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Review

Intra-abdominal adhesions: Cellular mechanisms and strategies for prevention

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ABSTRACT

Postoperative intra-abdominal adhesions represent a serious clinical problem. In this review, we have focused on recent progress in the cellular and humoral mechanisms underpinning adhesion formation, and have reviewed strategies that interfere with these pathways as a means to prevent their occurrence. Current and previous English-language literature on the pathogenesis of adhesion formation was identified. As the burden of surgical disease in the world population increases, and the frequency of reoperation increases, prevention of adhesion formation has become a pressing goal in surgical research.

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1. Introduction

Enduring as a surgical footprint, post-operative peritoneal adhesions present a challenging problem for surgeons and their patients. They develop following abdominal and pelvic surgery as a response to tissue trauma to peritoneal surfaces. They are nearly always encountered on reoperation: in a prospective analysis of 210 patients undergoing a laparotomy with one or more previous abdominal operations, 93% had adhesions, compared with 10.4% in first-time laparotomy patients.¹

In this review, we review the work that has been done to elucidate the pathophysiology of adhesion development with a focus on recent studies of the cellular and humoral mechanisms. In this context of new discoveries, we will discuss future techniques and research direction.

1.1. The spectrum and cost of morbidity

As the incidence of abdominal surgery increases worldwide, so does the incidence of adhesions; as longevity increases, so too does the incidence of relaparotomy. Though there are few cohort studies, the Surgical and Clinical Adhesions Research (SCAR) group was formed in the UK to address the issue. In one retrospective study of 29,970 patients in the UK, in the ten years following their abdominal or pelvic surgery, 34.6% were readmitted a mean of 2.1 times for a disorder directly or possibly related to adhesions.²

The most serious complication of adhesions is intestinal obstruction, accounting for more than 40% of all cases of

obstruction and 60–70% of small bowel obstructions.³ Adhesions can prevent a safe surgical entry into the abdomen, and also increase the risk of hemorrhage and intestinal perforation. They can preclude adequate surgical exposure, requiring dissection that prolongs operative time,⁴ or in the case of laparoscopy, hampering peritoneal insufflation. They are also a significant cause of female infertility and dyspareunia⁵ in addition to urologic dysfunction.⁶ Pelvic pain has also been linked to adhesions although this has been debated, and their lysis is usually ineffective at relieving it.⁷ The problem is a very costly one: reviewing one year in the U.S. alone, Ray et al. estimated adhesiolysis was responsible for 303,836 hospitalizations, amounting to 846,415 days of inpatient care and US\$1.3 billion in hospitalization and surgeon costs.⁵

2. Etiology and pathogenesis

2.1. The peritoneum

The biology of peritoneal repair is now known to involve a concert of chemical mediators, cytokines, cell types, degradation products, and proteases to accomplish healing. Histologically, the peritoneum consists of two layers: a mesothelium, one cell layer thick, and a connective tissue layer.⁸ The mesothelial layer is fragile and regenerates from injury by a simultaneous and rapid differentiation over the surface, rather than from centripetal migration from epithelial cells as is seen with healing skin.⁹ The implication is that large defects heal as rapidly as small ones. Interestingly, the mesothelial layer is coated with a surfactant-like agent, surface-active phospholipid (SAPL) which is theorized to serve as a “non-stick coating”.¹⁰

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Normal peritoneal fluid also contains many of the plasma proteins. There are also many chemical mediators present, such as interleukins, interferon-g, TNF-a, TGF-b, and VEGF.¹¹ Additionally there are circulating, free macrophages and other immune cells present in the peritoneal fluid.¹²

Healing following surgical injury to peritoneum follows one of two algorithms, as proposed by Duron et al.¹¹ The first consists of the proliferation and regeneration of the mesothelial cell layer from an origin that has yet to be clearly identified; likely candidates include totipotent underlying mesenchymal cells, or migration of cells from another site (periphery of injury, nearby sites, or via transformation of cells in peritoneal fluid).¹¹ The second is centered on the alteration of fibrinolysis, producing a “peritoneal scar,” and is of interest in the context of adhesion formation.

Fig. 1 synthesizes putative contributory factors for adhesion formation, and thereby potential targets for prophylaxis.

2.2. The role of fibrin

Many believe a tipping point in adhesion formation is the local balance between fibrin production and fibrinolysis. The inciting event of a surgical trauma or inflammation of the peritoneum results in a denuded surface, submesothelial damage and injury to blood vessels thereby invoking an inflammatory response.¹³ There is simultaneous activation of the coagulation cascade and fibrin deposition at the site,¹⁴ which is additive with any bleeding. Mediators such as histamine and PGE₂ cause increased permeability of the blood vessels in the traumatized area, and a serosanguinous exudate rich in inflammatory cells pours forth.^{13,15}

The exudate also contains substrates such as fibronectin, hyaluronic acid, various glycosaminoglycans (GAGs), and proteoglycans (PGs).¹⁴ The inactive fibrinogen turns to a tacky fibrin matrix gel, which may develop between two unrelated structures. Under

normal conditions, the majority of fibrinous connections are lysed within a few days by locally released proteases of the fibrinolytic system.¹⁵ It is theorized that if they persist, fibroblasts may proliferate within the substrate matrix, and establish more permanent connections.

The physiologic fibrinolytic sequence is normally initiated by plasmin. Plasmin is a fully active serine protease which is made from plasminogen by the action of plasminogen activators (PAs).¹¹ One PA in particular, tissue plasminogen activator (tPA), is responsible for producing 95% of the plasmin generated in the response to peritoneal injury.¹⁶ After surgery, tPA knockout mice are more susceptible to adhesions.¹⁷

In a pathological state, plasminogen activator inhibitors (PAIs) interfere with the action of PAs and the production of plasmin, ultimately leading to an altered ability to degrade fibrin split products (fibrinolysis). It has been discovered that in peritoneal inflammation and injury, there are two types of PAI produced: PAI-1 (the main fibrinolytic inhibitor) and PAI-2.^{18,19} PAI-1 specifically prevents the formation of plasmin by binding to and inhibiting the activities of tPA and uPA (urokinase-like plasminogen activator). These two serine proteases are the main activators of fibrinolysis, and thus inhibition of PAI-1 prevents the degradation of fibrin. Surgery dramatically diminishes fibrinolytic activity, by increasing levels of PAIs and by reducing tissue oxygenation.²⁰ Eventually, in the absence of an effective fibrinolytic response, there exists a fibrin gel matrix which may serve as the scaffolding for development of a mature adhesion.

2.3. Cellular players

Following trauma, initial inflammatory cells are predominantly neutrophils, with a shift to mostly macrophages at 24 h. Interestingly, macrophages at the peritoneal injury site after surgery have

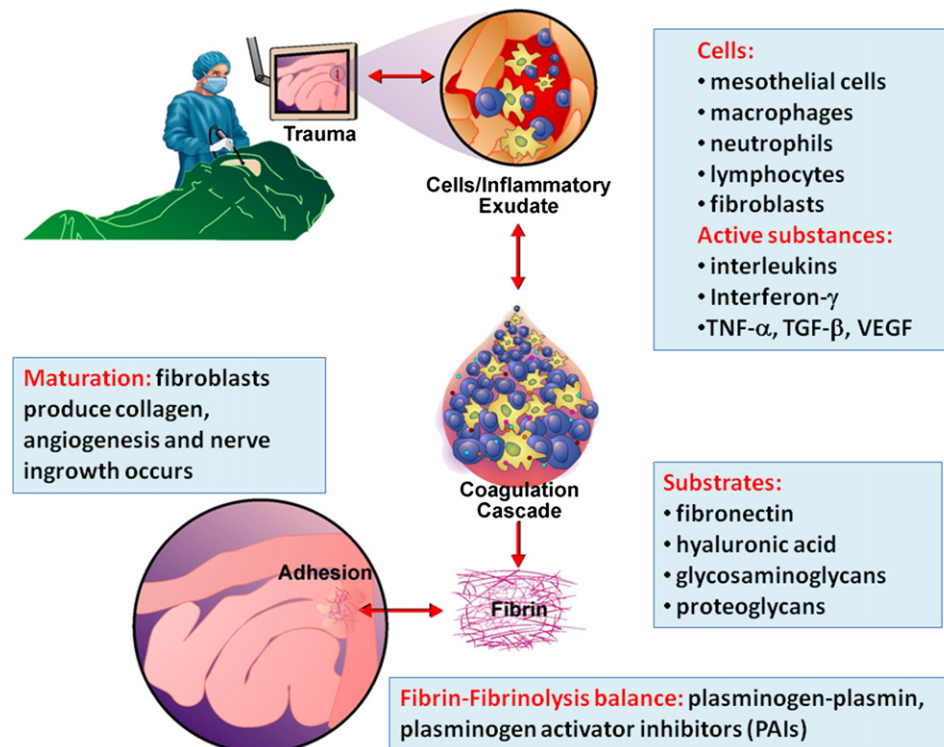


Fig. 1. Summary of post-surgical adhesion formation. Trauma to peritoneal and other intra-abdominal tissue results in an exudate rich in proinflammatory cytokines and various cell types. These in turn serve to activate the coagulation cascade and a fibrin mesh forms, eventually resorbing or maturing into an adhesive connection between the surfaces.

been found to differ from resident macrophages. These post-surgical macrophages secrete substances such as cyclooxygenase and lipoxygenase metabolites, plasminogen activator (PA), plasminogen activator inhibitor (PAI), collagenase, elastase, interleukins 1 and 6, tumor necrosis factor (TNF), leukotriene B₄, and prostaglandin E₂.^{13,21} They also have the ability to recruit new mesothelial cells to the site of the injury.²²

Peritoneal macrophages in particular have been implicated as key players in the immune response triggering adhesion formation. They have a unique autocrine activation system whereby a chemokine (CCL1) and its receptor (CCR8) are released in response to tissue damage. Migration of peritoneal macrophages (and the development of adhesions) has been interrupted and adhesion incidence reduced by abrogating the CCL1/CCR8 interaction.²³

There is some evidence to suggest that fibroblasts play a major role in adhesion maturation. Fibroblast content increases in the second week post-trauma, followed by the inclusion of vessel structures and connective tissue elements.^{24,25} At three weeks, the development of the adhesion becomes quite prominent.²⁶ Rout et al. isolated fibroblasts from normal peritoneum and adhesions, and found that they differed markedly in their phenotype.²⁷ There were marked effects of hypoxia and TGF- β on the expression of some of these products in the fibroblasts, suggesting some, but not exclusive, regulatory influence of these on the pathway.²⁷

Higher levels of degranulated mast cells have also been found in the presence of adhesions in rats,²⁸ and the early event of release of vascular endothelial growth factor (VEGF) by mast cells has been suggested to be important in adhesion development.²⁹ Further analysis of the cellular elements of adhesions by Binnebosel et al. has shown infiltrates of macrophages and T-cells, in consistent quantities regardless of the maturity of the adhesion.³⁰ This characterization of a state of chronic inflammation suggests T-cells may play a role in signaling pathways that maintain adhesions, and prompts consideration of adhesions as a dynamic process in remodeling tissue.³⁰ Certainly it is clear that adhesions can re-form after adhesiolysis.^{31–34}

The infiltration of T-cells and the perpetuation of chronic inflammation in the peritoneum proceed under the influence of many signals, including the promoting effects of IL-6 and other cytokines.³⁵ T-cell depletion and adoptive transfer experiments have confirmed that adhesion formation requires the presence of CD4⁺ alpha beta T cells, and the production of proinflammatory cytokines are dependent on T cells (IL-17 and others).³⁶ Since many fibrotic tissue disorders share a common etiology of T cell-mediated abnormalities in host defense, adhesions represent an example of this.

2.4. Humoral mediators

Immune responses, including cell trafficking, are accomplished at the cellular level by the orchestrated release of cytokines and chemokines. Whether adhesion formation represents an abnormal or disordered version of peritoneal healing may be considered by examining the roles of various signaling molecules that appear along the course of events.

2.4.1. TGF- β

Transforming growth factor beta (TGF- β) is the most studied cytokine in the pathophysiology of adhesion development, and has been suggested as the principal profibrotic mediator of the process.³⁷ In an animal model, it has been shown that intraperitoneal application of TGF- β to surgical adhesions resulted in worsening of the adhesions compared with controls not given TGF- β ³⁸ and animals given TGF- β -neutralizing antibody have shown reduced adhesion formation.³⁹ In humans, the relationship is less

clear. In vitro, TGF- β reduces peritoneal fibrinolytic capacity, an important step in disbanding of early adhesions.⁴⁰ Interestingly, it has been observed in human peritoneal tissue that TGF- β expression covaried with PAI-1, the main fibrinolytic inhibitor. Patients with more extensive adhesions had higher peritoneal concentrations of TGF- β .⁴¹

2.4.2. VEGF

Vascular endothelial growth factor (VEGF) is known as a potent angiogenic factor and may have a role in adhesion development.^{42,43} It is also directly involved in early inflammatory processes and wound healing by effects on fibroblast function.⁴⁴ In an animal model, intraperitoneal treatment with an antibody to VEGF has resulted in a lower incidence of advanced adhesions.⁴⁵

2.4.3. Interleukins

Other mediators, such as interleukins, are receiving attention for their role in adhesion development. Comparing serum and peritoneal fluid levels of interleukin-1 (IL-1), post-operative patients have a significantly higher level in the peritoneum, suggesting a possible local action of this interleukin.⁴⁶ Rats treated pre-operatively with anti-IL-1 had fewer adhesions postoperatively than controls.⁴⁷ Based on these and other observations, a likely mode of action of IL-1 is to promote adhesion formation by increasing fibrin deposits, reducing fibrinolysis, and stimulating mesothelialization of the structure.¹²

Interleukin-6, interleukin-8 and interleukin-10 are all theorized to participate in modulation of the cellular response to peritoneal injury, however the roles are still not clear.¹² Mesothelial cells are the principal IL-6 secreting cells in the peritoneal cavity, and on challenge by inflammation they produce large amounts of this cytokine.⁴⁸ Interleukin-6 is known for both pro- and anti-inflammatory effects. When complexed with its receptor (IL-6/sIL-6R) found on invading neutrophils, it influences a shift from leukocyte recruitment in the acute phase of inflammation to an influx of sustained mononuclear leukocytes.⁴⁹ A recent murine study found that adhesions were prevented when cold saline was infused intraperitoneally, and this correlated with lower serum IL-6 and elevated IL-10.⁵⁰ Intraperitoneal injection of exogenous IL-10 has been shown to reduce post-operative adhesion formation in a mouse model.⁵¹

2.4.4. Tumor necrosis factor- α

Tumor necrosis factor- α (TNF- α) is able to promote production of interleukins by mesothelial cells,⁵² and high levels of TNF- α in peritoneal fluid and serum postoperatively have correlated with adhesion severity in rats.⁵³ However, administration of neutralizing anti-TNF- α antibodies failed to reduce adhesion formation, and requires further study.⁴⁷

2.4.5. MMPS and TIMPS

Matrix metalloproteinase enzymes (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) vary between individuals, and lower levels of TIMP-2 in peritoneal fluid and serum is protective.⁵⁴

3. Prevention

Enormous effort both in the laboratory and the operating theater has been applied to reduce adhesion formation. The most common and modern approaches have been the use of a barrier between or over damaged surfaces, administration of pharmacological agents, or a combination of these. Recent reviews include three Cochrane reviews which compare existing evidence.^{55–57} Our

focus is on methods with particular reference to interruption and modification of cellular peritoneal healing.

3.1. Barriers

Preventing contact of two traumatized surfaces with a mechanical barrier has been a recurring theme in efforts to reduce adhesions. Many hold the view that critical events in adhesion formation occur by day 7,^{58–61} so perhaps a barrier need only be present during an early critical window.

The mesothelial cell layer of the peritoneum is coated with a natural anti-stick coating: a thin film of surface-active phospholipid.¹⁰ Experimental application of exogenous phospholipids has been promising; phosphatidylcholine, sphingolipid, and galactolipid⁶² have decreased the areas of post-operative adhesion in animal studies. Phosphatidylcholine has been shown in several studies to have a beneficial effect in the rat,^{63–66} but with the side effect of impaired healing of intestinal anastomoses at higher concentrations. Applying Poloxamer 407, a polymer of hydrophilic non-ionic surfactant, after adhesiotomy in an animal model has reduced the incidence of re-formation of adhesions. It has yet to be studied in humans.⁶⁷

Hyaluronic acid, also called hyaluronan or hyaluronate, has long been a subject of antiadhesion research. It is a naturally occurring glycosaminoglycan and forms a highly viscous solution to coat serosal surfaces. In a single intraperitoneal dose at time of operation, Treutner et al. found the mean area of adhesions reduced by 84% compared to control in their animal model.⁶² Other animal studies have shown a reduction of adhesion formation when the hyaluronic acid was applied before the trauma, but not a reduction in reformation after the division of existing adhesions.^{68,69}

The introduction of barriers into general clinical practice has been restricted by several factors. Though a few are commercially available, drawbacks include difficulties in preparation and application, the need for absolute hemostasis, insufficient pliability, intricate product fixation techniques, and incompatibility with laparoscopic surgical procedures.⁷⁰ Without clear understanding of how these agents might interfere with normal intra-abdominal wound healing, their use deserves caution.

3.2. Pharmacological methods

With the discovery of new components of adhesion formation, manipulating the cellular milieu to disfavor adhesiogenesis and promote normal peritoneal resolution becomes an appealing prospect.

Many different agents have been used in the effort to arrest the adhesion pathway or to tip the balance in the favor of fibrinolysis and adhesion resorption. Drugs may be administered systemically, or ideally, locally with minimal systemic effect. The peritoneal cavity is an efficient site for uptake of large molecules; even particles the size of cells may pass through the lymphatic lacunae located in the submesothelial layer.

The inflammatory component of the pathogenesis of adhesion formation has been targeted, and a variety of steroidal and anti-inflammatory drugs have been studied, including aspirin, dexamethasone, methylprednisolone, estrogen, progesterone and budesonide.^{71–78} However, the effectiveness of these agents has not been consistent in animal models and clinical trials.⁷⁹

Heparin has been suggested in an attempt to moderate activation of the clotting cascade and reduce fibrin deposition contributing to the process of adhesion formation. There is some evidence from animal models to suggest local intraperitoneal administration of low-dose heparin may result in fewer adhesions.⁸⁰ Removal of already-formed fibrin using trypsin, pepsin, papain, as well as

mechanical removal by lavage and by hand has produced inconsistent and anecdotal results.

Other targets of the fibrin-fibrinolysis pathway include use of fibrinolytic drugs and plasminogen activating factor.^{58,73,81–83} These have been effective in a dose-dependent manner,⁸⁴ but are noted to impair wound healing. Ancrod, an experimental defibrinogenating agent made from Malayan pit viper venom, has been used experimentally in combination with a hydrogel to reduce adhesions.⁸⁵ Since all fibrinolytic drugs can incite bleeding, acceptance for routine use in the prevention of post-operative adhesions is unlikely.

There may be a role for several medications approved for other indications, such as mitomycin C, paclitaxel, sirolimus and taurolidine. Mitomycin C is an antitumor antibiotic that can inhibit fibroblast proliferation for several weeks in vitro. It has been combined with a crosslinked hyaluronan hydrogel for the purposes of adhesion reduction in an animal model.⁷⁰ It has also been used locally in strabismus surgery to limit post-operative adhesion, a property which is attributed to its antifibrinolytic activity,⁸⁶ and

Table 1
Selected clinical and pre-clinical trials of barrier and pharmacological methods of adhesion prophylaxis.

	Reference	Model
<i>Barrier methods</i>		
Aloe vera gel	Aysan et al., 2009	Rat
Soybean oil	Aysan et al., 2009	Rat
Octyl methoxycinnamate	Aysan et al., 2009	Rat
Icodextrin	diZerega et al., 2002, Menzies et al., 2006	Clinical trial, Clinical trial
Phosphatidylcholine	Ar'Rajab et al., 1991, Roszga et al., 1990, Snoj et al., 1992, 1993, Treutner et al., 1995	Rat, Rat, Rat, Rabbit
SprayGel	Ferland et al., 2001	Pig
Poloxamer 407	Steinleitner et al., 1991	Rabbit
Interceed	DeLaco et al., 1998, Haney and Doty, 1992	Rabbit, Mouse
Gore-Tex Surgical Membrane	Haney and Doty, 1992	Mouse
Oxidized-regenerated cellulose	Haney and Doty, 1992	Mouse
Hyaluronic acid/hyaluronan/hyaluronate, and Septrafilm	Numerous.	Models have included mouse, rat, rabbit, as well as clinical trials
<i>Pharmacological methods</i>		
Aspirin	Golan et al., 1995	Rat
Dexamethasone	Buckenmaier et al., 1999, Gazzaniga et al., 1975, Hockel et al., 1987, Kucukozkan et al., 2004	Rat, Rat, Rat, Rabbit
Methylprednisolone	Gazzaniga et al., 1975	Rat
Estrogen	Bozkurt et al., 2009	Rat
Progesterone	Maurer and Bonaventura, 2003	Guinea pig
Budesonide	Yeo et al., 2003	Rabbit
Heparin	Bahadir et al., 2007, Fukasawa et al., 1991	Mouse, Rabbit
Tissue plasminogen activator	Buckenmaier et al., 1999 and others	Rat
Streptokinase	Buckenmaier et al., 1999	Rat
Urokinase	Buckenmaier et al., 1999	Rat
Ancrod	Chowdhury and Hubbell, 1996	Rat
Mitomycin C	Cubukcu et al., 2001 and 2002, Liu et al., 2005	Rat, Rat
Paclitaxel	Jackson et al., 2002	Rat
Tranilast	Petrilli et al., 2008	Rabbit
Methylene blue dye	Heydrick et al., 2007	Rat
Taurolidine	Bahadir et al., 2007, Tarhan et al., 2008, Treutner et al., 1995	Mouse, Rat, Rabbit

for prevention of recurrent intra-abdominal adhesions in rats.⁸⁷ Antiproliferative agents such as paclitaxel and sirolimus may also have promising applications in adhesion reduction devices. Paclitaxel-loaded crosslinked hyaluronic acid films reduced adhesion incidence in a rat model,⁸⁸ while sirolimus has been used experimentally in an animal aortic PTFE vascular graft model to reduce retroperitoneal adhesions.⁸⁹ Taurolidine is a drug with antimicrobial and anti-lipopolysaccharide properties, and has immune modulatory action via priming and activation of macrophages. It has also been tested in experimental animal models to reduce adhesions, with inconsistent results.^{62,90,91}

A summary of selected pre-clinical and clinical trials of devices and drugs is provided in Table 1. Given the location of drug delivery and barrier placement, there are obvious implications for biocompatibility and toxicity of any material used for adhesion prevention.¹² The future of adhesion prevention strategy likely has the most promise in a device which combines targeted pharmacology with a barrier method.

4. Conclusion

Postoperative adhesions represent a problem of considerable magnitude. Morbidity resulting from adhesive tissue following surgery may be substantial, and is a burden the patient carries for the rest of their lives. From our increased understanding of the multifactorial nature of adhesion pathogenesis, and our growing knowledge of the effects of cellular and molecular mediators of the process, there is hope that a preventative strategy will emerge.

Conflict of interest

All authors disclose there are no financial or personal relationships with other people or organizations that could inappropriately influence this work.

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Ethical approval

None declared.

Author contribution

- Allison H. Maciver MD
Contributed to the data collection, analysis and writing of the manuscript.
- Michael McCall MD
Contributed to the critical review of the manuscript.
- A.M. James Shapiro MD PhD
Contributed to the analysis of data and the writing and revision of the manuscript.

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