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REVIEW ARTICLE

Immunomodulation in surgical practice

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Abstract

Background. Immunomodulation may represent a potential way to improve surgical outcome. These types of interventions should be based on detailed knowledge of the underlying mechanisms involved. The aim of the present review is to summarize some experience on the acute phase response, potential ways of intervention and experiences from critical illness and HPB disease. *Discussion.* Mechanisms of the acute phase response are discussed including the individual parameters and local changes that take part. Mechanisms involved in failure of the gut barrier are presented and include changes in gut barrier permeability, effects on gut-associated immunocompetent cells, and systemic implications. As examples of HPB disease, mechanisms of the acute phase response and potential ways of intervention in obstructive jaundice and acute pancreatitis are discussed. Nutritional pharmacology and lessons learned from immunomodulation and immunonutrition in critical illness and major abdominal surgery, including upper GI and HPB surgery, are referred to. Overall, immunomodulation represents a potential tool to improve results but requires a thorough mapping of underlying mechanisms in order to achieve individualized treatment or prevention based on patients' specific needs.

Key Words: *immunomodulation, surgery, critical illness, acute phase response, cytokines, immunonutrition*

Introduction

Immunomodulation has been suggested as one way of optimizing the course of surgical patients, both as part of the perioperative management in elective surgical patients and in acute disease and critical illness. The concept has also been included in nutritional management and termed immunonutrition. Modulation of the acute phase response and immune function, however, requires a detailed knowledge about the acute inflammatory response and its mechanisms in order to understand and optimize selective intervention. This review discusses some of the mechanisms involved in the acute inflammatory response, that have the potential for intervention. It is understood that we still lack substantial information in order to treat and prevent by modulating the immune response in the most optimal and "tailored" fashion. However, some experience already exists as regards at which time point and with what agents we potentially can intervene in different disease processes, and lessons learned from treatment in critical illness are of value. Immunomodulation in HPB disease and surgery will also be discussed.

Surgery and the acute phase response

Major surgery results in an acute phase response where the magnitude of the response usually correlates with the extent of the surgical trauma. The surgical intervention also results in a transient immunosuppression and potential alterations in gastrointestinal tract function. In the normal situation, these alterations are restored within a few days unless complications occur [1].

The immune response caused by the surgical intervention may be followed by an excessive inflammatory response and paralysis of cell-mediated immunity. This effect of major surgery could be responsible for the increased susceptibility to subsequent septic complications [2]. It has been shown that laparoscopic surgery results in diminished tissue trauma as compared with open surgery [3]. Decreased surgical trauma by minimal invasive surgery together with, for example, optimal pain control, early enteral nutrition and mobilization, brought together as "facilitated" or "fast track surgery", probably diminishes the operative stress and acute inflammatory response (Figure 1) [4].
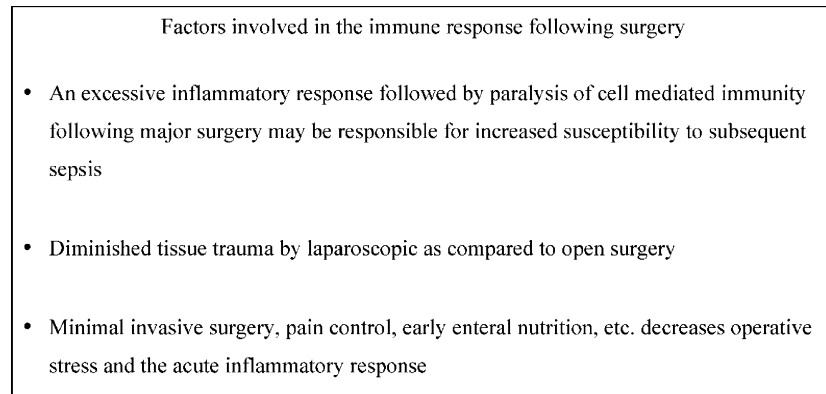
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Factors involved in the immune response following surgery

- An excessive inflammatory response followed by paralysis of cell mediated immunity following major surgery may be responsible for increased susceptibility to subsequent sepsis

- Diminished tissue trauma by laparoscopic as compared to open surgery

- Minimal invasive surgery, pain control, early enteral nutrition, etc. decreases operative stress and the acute inflammatory response

Figure 1. Surgery and the immune response.

The acute phase and inflammatory response following surgical trauma in critical illness seem to depend on the net of the pro- and anti-inflammatory responses that occur simultaneously. In critical illness and after major surgical trauma in general the overall response seems to be a hyperinflammatory response, which could include the development of the systemic inflammatory response syndrome (SIRS) that might proceed to the development of "early" multiple organ dysfunction syndrome (MODS). Later on during the course of disease, a net hypoinflammatory state may occur, sometimes termed the compensatory anti-inflammatory response syndrome (CARS). During this phase, a supervening infection or sepsis could further impair the condition and contribute to the development of "late" MODS [5].

The acute phase response

The acute phase response is the result of the action of pro- and anti-inflammatory factors as mentioned above. A number of pro-inflammatory mediators are known to play a major role in the complex acute phase response, among others the intracellular pro-inflammatory regulator nuclear factor kappa B (NF-κB), as well as cytokines like tumor necrosis factor (TNF)κ, interleukin (IL)-1, IL-6 and IL-8, and platelet activating factor. Upregulation of various adhesion molecules is also involved in the acute phase response and participates in the potential development of organ failure. Contributory factors also include endotoxin, oxygen free radicals, nitric oxide and histamine as well as enzymes like phospholipase A_2, especially when released from neutrophils that have migrated through the endothelial barrier into the tissues of various organs, thereby causing tissue injury and organ failure. Overall, the magnitude of the acute phase response and the cytokine and mediator release seems to correlate well with the potential development of systemic complications and remote organ failure, as has been shown both experimentally and in the clinical setting [6–9].

Local challenges may be followed by systemic effects, where the changes that occur merely depend on the magnitude of the local injury. Furthermore, local preventive and therapeutic interventions may also contribute to a normalization of the systemic response. For example, a gut-pulmonary axis been described where local injury to the gut will affect the lungs [10–12]. Similarly, a gut-liver axis has been described in which obstructive jaundice negatively affects gut barrier function and activation of host immune function [13].

Gut barrier failure and sepsis

The gastrointestinal tract has been called "the undrained abscess" of multiple organ failure [14]. The gut barrier has mostly been considered as a defense against permeability and the permeation of bacteria and toxins normally contained within the intestinal lumen. However, gut barrrier failure has been shown not only to represent an increase in intestinal permeability and translocation, but also concerns the activation of immunocompetent cells within the gut wall and associated lymph nodes. Overall, mucosa-associated lymphoid tissue (MALT) and gut-associated lymphoid tissue (GALT) probably represent one of our largest immunological "organs" [15]. The combination of increased barrier permeability and gut inflammation may end up in the interaction between polymorphonuclear leukocytes and the endothelial lining, potentially resulting in remote organ dysfunction, e.g. in the lungs (Figure 2).
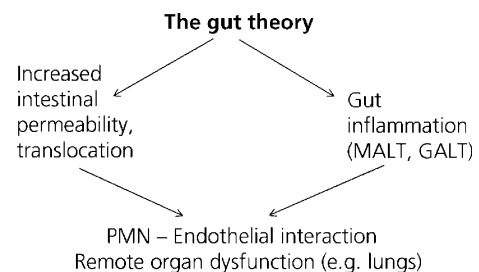

Figure 2. Gut barrier failure includes both an increase in intestinal permeability and a gut inflammatory state. MALT, mucosa-associated lymphoid tissue; GALT, gut-associated lymphoid tissue; PMN, polymorphonuclear leukocytes.

The complexicity underlying gut barrier failure is illustrated when summarizing some pathophysiological mechanisms involved in intestinal barrier failure in acute experimental pancreatitis (Figure 3) [15]. As can be seen, the complexicity in gut barrier dysfunction is substantial and involves a number of factors that individually represent potential targets for both preventive and therapeutic measures [15,16].

Why no magic bullets modulating the acute phase response?

A number of interventions have been tried individually in the clinical setting, based on successful experimental findings. Regrettably, the overall result has been a failure in demonstrating a beneficial clinical outcome with these types of interventions. Reasons for this might be the fact that there seems to be a limited window for potential therapeutic intervention, especially in critical illness, with complex mechanisms from the very onset and a rapid progression of the disease. Thus, treatment attempts at blocking various individual pro-inflammatory responses have failed. Moreover, we still lack a proper mapping of the actual course of the acute phase response, knowledge which could represent a basis for obtaining a more tailored and individualized type of treatment.

Potential interventions include gut protective strategies, modulation of SIRS, endothelial barrier dysfunction and MODS and the potential role of immunonutrition, in which case the route of administration and the addition of individual supplements with beneficial effects ("nutritional pharmacology") have to be addressed.

Concerning gut protection, the permeability as well as the gut inflammatory response have been addressed. The importance of luminal nutrition has to be emphasized, as enterocytes depend on glutamine to a large extent and colonocytes depend on short-chain fatty acids as energy source [17]. No parenteral supplementation will thus fully compensate for the lack of luminal nutrition and absence of these specific "nutrients".

Modulation of SIRS, endothelial barrier dysfunction and MODS may be achieved by for example the administration of anti-oxidants. Other potential ways of obtaining this could be by blocking pro-inflammatory cytokines, the administration of platelet activating factor antagonists, antibodies against adhesion molecules or agents binding endotoxin. Immunonutrition and the route of administration of nutrition have to be addressed, where the importance of gut luminal nutrition should be emphasized. Factors to consider are patients' basic nutritional requirements and additives if, for example, malnutrition, severe catabolism, complications, intensive care treatment, etc., exist. The administration of probiotics or synbiotics could also be of benefit. The role of key nutrients, often as supplements to nutritional formulas, on the acute inflammatory response, immune competence and gastrointestinal function has to be further investigated.

Obstructive jaundice–effects on immune function and outcome

Obstructive jaundice has been reported to be associated with an impaired immune function, including both the systemic and local defense. Alterations have been reported in gut barrier function, as well as the existence of endotoxemia. Overall, an increase in the incidence of postoperative complications including sepsis and infection has been seen in obstructive jaundice [18,19]. Host defense in subjects with obstructive jaundice is influenced in multiple ways. The overall reticuloendothelial system (RES) seems to be impaired and Kupffer cell function is altered. An impaired cellular immunity, including both the fixed reticuloendothelial system and macrophages has been reported, as well as a decrease in natural killer cell
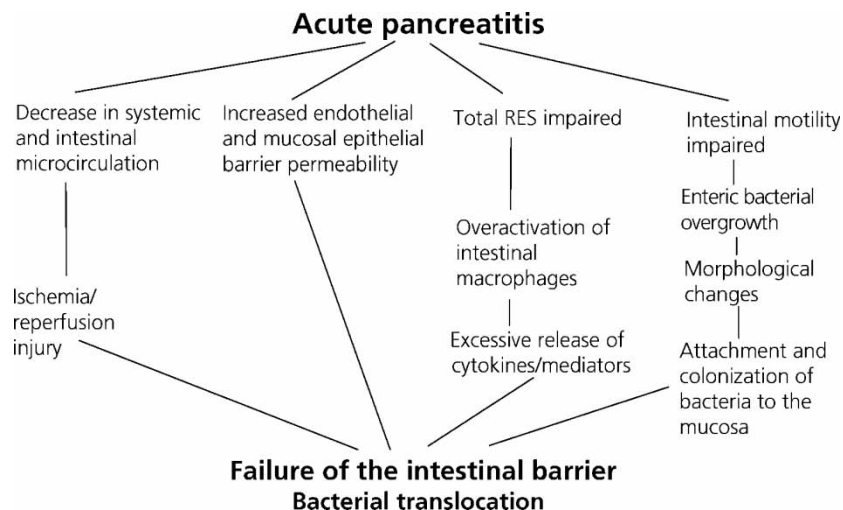

Figure 3. Interactive mechanisms underlying the development of intestinal barrier failure in acutew experimental pancreatitis. RES, reticuloendothelial system.

activity. Biliary obstruction has also been associated with an increase in cytokine release, including TNFα, IL-6 and IL-8, and upregulation of adhesion molecules.

Biliary obstruction results in an increase in intestinal permeability, upregulation of HLA-DR expression on enterocytes and GALT, suggesting an immune activation. There also seems to be an increase in the acute phase response and in circulating anti-endotoxin core antibodies. Following internal biliary drainage, a normalization of intestinal permeability occurs [20].

Additional surgery exaggerates the impaired gut barrier function and activation of host immune function seen in patients with obstructive jaundice, implying caution in order to minimize the risk of developing systemic complications [13]. The endotoxemia noted in biliary obstruction is considered to be due to a number of coinciding changes including an increase in intestinal permeability and a lack of bile flow to the gastrointestinal tract, with concomitant absence of bile salt neutralization of endotoxin. A decrease in the elimination of endotoxin could also be due to altered Kupffer cell function. Altogether this favours the occurrence of endotoxemia in jaundice and can be summarized as disturbances in the homeostasis of the suggested gut-liver axis [21]. A number of interventions have been tried to improve immune function in obstructive jaundice. For example, preoperative lactulose administration in biliary obstruction seems effective in experimental biliary obstruction [22,23]. Lactulose was also of benefit when administered together with deoxycholate for the prevention of postoperative renal dysfunction in jaundiced patients [24]. Mechanisms explaining the effect of lactulose may be inactivation of gut-derived endotoxin and endoxotin-induced TNF production [25,26].

The impaired RES function in obstructive jaundice is restored after internal biliary drainage but the recovery phase is prolonged. Also, intestinal permeability slowly recovers after internal biliary drainage. For both alterations, a period of up to 5 weeks seems to be required to regain normal function [20,27].

This prolonged recovery has been a contributing factor to questioning the routine use of preoperative biliary stenting in jaundiced patients [28]. Preoperative biliary drainage has even been reported to increase complications, including infectious complications, intra-abdominal abscess formation and postoperative death, in patients subjected to pancreaticoduodenectomy [29].

Immunomodulation has been tried in obstructive jaundice. Experimentally, the administration of an immunostimulating compound (muramyl dipeptide) improved RES recovery in jaundiced rats treated with internal biliary decompression [30,31]. Immunomodulation by the use of muramyl tripeptide phosphatidyl-ethanolamine inhibited bacterial translocation, probably by activation of mucosal macrophages in experimental biliary obstruction [32].

Acute pancreatitis and the inflammatory response

Acute pancreatitis is a pronounced pro-inflammatory condition, especially in fulminant cases. Central mechanisms include the existence of ischemia and reperfusion injury and increased endothelial barrier permeability. Experimentally, treatment with, for example, platelet activating factor inhibitors, antibodies against adhesion molecules and tromboxane A_2, has been effective against microcirculatory and endothelial barrier permeability derangements [33,34].

Oxygen free radicals play a crucial pathophysiological role, especially during the early stages of acute pancreatitis and are produced in response to ischemia/reperfusion. Antioxidants have partly been effective in experimental acute pancreatitis, decreasing the magnitude of endothelial barrier dysfunction in remote organs. Clinical data supporting an effect by antioxidant administration alone is, however, lacking [35–37].

Immunomodulation may also be achieved by the administration of steroids. Beneficial effects have been reported in experimental pancreatitis following administration of steroids [38] but this has not been reproduced clinically [39]. The use of glucocorticoids may, however, be of value, as part of a multimodal treatment strategy, as they suppress the inflammatory response, potentially by the inhibition NF-κB, a dominant intracellular regulator of the pro-inflammatory response [40,41]. Experimentally, specific inhibition of NF-κB has improved outcome [42–44].

Cytokine release, including IL-6 and IL-8, has been identified as an early predictor of severity in acute pancreatitis [45–47]. Treatment with IL-10 and selective inhibition of IL-1 β and IL-8 have been shown to be of benefit in experimental acute pancreatitis [48–50]. The expression of adhesion molecules is central in the development of endothelial barrier dysfunction, regulates transmigration of neutrophils and concomitant development of organ dysfunction.

Experimentally, treatment with antibodies against adhesion molecules like ICAM-1 and PECAM-1 has been effective [51–54]. Combining various agents in a "multimodal treatment" directed against various pathophysiological mechanisms in acute pancreatitis has been tried experimentally. The combination of the broad-acting antioxidant N-acetylcysteine, the PAF inhibitor lexipafant and monoclonal antibodies against the adhesion molecule PECAM-1 was effective when administered in animals with ongoing organ failure in a model of taurodeoxycholate-induced acute pancreatitis. By this treatment, the acute phase response and organ dysfunction decreased, and gut barrier failure and translocation could be prevented [55]. Clinical evidence for the

effectiveness of this type of "cocktail regimen" is still not available.

Anticoagulation and anti-inflammation

Attention has recently been paid to the anti-inflammatory properties possessed by various anticoagulating agents. Activated protein C blunts the anti-inflammatory response to sepsis [56] and the use of recombinant activated protein C has been shown to reduce mortality in severe sepsis [57]. Anti-inflammatory properties have also been proposed when inhibiting other factors of the coagulation cascade, like inhibition of tissue factor pathway inhibitor, factor Xa and factor VII [58,59]. This field of potential intervention is presently under investigation and the future will tell us about the value of this strategy, taking the increased risk of bleeding into account.

Nutritional pharmacology

Arginine

The amino acid arginine possesses cytoprotective effects in ischemia and reperfusion and can form nitric oxide, citrulline, ornithine, growth factors, etc., and exerts numerous beneficial effects on the immune system. Arginine induces secretion of numerous hormones like pituitary growth hormone, insulin-like growth factor IgF-1, insulin, vasopressin, catecholamines, and somatostatin. Arginine also inhibits NF-κB translocation and decreases the release of IL-6, TNFα, IL-18, blocks adhesion molecules and inhibits lipid peroxidation [60].

Glutamine

Glutamine is a non-essential glycogenic amino acid and the preferred fuel for lymphocytes, enterocytes, and neutrophils. Glutamine also improves neutrophil, lymphocyte, and intestinal function [61]. This amino acid also maintains a normal GALT function and respiratory immunity [60].

Omega 3 Fatty Acids

Omega 3 polyunsaturated fatty acids (PUFA) represent essential fatty acids that possess immunomodulating effects due to their rapid incorporation into cell membranes. Thereby, they have influence on membrane stability, fluidity, cell mobility, and intra-cellular signaling pathways, as well as gene expression and cell differentiation. Omega 3 fatty acids are claimed to provide protection against infection [62]. Omega 3 fatty acids regulate the immune response by increasing membrane fluidity, introducing free radical lipid peroxide and by providing precursors in eicosanoid metabolism.

Nucleotides

Immunosuppression may partly be caused by nucleotide restriction. T-cell-dependent antibody production and lymphocyte function also seem to depend on nucleotide supplementation [63].

Lessons learned from immunomodulation and immunonutrition in critical illness and in association with major surgery

High-dose parenteral glutamine supplementation was followed by a reduction in infectious complications and shortened hospital stay in surgical patients and reduced complications and mortality in critically ill patients [64]. Glutamine-containing parenteral nutrition in critically ill ICU patients unable to receive enteral nutrition improved survival as evaluated after 6 months and reduced hospital costs per survivor [65]. A glutamine-containing enteral feed in the ICU reduced costs per survivor by 30% [66].

As mentioned above, the use of activated protein C reduces mortality in patients with severe sepsis [57]. The use of low-dose steroids decreases mortality in patients with septic shock and proven adrenalin insufficiency [67]. Intensive insulin therapy, maintaining "normal" glucose levels, reduced mortality in intensive care, especially deaths due to multiple organ failure in patients with a proven septic focus [68]. Perioperative omega 3 fatty acids downregulate the inflammatory response, diminish postoperative immunosuppression and shorten postoperative intensive care. Furthermore, the incidence of severe infections is reduced [69].

Immunonutrition (including arginine, glutamine, nucleotides, and omega 3 fatty acids) decreases infectious complications and the length of hospital stay in the critically ill, and especially in surgical patients. There does not, however, seem to be any effect of immunonutrition on mortality [70–74]. An important observation in a recent review is that mortality tends to increase in a subgroup of critically ill patients, especially when using products other than those high in arginine [75]. The reason for this is to be speculated upon but further emphasis may be directed at a more tailored type of immunomodulation, taking the actual immune function of the individual patient into consideration.

Perioperative immunonutrition in upper GI and HPB surgery

Preoperative immunonutrition for 5 days has been reported to improve outcome, including an improved immunometabolic response, a decreased infection rate, and reduced treatment costs of complications. There seems to be no additional benefit of postoperative prolongation of the immunonutrition [76,77].

In acute pancreatitis, the use of a platelet-activating factor antagonist initially seemed promising with a decrease in the incidence of organ failure and organ failure score [78,79], while later studies could not confirm the beneficial effects of lexipafant alone in acute pancreatitis [80,81].

In acute pancreatitis, early enteral nutrition seems feasible and reduces costs (at least of the nutritional supply), reduces septic complications, and the inflammatory response [82–85]. Overall, these studies have limitations due to a small number of included patients, a delay prior to initiation of the enteral nutrition, varying severity of pancreatitis, and a distal tube positioning. The supplementation with lactobacilli and fibers in early enteral nutrition reduced the incidence of pancreatic sepsis and the need for surgical intervention in patients with prognostic severe acute pancreatitis [86].

For pancreatic cancer, the condition seems to be associated with a frequent pro-inflammatory response with increases in, for example, CRP levels. A predominant problem in patients with irresectable pancreatic cancer, or recurrence after radically attempted resection, is cancer cachexia which seems to depend on the acute phase response [87]. A positive effect on the acute phase response, cancer-associated cachexia and quality of life has been reported following the administration of EPA (eicosapentaenoic acid, an omega 3 PUFA) [88]. Further support for a pro-inflammatory response in pancreatic cancer is the finding of an increased expression of cyclooxygenase (COX)-2 in pancreatic cancer and that resting energy expenditure decreased, implying a reduction in acute phase protein production, with ibuprofen administration in pancreatic cancer patients [89,90].

Conclusion and future aspects

In general, it seems that a limited window for intervention exists for modulation of the acute inflammatory response due to its complexity. Multiple mediators are involved and thereby a multimodal approach seems reasonable. From a nutritional point of view, emphasis should be put on the importance of enteral nutrition. Preoperative immunomodulation is probably becoming more established and could be offered as an oral formula. Additional specific nutrients and compounds are awaited, the indications for which should be based on the knowledge derived from a detailed mapping of the dynamics of the acute phase response, rendering possibilities for a future tailored and individualized treatment.

Acknowledgements

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