The Perioperative Immune Response

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Abstract

Purpose of Review

A host of immune modulators are now available in clinical practice. The perioperative period is characterised by profound alterations in host immunity, which can result in poor outcomes, which include infection, cancer recurrence and organ failure. Manipulation of the peri-operative immune response has the potential to improve outcomes. A complete understanding of the mechanisms and clinical consequences of altered immune function in this setting is therefore imperative.

Recent findings

Recent *in vivo* data has emerged which furthers our understanding of the interaction between tissue damage, immune modulation and clinical outcomes by utilising novel laboratory techniques capable of monitoring single cell immune signatures. Traditional gene expression assays have continued to demonstrate their utility and have been instrumental in defining the host response to perioperative allogeneic blood transfusion. These mechanistic studies are complemented by large clinical studies describing associations between anaesthetic modalities and immune-related outcomes.

Summary

Laboratory techniques are now available that can monitor the perioperative immune response and could be further developed to introduce personalised care pathways. Consideration must also be given to anaesthesia techniques and perioperative treatments that, whilst not immediately harmful, may be associated with poor outcomes temporally distant from the treatment, secondary to induced immunosuppression.

Introduction

Tissue damage is inevitable following major surgery and induces a complex host immune response. This is initiated by receptor-mediated detection of specific intracellular compounds released by damaged cells. These are collectively referred to as alarmins and they induce an inflammatory cascade, the ultimate aim of which is tissue repair and the restoration of homeostasis. However, inter-individual variability exists in the host response to alarmin release and a dysregulated, poorly coordinated immune response to tissue damage is a major contributor to perioperative organ injury and the development of a state of prolonged immunoparesis. Perioperative large-scale alterations in immune and inflammatory pathways are associated with many clinically important post-operative complications, which include infections, renal injury and cancer recurrence. In addition to tissue damage, many additional factors influence the perioperative host immune response. These include the administration of anaesthetic agents, regional anaesthesia, analgesics, anti-emetics, blood products and the underlying disease process. This review will discuss recent advances in our understanding of this response, potential triggers and the clinical consequences of altered perioperative immunity.

The immune response to major tissue damage

The immune response to major tissue damage has been extensively characterised [1*]. Although severe traumatic injury as a model provides information that is highly relevant and applicable to perioperative medicine, the picture is clouded by confounding influences such as hypoperfusion and the subsequent reperfusion injury, the frequent transfusion of allogenic blood products and neuro-inflammatory mediated changes secondary to an often coexisting traumatic brain injury [1*]. The key link between tissue damage and subsequent inflammation is the release of alarmins [2].

Alarmins, often termed Damage-Associated Molecular Pattern molecules (DAMPs), are a group of structurally diverse compounds released following tissue damage as cells undergo physiological stress or necrosis [3]. DAMPs are the endogenous equivalent of Pathogen Associated Molecular Pattern molecules (PAMPs) that initiate an immune response in the setting of infection. Indeed, DAMPs such as high-mobility-group box (HMGB) 1 and mitochondrial DNA (mtDNA) bear significant structural homology to their PAMP analogues and often activate the same pattern recognition receptors (PRRs) [3, 4]. This, in part, explains why the clinical pictures of severe sterile inflammation and sepsis can be difficult or impossible to distinguish. A wide variety of PRRs have been described including the membrane bound Toll-like receptors (TLRs) and the cytoplasmic NOD-like receptors (NLRs) [3, 5]. Activation of PRRs induces an enzymatic cascade, which results in down-stream phosphorylation of transcription factors such as NF-κB, which in turn alters cytokine transcription (Figure 1). Immune cell subtypes are activated dependent on their expression of specific PRRs on their cell surface at the time of alarmin release [5]. Alarmins not only activate this innate response but also provide a vital link between the innate and adaptive immune systems by activating antigen-presenting cells such as monocytes and dendritic cells [6].

Until quite recently, studies exploring the inflammatory response to major tissue damage have been mainly limited to a reductionist approach where correlations have been sought between clinical end points and a limited number of candidate mediators. The success of this approach has varied depending on the end point chosen and the assay methodology, with quantitative polymerase chain reaction (qPCR) quantification of messenger RNA (mRNA) transcripts proving more sensitive than enzyme linked immunosorbant assays (ELISA) quantification of protein product. Levels of interleukin 6 (IL-6) and IL-10 consistently rise in proportion to the extent of the tissue damage and levels are associated with a greater incidence of subsequent nosocomial infection [7-10]. As arguably the most potent anti-inflammatory cytokine it is unsurprising that high IL-10 levels are associated with later infection. However, although IL-6 is traditionally considered a pro-inflammatory cytokine it also up-regulates suppressor of cytokine signalling (SOCS)-1 expression and inhibits T helper cell type 1 (T_h1)

differentiation [11]. In this manner, IL-6 could plausibly exert an effect that limits effective host bactericidal capacity. Similarly, the expression of Human Leukocyte Antigen DR on the surface of monocytes (mHLA-DR) consistently falls following tissue damage and is related to nosocomial infection [12, 13]. Again this is unsurprising as the maintenance of adequate Major Histocompatibility Complex (MHC) class II molecules such as HLA-DR on the surface of antigen presenting cells is crucial to maintain immune competence. Others have proposed genomic signatures where higher ratios of anti-inflammatory to pro-inflammatory cytokines correlate with postoperative infection [14]. What remains elusive is the mechanism whereby alarmin release and the subsequent enzymatic cascades lead to an immunosuppressed phenotype and the survival advantage, if any, of this trait.

Advances in technology recently permitted the simultaneous analysis of the leukocyte transcriptome of 20,720 genes in patients following severe blunt trauma and burn injury in a landmark paper [15]. Following these stimuli, which would clearly result in significant alarmin release, 80% of cellular pathways and functions were altered. Innate immunity pathways, B-cell receptor signalling and IL-10 signalling all demonstrated up-regulated gene expression whereas antigen presentation and T-cell activation were down-regulated. Importantly, it was the overall magnitude of the genomic alterations that correlated with nosocomial infections and organ impairment as opposed to differential activation of specific pathways. Although this snapshot of the transcriptome was within 12 hours of injury, in some cases patients had undergone extensive resuscitation and therefore this heterogeneous picture should be interpreted with caution in the context of the perioperative patient. This paper has however helped to re-define the previously proposed bimodal inflammatory response model to tissue damage, suggesting concomitant activation of pro-inflammatory and anti-inflammatory pathways.

Further application of advanced technology has seen investigators utilise mass cytometry to detect surgery-induced immune perturbations in clinical samples and relate these findings to post-operative recovery [16**]. Mass cytometry involves using antibodies to tag cellular components prior to nebulising the cells and then using a time of flight mass spectrometer for analysis. This complex technique has

extensively described the immune response in peripheral blood following elective hip arthroplasty and has demonstrated a time-dependent and cell type specific activation of immune signalling networks. Over the early post-operative period there is an expansion of Natural Killer (NK) cells, neutrophils and $CD14^+$ monocytes, which is followed, within 24 hours, by contraction of $CD4^+$ and $CD8^+$ T cells. Most notable was a six-fold expansion of $CD33^+CD11b^+CD14^+HLA\text{-}DR^{low}$ monocytes with phenotypic similarities to myeloid derived suppressor cells (MDSCs). MDSCs are a heterogeneous group of immunosuppressive cells [17] that remain poorly defined in terms of cell surface markers and directly suppress T cell functions through a variety of mechanisms including the production of reactive oxygen species (ROS) [18] and Arginase-1 [19] as well as IL-10 and TGF-β release [20]. In addition to the monocyte derived MDSCs that expand following hip arthroplasty, a distinct subset of $CD62L^{dim}$ neutrophil-derived MDSCs appear shortly after blunt trauma and tissue injury and induce T cell suppression in a Mac-1 (CD11b) dependent fashion [21, 22]. Further characterisation of the expansion of MDSCs in the post-operative period may provide a vital link between alarmin release and an immunosuppressed phenotype. An analysis of surgery induced changes in the phosphorylation of intracellular signalling proteins in different immune subsets provides interesting correlations, particularly in the $CD14^+HLA\text{-}DR^{low}$ monocyte clusters where immune correlates, such as STAT3 signalling, account for up to 60% of the variability in post-operative recovery [16]. It is particularly relevant that in another cohort pre-operative differences in monocyte STAT signalling pathways correlate to post-operative complications [23*].

These data demonstrate that our understanding of the immune response to surgery and tissue damage is rapidly expanding in tandem with available technology and provides opportunities for the identification of therapeutic targets and predictive biomarkers.

Anaesthesia, analgesics & the inflammatory response

Whilst the presence of significant tissue damage exerts the dominant influence on altered perioperative immunity, the administration of anaesthetic agents has additional and complex effects. In the clinical scenario it can be very difficult to confidently separate the immune modulating effects of anaesthesia from the response to surgery and tissue damage and consequently much of the available mechanistic data is generated either from *in vitro* experimental work or animal models. Broadly speaking, the overriding effect of anaesthesia on the immune system is one of suppression and is mediated both directly and indirectly. Inhalational and intravenous anaesthetics induce lymphocyte apoptosis and impair neutrophil phagocytosis [24]. Secondary immunosuppressive effects are mediated through modulation of the neural immune-regulatory circuit and activation of cholinergic anti-inflammatory pathways and also as a consequence of altered adrenocortical functions [25]. Opioids are administered frequently during anaesthesia and their inhibition of innate and adaptive immunity is well described [26]. Natural killer cells, a key facet of innate immunity and host tumour surveillance, are suppressed by both anaesthesia and opioids [27]. Clearly, the choice of anaesthetic technique may have important clinical implications independent of the surgical procedure. The presence of an anaesthesia-induced immunocompromised phenotype may affect outcome in different ways but in the perioperative setting it is the creation of a pro-tumour and pro-infection cytokine and inflammatory milieu that is of key concern. Cancer and infection are intimately linked as both flourish in an environment of T cell exhaustion and lymphocyte anergy, such as is observed in the perioperative period [28*]. It is also notable that both conditions themselves also induce this phenotype, which has additional implications for those patients with chronic infections and malignancies that undergo operative treatment.

Although the hormonal stress response is not completed ablated by the use of regional anaesthesia, avoiding general anaesthesia is associated with a blunted response and lower peak levels of serum cortisol [29]. Interestingly, in a large cohort of patients undergoing knee arthroplasty the administration of neuraxial anaesthesia alone when compared to general anaesthesia alone was associated with a decreased

incidence of post-operative infections [30]. The odds of pneumonia occurrence were 0.51 in those patients receiving neuraxial anaesthesia alone when compared to general anaesthesia alone in this cohort. Whilst this study was not randomised it is important that the association remained following a propensity-matched analysis. A strategy of limiting, but not excluding, inhalational and intravenous anaesthetics by combining epidural and general anaesthesia has suggested subtle advantages above general anaesthesia alone in terms of the duration of post-operative immunosuppression, reduction in absolute T lymphocyte count and the relative proportions of T_h1, T_h2 and T_{reg} cell subsets [31, 32]. However, the clinical benefit of this combined approach remains unclear. A meta-analysis of studies comparing a technique of combined epidural and general anaesthesia versus general anaesthesia alone failed to convincingly demonstrate a benefit in terms of cancer recurrence [33]. However, in a review of nearly 400,000 patients undergoing hip or knee arthroplasty, whilst the benefit of neuraxial anaesthesia alone was replicated in terms of lesser infection risk any protective effect appeared markedly reduced in the cohort that received a combined general and regional anaesthesia technique [34]. In each of the above studies the absence of randomisation makes interpretation difficult. Consequently, these studies are prone to inherent biases making it impossible to draw definitive conclusions and they should be viewed as hypothesis generating. This viewpoint is supported by a recent consensus statement expressing concern that experimental evidence suggests a link between anaesthestic technique and cancer recurrence yet accepts that there is insufficient clinical evidence to justify any change in practice and calls for the conduct of definitive randomised clinical trials [35].

Common adjunctive perioperative treatments & inflammation

Dexamethasone is frequently administered during anaesthesia as an effective prophylactic anti-emetic. Single doses have additional beneficial effects such as enhanced analgesia and reduced surgical site swelling. However, it is a potent glucocorticoid and even single doses can display effects on

adrenocortical functions a number of days following administration [36]. Although there is clear physiological rationale for implicating dexamethasone in enhancing the risk of postoperative infection the clinical data have been conflicting [37-39]. A recent meta-analysis of randomised controlled trials using single-dose dexamethasone found no association with post-operative infection [40]. These results should however be interpreted cautiously as the dexamethasone group also received less opioids, thereby introducing a potential source of bias.

Other ubiquitously prescribed perioperative treatments with potential immunomodulating properties, such as paracetamol, NSAIDs and gabapentinoids, have not demonstrated clear associations with important immune outcomes such as infection [41].

The immunomodulating qualities of perioperative allogenic blood transfusion have long been appreciated and have even been exploited to prevent renal allograft rejection in the era prior to the development of effective immunosuppressants [42]. The unintended clinical consequences of perioperative immune modulation by allogeneic blood, particularly following colorectal surgery, include an increased susceptibility to infectious complications and also cancer recurrence [43-45]. More recently, similar links between transfusion and cancer recurrence have also been reported following surgery for prostate, hepatic, and head-and-neck cancers [46-48]. Progress towards identifying a plausible mechanism has been made by our group's identification of a pattern of gene expression, consistent with immunosuppression, associated with blood transfusion in two separate cohorts of patients; those undergoing major elective gastrointestinal surgery and also following severe traumatic injury [49*, 50*]. The observed pattern of cytokine production could classically be described as both a pro-infection and pro-tumour environment and indeed in the trauma cohort an association was also observed between blood transfusion and infectious complications [50*]. Interestingly, blood stored for prolonged periods prior to administration may be particularly deleterious with *in vivo* models suggesting that aged red blood cells may exert enhanced tumour progression [51]. Our group has also recently demonstrated that the severity of post-traumatic immunosuppression is related to the duration of storage blood products thereby suggesting a

mechanistic link [52]. These data support the hypothesis that aged red blood cells may promote tumour recurrence and increase susceptibility to infectious complications through modulation of the immune system.

Epigenetics and immune responsiveness

Epigenetics is an umbrella term that describes host mechanisms of altering gene expression that do not require a change in the underlying DNA sequence. The enzymatic conversion of cytosine to 5-methylcytosine and the methylation or acetylation of chromatin usually causes transcriptional repression by impeding access to promoter regions whereas the overexpression of micro RNAs (miRs) can both inhibit transcription and target messenger RNA (mRNA) for degradation. Cancer research has pioneered the study of epigenetic modifications that promote an immunosuppressed phenotype thereby facilitating immune evasion by cancerous cells and has also been at the forefront of developing epigenetic modifying agents that can target these processes [53*]. In the perioperative period epigenetic studies have largely focused on acute and chronic pain processes, although data supportive of a key role in inflammation and immunosuppression have emerged [54]. For example, the use of opioids in the perioperative period promotes global DNA methylation in peripheral blood leukocytes [55]. This is consistent with the transcriptional repression of pro-inflammatory genes, which may have longer-term implications as epigenetic alterations persist. Furthermore, our group have described the post-traumatic production of miRNAs with sequence complementarity to the mRNA transcripts of key cytokines whose expression levels change markedly following tissue damage [56]. This may represent an epigenetic regulation of the response to tissue damage through the targeted degradation of pro-inflammatory mRNAs by miRs. In this setting miR levels also correlate with nosocomial pneumonia. Although the study of epigenetics in the perioperative period is in its infancy the therapeutic and diagnostic implications may be substantial.

Conclusions

Rapid advances in our understanding of perioperative inflammatory processes, their causes and consequences coincides with development of multiple, clinically applicable immune and epigenetic modulators such as growth factors, antibodies, DNA hypomethylating agents, histone deacetylase inhibitors and micro RNA mimics. The prospect of manipulating an errant immune response to major surgery is no longer aspirational. Personalised medicine has become a reality for many patients suffering from a variety of immune related disorders such as myelodysplasia, rheumatoid arthritis and inflammatory bowel disease. These patients now routinely benefit from therapies that target specific facets of a pathological immune response and the challenge for perioperative medicine is to distinguish between protective and pathogenic immune responses in the perioperative period and to identify modifiable immune pathways that when altered can impact on important clinical endpoints.

Uniquely, the elective nature of the majority of surgical procedures introduces the possibility of developing a pre-emptive, preventative, immunotherapy strategy that may ultimately prove advantageous. The potential for pre-emptive or early therapies for those undergoing scheduled procedures vastly increases the prospects of success of any intervention for the perioperative patient. To achieve this ultimate aim basic scientists must continue to define pathological inflammatory pathways and collaborate with translational scientists identifying interventions suitable for clinical use. Clinical trialists must also be engaged with this process so that potential patient benefits are revealed in well-designed clinical trials.

Key Points

1. **The immunological response to tissue damage is broad but predominately immunosuppressive in nature.**
2. **Anaesthetic technique plays a key role in modulating the immune response, with neuraxial anaesthesia potentially reducing the incidence of nocosomial infections through the avoidance of general anaesthetic agents.**
3. **The role of allogeneic blood transfusion augments the immune response seen to tissue damage.**
4. **Laboratory techniques are now available that can monitor the perioperative immune response and could be further developed to introduce personalised care pathways to manipulate an errant immune response.**

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Legend

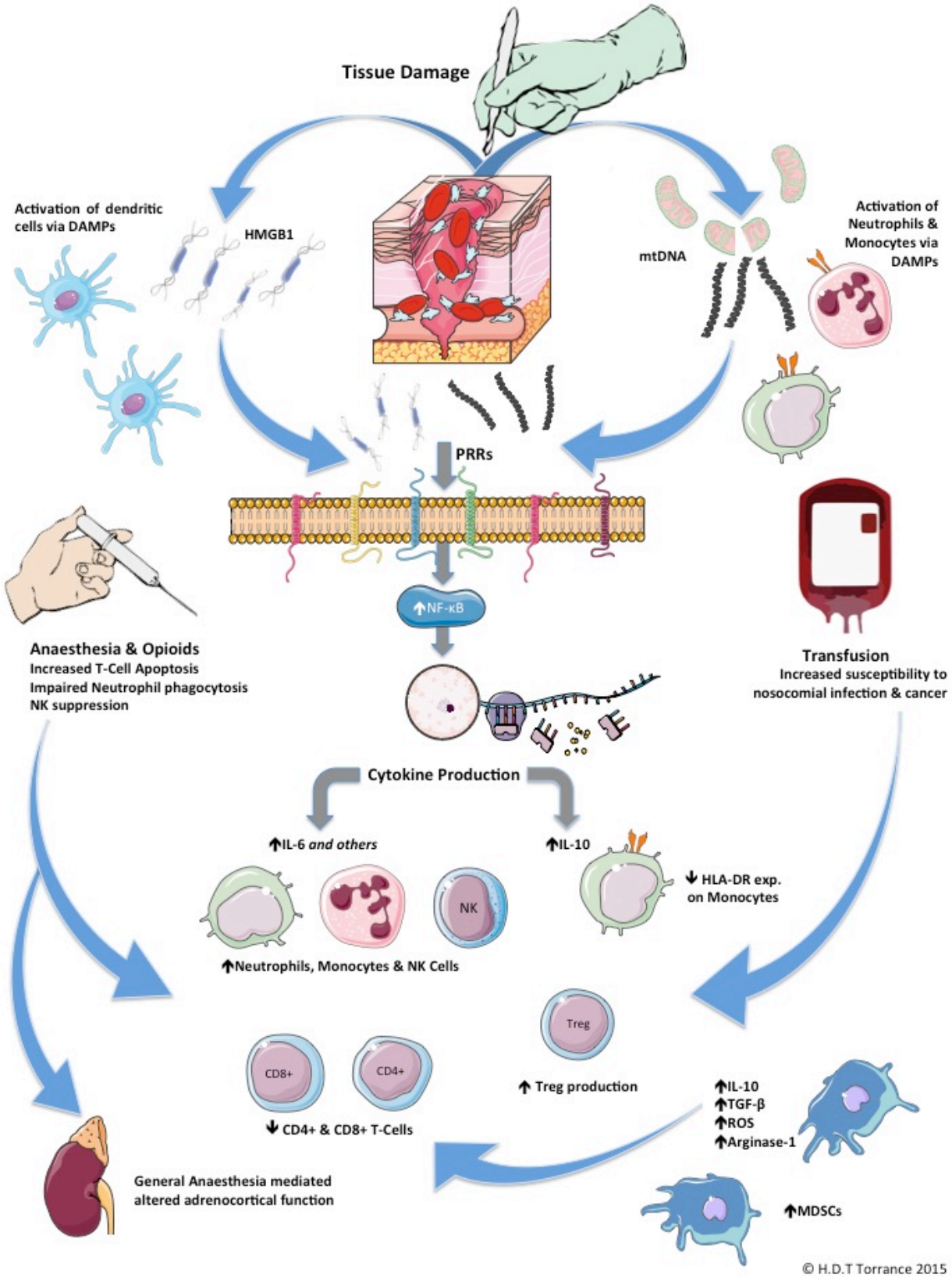
Fig. 1: Pathways of immune activation following tissue damage

Tissue damage leads to the release of Damage Activated Molecular Patterns (DAMPs) into the circulation, in this case illustrated by high-mobility-group box (HMGB) 1 and mitochondrial DNA (mtDNA), causing activation of pattern recognition receptors (PRRs). DAMPs also independently activate neutrophils, monocytes and dendritic cells.

Activation of PRRs causes the triggering of signalling pathways and transcription factors such as NF-kB. NF-kB then translocates to the nucleus, promoting cytokine gene transcription. Protein translation results in the secretion of cytokines and chemokines.

Postoperatively, increases in neutrophils, monocytes and natural killer (NK) cells are seen along with later decreases in CD4+ and CD8+ T-cells. IL-6 and IL-10 consistently increase during this phase and IL-10 is associated with downregulation of HLA-DR expression on the surface of circulating monocytes. Immunosuppressive T_{reg} cells and myeloid derived suppressor cells (MDSCs) increase postoperatively. MDSCs cause T-cells suppression via the secretion of reactive oxygen species (ROS), arginine-1 as well as the immunosuppressive cytokines, IL-10 and TGF-β, amongst other mechanisms. Treg cells are known producers immunosuppressive cytokines; IL-10, TGF-β and IL-4.

The transfusion of blood and blood products is known to contribute to this immunosuppressive environment, while anaesthetics and opioids cause increase T-cell apoptosis, impair neutrophil phagocytosis and suppress NK cells suppression. Anaesthetics mediate secondary effects through altered adrenocortical function and central mechanisms.


Tissue Damage
Activation of dendritic cells via DAMPs
HMGB1
mtDNA
Activation of Neutrophils & Monocytes via DAMPs
PRRs
↑NF-κB
Anaesthesia & Opioids
Increased T-Cell Apoptosis
Impaired Neutrophil phagocytosis
NK suppression
Transfusion
Increased susceptibility to nosocomial infection & cancer
Cytokine Production
↑IL-6 and others
↑IL-10
↓ HLA-DR exp. on Monocytes
NK
↑Neutrophils, Monocytes & NK Cells
Treg
CD8+
CD4+
↑ Treg production
↓ CD4+ & CD8+ T-Cells
↑IL-10
↑TGF-β
↑ROS
↑Arginase-1
↑MDSCs
General Anaesthesia mediated altered adrenocortical function
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