Major surgery and the immune system: from pathophysiology to treatment

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Abstract

Purpose of the review

The purpose of this review is to provide an overview of the immune response to major surgery, and the ways in which it may be modulated to improve postoperative outcomes.

Recent findings

Data from patients who have undergone a variety of tissue injuries (surgery, burns, sepsis, trauma) have shown the presence of a conserved "genomic storm" that alters the leukocyte transcriptome, with up-regulation of the innate immune response and concomitant down-regulation of the adaptive immune response. The innate and adaptive immune systems are often regarded largely distinct. However, more recent evidence suggests there are critical connections between the two arms of the immune response, whereby innate immune cells are able to suppress the adaptive response.

Summary

The immune system is critical to the host response to tissue injury occurring due to surgery. However, the physiological processes required to resolve the surgical insult can also contribute to sequelae such as cognitive decline, pneumonia, and acute kidney injury. Our understanding of the immune pathogenesis underlying these complications is improving, leading to interest in the development of immunomodulatory therapies, which aim to permit host defence whilst ameliorating post-operative complications.

Keywords: innate immunity; adaptive immunity; postoperative complications;

Introduction

The concept that injury is associated with an initial systemic inflammatory response followed by a compensatory anti-inflammatory response syndrome is well established [1]. Data from studies of patients who have undergone a variety of tissue injuries (surgery, burns, sepsis, trauma) have shown the presence of a conserved "genomic storm" that dynamically alters the leukocyte transcriptome, with up-regulation of the innate immune response and a concomitant down-regulation of the adaptive immune response. These early (within hours of tissue injury) transcriptional changes have been shown to be predictive of clinical outcomes across a range of settings [2-4]. Given that the pattern of the immune response to injury is broadly consistent across a range of insults, and that surgery often includes exposure to infective as well as non-infective insults, it is likely that much of the data derived from experiments aimed to understand the pathobiology of sepsis may have relevance in the perioperative setting. In this review we consider the impact of major surgery on the various components of the immune system, the ways in which these responses often lead to unintended post-operative complications, and some of the potential immunomodulatory therapies currently under investigation.

The innate immune response

The first line of immune defence is refered to as the innate immune response, a series of sterotyped and non-specific responses designed to rapidly react to the detection of pathogen associated molecular patterns (PAMPS) and damage-associated molecular patterns (DAMPS) that arise as a result of sterile or infective tissue damage. The roles of the innate immune response include the recruitment immune cells to the site of injury through the generation of inflammatory mediators, activation of the complement cascade, and presentation of detected antigens to the adaptive immune system to facilitate a more specific immune response.

Neutrophils are the principal effectors of the innate immune response. These highly motile cells are able to respond to the finest of chemotactic trails, are activated by both DAMPS and PAMPS, and engulf pathogens through a process called phagocytosis. Once a pathogen has been engulfed the neutrophil releases a variety of noxious substances (including reactive oxygen species, proteolytic enzymes, and antimicrobial peptides) within the cell in an attempt to kill the pathogen. In addition to bacterial killing, neutrophils release a variety

of extracellular mediators designed to attract other immune cells to the site of injury as a means of further elaboration of the immune response. Rapid alterations in both the phenotype and function of neutrophils have been described after both sterile and non-sterile tissue injury [5,6]. A sub-group of neutrophils have been identified in both experimental models and injured patients which supress the proliferation of T cells, thus providing a mechanism for cross-talk between the innate and adaptive immune systems [6].

Monocytes, and their derivative off-spring macrophages and dendritic cells, have three main functions: phagocytosis, antigen presentation, and cytokine production. Monocytes undertake phagocytosis using opsonising proteins such as antibodies or complement that coat the pathogen, as well as by directly binding to pathogen via pattern-recognition receptors (PRR). The fragments of pathogen that remain after phagocytosis / killing serve as antigens by becoming incorporated into major histocompatibility complex (MHC) molecules, which are trafficked to the cell surface and subsequently presented to the cells of the adaptive immune system, leading to generation of a specific immune response. Microbial products can directly activate monocytes, leading to the production of cytokines that perpetuate the immune response, but also contribute to the resolution of inflammation.

Classically, the clearance of free-flowing pathogens from the blood stream has been thought to be undertaken by the relatively immobile mononuclear cells within the liver and spleen. The liver and spleen, in contrast to the lungs, do no receive the entire cardiac output, which somewhat reduces the efficiency of this potential bacterial clearance mechanism. This paradigm is also somewhat at odds with the clinical observation that neutropenia, rather than macrophage dysfunction, is the major risk factor for bacterial infection. Recent evidence from studies undertaken in human and murine models of inflammation suggest that neutrophils exposed to inflammatory mediators are rapidly recruited to the pulmonary endothelium, where they may play a key role in host defence by eliminating pathogens sequestered within the lung [7,8].

In patients undergoing major surgery, infectious post-operative complications have been shown to have a reproducible association with the loss of Human Leukocyte Anigen-DR (HLA-DR) from the cell surface of monocytes, accompanied by the presence of increased numbers of myeloid-derived supressor cells. Recent data from Longbottom and colleagues has demonstrated that the loss of HLA-DR from the monocyte is mediated by soluble factors still present in the circulation 24-hours after surgery, and is not a direct

consequence of surgical tissue damage, anaethesia, or endotoxin release occurring at the time of surgery, suggesting that post-operative immunomodulation may be a viable therapeutic strategy [9].

The adaptive immune response

The adaptive immune system consists of two major cell types, B and T lymphocytes. In contrast to the innate immune cell pattern recognition receptors (PRRs) that sense common patterns on antigens, adaptive immune cells express specific antigen detecting receptors on the cell surface (B cell receptors (BCR) and T cell receptors (TCR)). The close interlinkage between the adaptive and innate immune system means that when danger signals arising from tissue damage (DAMPs) during tissue level trauma (from surgery, trauma, or burns) activate the innate immune system, it also leads to profound changes in the adaptive immune system [10]. The resulting host immune state is best conceptualised as a concomitant pro and anti-inflammatory response in the innate immune system and profound suppression of adaptive immunity including down regulation of most T cell responses, albeit with enhanced BCR signalling [4]. These adaptive immune system changes are more pronounced in patients with pre-existing conditions that alter lymphocyte biology (such as cancer) and further increase the risk of adverse outcomes in this population [11]. Xiao and colleagues also highlight that the immune changes seen at the leukocyte transcriptome level in trauma and surgery are very similar to that seen in sepsis using an endotoxemia model [4]. These changes in the adaptive immune system are likely to be heterogeneously distributed resulting in different patient phenotypes, with up or down regulation of antigen presentation pathways, BCR signalling, TCR signalling, apoptosis pathways, impaired lymphocyte function, impaired metabolic activity, loss of memory B cells, and features of T cell exhaustion [12-15]. Importantly, these changes increase the risk of adverse outcomes [16] and could be useful in stratifying risk of nosocomial infections in post-surgical patients with critical illness [17].

The major immune cell interactions ocurring after tissue injury are summarise in Figure one.

Special circumstances

Cancer surgery

Whilst the compensatory anti-inflammatory response observed after major surgery is a necessary requirement for wound healing, in the setting of cancer this response has other potentially more deleterious

actions, including direct effects on malignant tissue to promote cancer cell motility, invasion, and proliferation. In addition, there is a supression of the cells involved in immune surveillance and the host response to the detection of malignant cells. Further, the choice of anesthetic and other perioperative medications (e.g. analgesia) may influence the development of postoperative immunosupression and promote cancer cell proliferation. The impact of anesthetic management during cancer surgery has recently been comprehensively reviewed [18].

Organ transplantation

Solid organ transplantation has been one of the major surgical advances of the past 65 years. However, graft rejection is an important post-operative complication that necessitates immunosuppressive therapy from the perioperative period onwards to prevent rejection and the associated mortality and morbidity. There are a number of classes of immunosuppressive drugs which act on different components of the immune system, as well as considerable variability in the use of these agents. There are many complications of post-operative immunosupressive therapy, however one of the more serious is post-transplantation lymphoprolierative disorder (PTLD). The risk of PTLD after solid organ transplantation varies with the type of organ transplanted, the mismatch between the Epstein-Barr viral status of the transplant donor relative to the recipient, as well as the intensity, duration and nature of the immunosupressive therapy regimen [19].

Post-operative complications

Pneumonia

Post-operative pulmonary complications occur in approximately 10% of patients undergoing general anesthesia for surgery. In a recent large multicenter observational study, pneumonia occurred within the first five days of 0.4% of post-operative patients [20]. The pathogenesis of post-operative pneumonia is likely multifactorial, with pre-operative (e.g. smoking, comorbidities), intraoperative (e.g. duration of procedure, mechanical ventilation strategy), and post-operative (e.g. analgesia, mobilsation) factors all contributing. However, it is has been shown that complement-mediated innate immune dysfunction may also contribute by the induction of a prolonged phagocytic defect [17, 21].

Cognitive decline

Cognitive dysfunction after surgery is a well-recognised phenomenon. Cross-talk between the brain and immune system is bidirectional; The injured brain exacerbates both the systemic inflammatory response and the associated immunoparesis through parasympathetic and sympathetic pathways, and the complement system has been shown to be an early mediator of neuroinflammation, leading to cognitive dysfunction [22]. Further, damage arising from proinflammatory cytokines released in response to the surgical insult may reduce the integrity of the blood-brain barrier allowing inflammatory mediators and immune cells to enter the brain. Receptors for pro-inflammatory cytokines are highly expressed in the hippocampus, and persistent activation of hippocampal microglial cells may lead to irreversible cognitive decline [23].

Acute kidney injury

Acute kidney injury (AKI) is a common complication in patients undergoing surgery. The aetiology usually multifactorial, with ischaemia, inflammation, and toxins all interacting with a pre-exisintg patient factors. The potential contribution of inflammation to renal injury was elegantly highlighted by Imai and colleagues [24], who demonstrated that injurious mechanical ventilation may lead to epithelial cell apoptosis in the kidney, via the release of soluble inflammatory mediators from a remote site of injury. It is enticing to speculate that the release of inflammatory cytokines as a consequence of the immune response to surgically-induced tissue injury may lead to similar effects.

Immunomodulatory pharmacotherapy for immune dysfunction

There has been much recent interest in the potential for immunomodulatory therapies to improve clinical outcomes by ameliorating the deranged immune responses observed after injury. Pinder and colleagues undertook a clinical trial of granulocyte-macrophage colony stimulating factor (GM-CSF) therapy in critically ill adults with impaired neutrophil phagocytosis [25]. Whilst the trial did not reach the primary end point, it did suggest that GM-CSF may improve moncyte expression of HLA-DR, (which as mentioned above is is associated with the development of post-operative infectious complications) as well as improving the proportion of patients with improved neutrophil phagocytosis. However, further clinical trials focussed on this end point will be required.

Whilst GM-CSF may improve monocyte HLA-DR expression in critically ill patients, other mechanisms may also be involved. Longbottom and colleagues [9] investigated the hypothesis that increased serum IL-6 concentrations following elective surgery promote immunosuppression that may be reversed with interferon-gamma treatment. Peripheral blood mononuclear cells (PBMC) from healthy donors showed reduced expression of HLA-DR when exposed to serum obtained from post-operative patients, when compared to preoperative serum, and this decrease was prevented by the addition to interferon-gamma, but not IL-6 neutraling antibody.

Conclusion

The response of the immune system to insults such as major surgery is designed to maximise host defence and promote healing, as a consequence an early systemic inflammatory response is accompanied by a compensatory anti-inflammatory response. The biology underlying these two responses is not fully elucidated. However, recent data has highlighted that cross-talk between the innate and adaptive immune responses may be contributory - a subset of neutrophils has been identified in injured patients, which are able to suppress T cell proliferation and hence the downstream actions of the adaptive immune response.

Whilst the responses of the immune system to injury are required to protect the host, they often also contribute to post-operative complications such as pneumonia, cognitive decline, and acute kidney injury. This duality has led to developing interest in the potential of immunomodulatory therapies that might permit the beneficial effects of the immune response, whilst minimising post-operative complications – a complex undertaking, and one which is not yet ready for routine clinical use.

Key points

1. The response of the immune system to insults such as major surgery is designed to maximise host defence and promote healing, as a consequence an early systemic inflammatory response is accompanied by a compensatory anti-inflammatory response.

2. Cross-talk between the innate and adaptive immune responses may occur, e.g. a subset of neutrophils has been identified that are able to suppress T cell proliferation, and hence downstream actions of the adaptive immune response.

3. The immune response to injury is generated to protect the host, however these responses often also contribute to post-operative complications such as pneumonia, cognitive decline, and acute kidney injury.

Acknowledgments

None

Financial support and sponsorship

Dr Shankar Hari holds an NIHR Clinician Scientist Award (CS-2016-16-011). Work in Dr Summers' laboratory is supported by the Wellcome Trust, the Medical Research Council, GlaxoSmithKline plc, and the Cambridge NIHR Biomedical Research Centre.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care

Conflicts of interest

None.

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Figure legend

Figure one: The major interactions between innate and adaptive immune cells in response to tissue injury.

The cells of the innate immune system (neutrophils, monocytes, macrophages) detect pathogen- and damage- associated molecular pattersn (PAMPs and DAMPs), which leads to a variety of responses including cytokine/chemokine production, phagocytosis, and interactions with the cells of the adaptive immune system. Monocyte-macrophages act as antigen presentation cells to elict specific immune (antibody-mediated) responses from B cells, which also requires co-signals from T cells. Whilst it is important that inflammation is occurrs, resolution of tissue injury is also critical to the healing process. A subset of neutrophils are able to interact with T cells to suppress their proliferation, and hence reduce the adaptive immune response, limiting tissue injury and promoting resolution.