall) and lowest at sites without surgical procedures or adhesiolysis. The likelihood of recurrence for all sites, from most encountered to least encountered was as follows: 2b—adhesiolysis and treatment of pathology >2a—sites of adhesiolysis alone >1b—sites of surgical procedures without adhesions >1a—de novo formation.[11] These findings of adhesion development provide a basis for understanding the potential efficacy of surgical approaches or anti-adhesion adjuvants to target therapies for postoperative adhesions 1a > 1b > 2a > 2b.[11]

Normal peritoneal repair

The peritoneal surface is a serous membrane lined by mesothelial cells loosely attached to the basement membrane, under which lies the extracellular matrix. The extracellular matrix contains many components essential to healing, including collagen (specifically collagen I and collagen III), fibronectin, glycoproteins, fibroblasts, macrophages, along with blood and lymphatic vessels.[11,12] Normal peritoneal repair is a complex process involving the interplay of several events including inflammation, angiogenesis, cell migration, and turnover of the extracellular matrix.[2] Once the peritoneal surface is injured, this triggers an exudation of a high-protein fluid, known as the provisional matrix, containing fibrin, histamines, monocytes, plasma cells, polymorphonuclearcytes (PMNs), macrophages, mesothelial cells, and histiocytes.[2,11,13] This fluid coagulates within 3 h and forms fibrous bands between corresponding surfaces and maintains their contact.[2] In response to injury, macrophages exhibit increased phagocytic, respiratory burst and secretory activity; they also recruit new mesothelial and fibroblast cells and are the major components of the leukocyte populations after day 5.[11] Normal fibrinolysis inhibits the development of adhesions within 72 h. If this mass persists during the period of peritoneal repair (usually 3–5 days), then underlying fibroblasts migrate into the fibrinous mass. Fibroblasts deposit extracellular matrix, including collagen and fibronectin, which form the scaffold for sheets of mesothelial cells, leading to reepithelialization and thus adhesion formation.[14]

Essential to the peritoneal healing process is an autocrine/paracrine feedback, as the peritoneum is constantly exposed to growth factors and cytokines in the peritoneal fluid (Table 1). These are synthesized by mesothelial cells and activated macrophages within the wound and must be optimal, precise, and synchronized for healing to occur. If these factors are inhibited, interrupted, or overexpressed, this can lead to nonhealing or adhesion formation.[12] In addition to the feedback system, a variety of other processes affect peritoneal healing including migration; proliferation; apoptosis; and/or differentiation of many cells types, including inflammatory cells, immune cells, mesothelial, cells and fibroblasts. These cells then produce molecules, which regulate proteolysis, tissue remodeling, angiogenesis, and synthesis and deposition of the ECM.[12]

The peritoneal lining has intrinsic fibrinolytic activity, which modulates fibrin degradation that results from fibrin deposition after injury.[11] If this activity is decreased (via hypoxia, trauma, or infection), then there is an increased incidence of adhesions.[11] Therefore, normal peritoneal healing and adhesion formation can be seen as alternate pathways following peritoneal injury.[11]

Factors involved in adhesion formation

Plasminogen activators

Plasminogen activators are serine proteases that convert plasminogen into plasmin, and limit adhesion development of the mesothelial cells lining the peritoneal cavity.[14] They are ubiquitous enzymes, which are secreted by many cell types and play a central role in regulating proteolysis in a wide variety of processes, including tissue remodeling, cell migration, fibrinolysis, tumor metastasis, and invasiveness.[14] With loss of mesothelial cells and decreased plasminogen activator activity (PAA), underlying fibroblasts are exposed and adhesions result between two adjacent surfaces.[14] In a classic study by Rafferty, free peritoneal grafts with markedly decreased PAA had resultant adhesion formation. Those grafts in which PAA was not reduced after injury had degradation of the fibrinous mass prior to fibroblast ingrowth and resultant healing of the peritoneal surface without adhesion development.[14] Thus, if sufficient PAA is present after injury, the fibrinous mass will be degraded by proteolytic activity and the scaffolding required by fibroblasts for invasion will be eliminated, leading to normal healing without adhesion development.[15] By contrast, if PAA is decreased or absent, the fibrinous mass will form a clot, which is invaded by fibroblasts, collagen, and other proteins from the ECM. Mesothelial cells then re-epithelialize and an adhesion develops.[15]

There are two types of plasminogen activators: tissue type plasminogen activator (tPA) and urokinase type plasminogen activator (uPA), both of which are inhibited predominantly by plasminogen activator inhibitor-1 (PAI-1), the major plasminogen activator inhibitor in plasma.

Tissue plasminogen activator (tPA)

Tissue plasminogen activator is the main plasminogen activator in mesothelial cells, and it has also been identified in underlying fibroblasts.[14] Both peritoneal and adhesion fibroblasts have basal tPA levels, but they are 45% higher in normal peritoneal fibroblasts.[14] In comparison to normal fibroblasts, adhesion fibroblasts have decreased tPA and increased PAI-1, which promotes adhesion development. In a hypoxic mileu, fibroblasts demonstrate a decreased ability to degrade the fibrinous mass over injured surfaces. While normal fibroblasts have decreased tPA under hypoxic conditions, it is almost non-existent in adhesion fibroblasts. Also, the PAI-1 is increased in both normal and adhesion fibroblasts during hypoxic conditions.[14] These findings support further the idea that peritoneal healing and adhesion formation can be seen as alternate pathways of peritoneal healing.

Cytokines

Transforming growth factor beta-1 (TGF-β1)

Transforming growth factor beta-1 (TGF-β1) is an inflammatory cytokine that controls cellular proliferation, differentiation, apoptosis, tissue morphogeneis, and wound healing.[16] It occurs in mesothelial cells and fibroblasts and is increased in response to peritoneal healing. Having both an inactive and an active form, its active form stimulates enhanced extracellular matrix deposition through enhancement of angiogenesis and impairment of both matrix metalloproteases and plasminogen activator.[15] This enhancement of the ECM contributes to adhesion development, and an increase in TGF-β1 has been shown to be associated with adhesion development as demonstrated in peritoneal fluid and adhesions in animal models.[15]

In response to tissue injury, there is a localized increase in TGF-β1. It has a potent effect on macrophage and fibroblast activity during wound activity and has been shown to alter the adhesive properties of cells as well as influencing the expression of integrin subunits and cytoskeletal proteins.[2] TGF-β1 may promote postoperative