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Response to pathological processes in the peritoneal cavity—Sepsis, tumours, adhesions, and ascites

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ABSTRACT

The peritoneum is one of the commonest sites for pathological processes in pediatric surgery. Its response to pathological processes is characterized by an inflammatory reaction with specific pathways depending on the type of injury or peritoneal process involved. This review discusses the current understanding of peritoneal inflammation, adhesion formation, intra-abdominal sepsis, peritoneal metastasis, and ascites and briefly reviews new therapeutic strategies to treat or prevent these pathological entities. Recent studies have improved the understanding of peritoneal responses, resulting in possible new targets for prevention and therapy.

Introduction

The peritoneal cavity is a confined space between the parietal peritoneum lining the abdominal wall, the retroperitoneum, and the visceral peritoneum covering the abdominal organs. Its total surface area is almost equal to the body surface area of the skin.[1] The peritoneum is a serous membrane of mesodermal origin, consisting of a monolayer of flat mesothelial cells anchored to the basement membrane. The subjacent connective tissue consists mainly of loose collagen fibers, including fibroblasts, blood and lymphatic vessels, as well as nerve fibers. The mesothelial cells play an active role in the physiological function as well as in pathological processes of the peritoneum. The peritoneal cavity contains less than 100 ml of serous fluid, an ultra-filtrate of plasma, which together with hyaluronan and a surfactant, produced by mesothelial cells, facilitates frictionless movement of the abdominal organs.[2] The peritoneum acts as a bidirectional semi-permeable membrane. The peritoneal mesothelial cells are interrupted by intermesothelial gaps (stomata of von Recklinghausen), which adapt to pathological conditions by retraction of the cell margins in response to pathological stimuli and in relation with diaphragmatic movements. At these stomata the peritoneal cavity is directly exposed to the extracellular matrix.[3] The action of the diaphragm generates a cephalad flow of peritoneal fluid through the stomata.[4] Under normal circumstances, approximately one-third of the peritoneal fluid drains through the diaphragmatic stomata into the main thoracic lymphatic ducts, the remainder exits through the parietal peritoneum.

The peritoneal defense mechanism can be triggered by various types of pathological processes "injuring" the peritoneum. Apart from (surgical) trauma, injury can be caused by invasive pathogens and tumor. The peritoneum responds to injury with an inflammatory reaction. This inflammatory reaction comprises four interacting pathways: immunological, humoral, coagulation, and neurological. In this article, we aim to give a comprehensive overview of the response to pathological processes in the peritoneal cavity.

General peritoneal response to injury

Injury of the peritoneum, whether surgical, inflammatory, or ischemic, causes a complex inflammatory reaction. This response has an integral role in wound healing and tissue repair to heal any sustained damage. The disruption of the cellular membrane, through apoptosis or necrosis, causes a release of intracellular molecules such as DNA, ATP, and IL-1α in the extracellular space.[5–7] These have been named as Damage-Associated Molecular Pattern molecules (DAMPs), but the mechanisms by which they generate an inflammatory response are not fully understood. The DAMPs induce a local cascade through activating receptors on mesothelial and local inflammatory cells. The mesothelial and local inflammatory cells produce chemoattractants (IL-8 and MCP-1), cytokines (TNF α, IL-1β, and IL-6), and growth factors (TGF β, IGF-1, and PDGF), which result in neutrophil extravasation which infiltrate the damaged area.[8] Mast cells are abundantly present around bowel mucosa and are believed to play an important role in the inflammatory response of the peritoneum by inducing vasodilation through release of histamine.

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They can also be activated by DAMPs and activate several local immunological and endothelial cells and nerve fibers.[9] Neutrophils persist at the injured site for 1–2 days and are followed by monocytes recruited in the same manner; these differentiate into macrophages which contribute to the inflammatory reaction. The primary injury of the peritoneum not only leaves a denuded area with damaged mesothelial cells but also causes bleeding and extravasation of plasma proteins. Coagulation is up-regulated through the expression of tissue factor (TF) by macrophages and mesothelial cells. Interaction of TF with plasma proteins and thrombocytes forms a transient fibrinous matrix. The formation of an extensive fibrinous matrix is possible because the balance between coagulation and fibrinolysis is disturbed. The fibrinogen split products are known to promote pleural mesothelial proliferation, this might also be the case with peritoneal mesothelial cells.[10] Fibrinolysis, however, is decreased because there is an up-regulation of plasminogen activator inhibitor 1 (PAI-1) and a down-regulation of tissue-type plasminogen activator (t-PA). There is increasing evidence that inflammation and coagulation significantly affect each other. Coagulation is induced by inflammatory cytokines, while the coagulation-induced modulation of inflammatory activity is driven by specific cell receptors on inflammatory cells and endothelial cells.[7] Moreover, thrombocytes play their part in inflammation through storage and release of the pro- and anti-inflammatory factors TGF β and IL-1.[5]

The neurological pathway of the inflammatory response of the peritoneum is activated by IL-1 binding to paraganglia cells. The "inflammatory reflex" is formed by signaling through afferent fibers of the vagus nerve to parasympathetic regions in the brainstem, leading to the release of neuropeptides from efferent nerve fibers and a resultant feedback on inflammation.[11] Different neuropeptides can lead to either anti-inflammatory (e.g., acetylcholine) or pro-inflammatory (e.g., substance P) effects on inflammation.

While in the past resolution of inflammation has always been seen as a passive process, the discovery of locally acting mediators (pro-resolving mediators) has changed this view.[12] These pro-resolving mediators are produced via transcellular biosynthesis (i.e., between neutrophils and thrombocytes) and down-regulate the inflammatory reaction.

Adhesion formation

Healing of the injured peritoneum can result in the formation of peritoneal adhesions. As mentioned, injury of the peritoneum leads to a denuded surface with submesothelial damage evoking an inflammatory response. Simultaneously the coagulation cascade is activated and fibrin deposited at the site. A serosanguinous exudate rich in inflammatory cells, fibronectin, glycosaminoglycans, and proteoglycans is secreted through increased vascular permeability. This results in fibrin deposits that form an adhesion between two formerly unconnected structures. Under normal circumstances, these fibrin deposits are degraded by fibrinolysis. This process of fibrinolysis is driven by the enzyme plasmin produced by macrophages and mesothelial cells. Plasmin is derived from its inactive substrate plasminogen by tissue-type plasminogen activator (t-PA) and urokinase-like plasminogen activator (u-PA). In its turn, t-PA is inhibited in its reaction by plasminogen activator inhibitor 1 (PAI-1) to keep the balance. However, peritoneal trauma leads to the absence of adequate fibrinolytic activity of the mesothelium and a mismatch in the fibrinolytic balance in favor of the persistence of fibrin clots.[13] Neighboring organs or the abdominal wall ma y adhere, generating a fibrin bridge between the attached tissues.[14] Under the actions of various cytokines, these fibrin bands are transformed into granulation tissue by the ingrowth of capillaries and fibroblasts and subsequently converted into permanent, collagenous, and highly organized tissue containing nerve fibers and vessels.

Adhesions frequently cause long-term complications after abdominal and pelvic surgery. After pediatric abdominal surgery, the incidence of adhesive small bowel obstruction can be as high as 15.6%, for example, after treatment of gastroschisis and omphalocele in neonates.[15,16] Other important clinical consequences of adhesions include infertility, chronic abdominal pain, malabsorption, and technical difficulties at reoperation. Many pharmacological methods and barriers have been used for adhesion prevention but only few have been proven to be successful. Prevention of adherence of adjacent structures by keeping them apart seems most efficacious. In a recent systematic review, the efficacy and safety of the four adhesion barriers approved for use in Europe and the USA were evaluated, showing evidence that membranes of oxidized regenerated cellulose and hyaluronate carboxymethylcellulose reduce adhesion formation.[17] Moreover, there is evidence that hyaluronate carboxymethylcellulose reduces the number of reoperations for adhesive small bowel obstruction. Evidence for efficacy on other clinically critical outcomes is lacking. Of the liquid adhesion barriers that are available in the market, icodextrin 4% solution is the most widely used. There is, however, limited evidence for the beneficial effect of icodextrin on the incidence of small bowel obstruction or other adhesion-related complications.[17,18]

An understanding of the pathological processes enables the modulation of the peritoneal environment and fibrinolytic capacity, which seems to harbor a therapeutic opportunity to prevent postsurgical adhesion formation. Intraperitoneal treatment with recombinant human plasminogen activator (rPA) was effective in preventing postoperative adhesion formation in experimental studies.[13] A pilot study in humans, however, showed no reduction of adhesions.[19] Since there was no measurable elevation of plasma t-PA level in the treatment group, this negative result was ascribed to too small a dosage.

An interesting option to potentially combine anti-inflammatory, anti-coagulatory, and profibrinolytic properties is the use of statins. Beside their cholesterol-lowering capacity, there is accumulating evidence that statins effectively lower plasma levels of CRP, have potent anti-inflammatory properties, and are effective stimulators of fibrinolytic activity by increasing t-PA and lowering PAI-1.[20,21] Also, the use of an angiotensin-II receptor blocker has potential efficacy in adhesion prevention through decreasing TGF β. The intraperitoneal administration of these agents alone and combined effectively reduced postsurgical adhesions in mice.[22] However, no data on efficacy in humans are available yet. Another potentially viable therapeutic target is substance P (a specific pro-inflammatory neuropeptide).[23] The effects associated with substance P are increasing inflammatory cytokine mRNA expression, stimulating angiogenesis, and proliferation of fibroblasts. This is mainly mediated through binding to neurokinin-1 receptor. Binding to the neurokinin-1 receptor can be inhibited through intraperitoneal administration of a neurokinin-1 receptor antagonist. In rats, interference with the actions of substance P with this antagonist showed early effects on the mRNA expression of several key mediators of adhesiogenesis.[24]

Intra-abdominal infection, abscess formation, and peritonitis

Intra-abdominal infection encompasses all forms of bacterial peritonitis, intra-abdominal abscesses, and infections of intra-abdominal organs. Perforation of a hollow organ is the leading cause of intra-abdominal infection, followed by postoperative peritonitis, ischemic damage of the bowel wall, infection of intra-abdominal organs, and translocation in nonbacterial peritonitis.[25]

Within minutes of bacterial invasion, a substantial proportion of the bacteria are absorbed from the peritoneal cavity through the stomata of von Recklinghausen in the diaphragmatic peritoneum