Neuroendocrine and Immune Responses to Surgery
R Scholl, A Bekker, R Babu

Abstract
Surgery elicits profound changes in the neuroendocrine, metabolic, and immune systems, which collectively constitutes the "stress response". These responses have been implicated in the development of a number of postoperative complications such as postoperative delirium, cognitive dysfunction, infection, and cancer recurrence. This review describes how 'surgical stress' and inflammatory responses affects the immune system as well as the patient's susceptibility to these untoward events. The immune system is composed of two major subdivisions, the innate or non-specific immune system and the adaptive or specific immune system. Each subdivision has humoral and cellular elements which allow the immune system to protect the body from foreign pathogens and cancer. The ‘Stress response’ results in the systemic release of cortisol, catecholamines, acute phase reactants, and cytokines which modulate the activity of both innate and adaptive components. There is a sensitive balance between pro- and anti-inflammatory cytokines after injury/surgery. Deficient responses may result in infections secondary to immunosuppression. On the other hand the excessive responses may lead to systemic inflammatory response syndrome (SIRS) and multi-organ failure (MOF). Additionally, we discuss how anesthesia and variable perioperative factors, such as blood transfusions, pain, and hyperglycemia can further disrupt immune performance. Understanding these postsurgical disruptions in immune homeostasis may aid the surgeon and anesthesiologist in choosing surgical and anesthetic techniques that preserve and/or enhance immune function.

INTRODUCTION
The immune system is a complex interaction between cells, molecules, and organs to defend the body against pathogens and foreign substances. Its primary role is to distinguish between “self” versus “nonself” and to effectively remove “nonself” antigens from the body (1). Dysregulation in immune function and inflammatory cascades can lead to a number of deleterious conditions, such as autoimmune disease, cognitive impairment, cancer, and infection/sepsis (2). The two major branches of the immune system are non-specific innate immunity and adaptive or specific acquired immunity. They each are comprised of both cellular and noncellular (humoral) components (Table 1) (1).

Table 1: Cellular and Humoral Components of Innate and Adaptive Immunity

<table>
<thead>
<tr>
<th>Immunity</th>
<th>Cellular Components</th>
<th>Humoral Components</th>
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</thead>
<tbody>
<tr>
<td>Innate</td>
<td>Phagocytic cells: macrophages, neutrophils</td>
<td>Complement</td>
</tr>
<tr>
<td></td>
<td>Natural killer (NK) cells</td>
<td>Acute phase reactants (APR):</td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td>- Immunoglobulin</td>
</tr>
<tr>
<td></td>
<td>Antigen Presenting Cells (APC)</td>
<td>- Immunosuppressive acute phase protein</td>
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<tr>
<td></td>
<td></td>
<td>- C-reactive protein (CRP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cytokines</td>
</tr>
<tr>
<td>Adaptive</td>
<td>T lymphocytes:</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td></td>
<td>- Helper T (CD4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- CD4+ T (CD8)</td>
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<tr>
<td></td>
<td>- CD8+ T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Suppressor T</td>
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</table>

Innate immunity can be thought of the body’s first line of defense and includes physical barriers, such as skin and mucous membranes, as well as pre-formed molecules and cells. Innate immunity is nonspecific, rapid, and does not require prior antigenic exposure for activation (1, 3, 4, 5). For example, cells involved in innate immunity detect evolutionary conserved microbial sequences that are invariant among a class of pathogens allowing them to initiate an immediate attack without previous pathogen contact (4).

Conversely, adaptive or acquired immunity is specific, requires prior antigenic exposure, is enhanced by repeat
exposure to pathogen (secondary response), and has memory (6). Initiation of the immune response begins when a mononuclear phagocyte ingests an antigen and then presents the antigenic peptide fragment on its membrane (antigen presenting cell [APC]). This stimulates the production and amplification of T and B-lymphocyte clones specific for that antigen (1, 5).

T-lymphocytes can be divided into four major types: helper, cytotoxic, memory, and regulatory/suppressor T-cells. Helper T-cells (T<sub>H</sub>) release a variety of cytokines that enhance the activity and proliferation of other components of the immune system. Helper T-cells differentiate from a precursor helper T-cell (Th0) into Th1 or Th2 cells based on the immune challenge and the host’s cytokine/hormonal milieu. Th1 cells bolster cell-mediated immunity (CMI) whereas Th2 cells support humoral immunity (3, 5). A balance between Th1 vs. Th2 responses is critical in maintaining immune homeostasis (5).

Cytotoxic T-cells (T<sub>C</sub>), also known as CD8+ cells, are involved in directing apoptosis in tumor and virally infected cells and are also implicated in transplant rejection. Memory T-cells are not directly involved in removing pathogens but rather “remember” past infections; thus, the term antigen-experienced T-cell. Upon a second exposure to the antigen, these cells can elicit a stronger and faster immune response, i.e. “secondary response”, by reproducing into effective T lymphocyte subsets.

The last major class of T-cells are regulatory/suppressor T-lymphocytes. They function in preventing excessive reaction after an immune challenge is resolved and in regulating responses that may attack one’s tissues (autoimmunity).

B-lymphocytes are responsible for the humoral element in adaptive immunity. Helper T-lymphocytes secrete cytokines that assist the maturation of B-cells into antibody-secreting plasma cells or memory B-cells. Plasma cells secrete antibodies which bind to their complementary pathogen resulting in easy removal by phagocytic cells (opsonization). Repeat exposure to an antigen activates memory B-cells out of dormancy where they initiate a rapid secondary humoral immune response.

**SURGICAL STRESS RESPONSE**

The ‘surgical stress’ response reflects a combination of endocrinological, immunological, and hematological changes occurring after injury/trauma. The degree of the response is proportional to the magnitude of injury and reflects increased demands on organ function (7, 8). Evolutionarily, the ‘stress response’ was protective. It allowed animals to survive without food until their injuries healed by catabolizing stored body fuels and retaining water and salt. However, it is now often thought to be detrimental in modern surgical practice and efforts are made to minimize the response with minimally invasive techniques and potential benefits of regional anesthesia (9).

The ‘stress’ response begins by activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, via afferent nerves from the site of tissue damage. This results in secretion of ACTH, cortisol, catecholamines, aldosterone, AVP, and glucagon in an effort to provide the host with energy, retain fluid and salt, and maintain cardiovascular homeostasis. This high ‘stress’ state, however, can result in harmful outcomes to the host such as hyperglycemia, cardiovascular instability (hypertension, tachycardia), and immunosuppression (3, 7, 9, 10).

The hypersecretion of cortisol and catecholamines, due to surgical stress, has both anti-inflammatory and immunosuppressant effects (10, 11). Cortisol interferes with production of cytokines, prostaglandins and histamine, impedes aggregation of macrophages and neutrophils at site of injury, and decreases phagocytosis. In addition, it induces apoptosis in T lymphocytes and promotes Th2 cell dominance (antibody/allergic) (9, 10, 12). The Th2 response is proportional to the degree of surgical tissue damage and results in deficient NK cell function and capacity to clear microbial infections (13).

**POSTSURGICAL PRO- AND ANTI-INFLAMMATORY CYTOKINE CASCADES**

Cytokines are small proteins produced on demand by a variety of cells, macrophages, immunocytes, and endothelial cells, with diverse biological activity both locally and systemically. They are involved with the immune system in modulating the response to surgical stress and infection (5, 13).

The immunoinflammatory changes to surgery are related to the extent of surgical trauma and neuroendocrine stress response (8, 14). There is a delicate balance between the release of pro and anti-inflammatory cytokines. An exaggerated pro-inflammatory response, i.e. systemic inflammatory response (SIRS) may lead to hemodynamic decompensation and multi-organ failure (MOF)(8, 24). At the same time, a compensatory anti-inflammatory response
can have significant post-operative morbidity from immunosuppression: nosocomial infections and tumor progression (2, 5, 13, 15). Multiple regulatory mechanisms exist in an effort to maintain homeostasis and avoid an unbalanced inflammatory state.

In response to surgery (tissue damage), there is an acute hyperinflammatory phase whereby phagocytic and endothelial cells release IL-1 and TNF-α. Later, these cytokines activate the inflammatory cascade both locally and systemically in an attempt to control tissue damage, kill pathogens, and maintain homeostasis (Table 2) (13). IL-1 and TNF-α trigger the second cytokine release of IL-6. IL-6 has been shown to correlate with the degree of surgical injury and exerts both pro- and anti-inflammatory effects (Table 3) (2, 9, 10, 13, 15, 24).

The early proinflammatory response following surgery is a result of a predominance of the Th1 cytokines (IL-2, IL-12, INF-γ). However, the increased surgical stress release of glucocorticoids, catecholamines, and acute phase reactants, often results in a shift towards the anti-inflammatory Th2 predominance (cytokines IL-4, IL-5, IL-6, IL-10, and IL-13) later in the postsurgical period with consequent depressed cellular immunity (Figure 1)(3, 4, 10, 13, 16, 24).

Understanding the conflicting components of both exaggerated inflammation and immunosuppression following surgery may help predict the development of complications and the role of immunomodulators in preventing immunoinflammatory dysregulation (11, 13, 15).

<table>
<thead>
<tr>
<th>Local Effects</th>
<th>Systemic Effects</th>
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<tbody>
<tr>
<td>Upregulation of cell adhesion molecules (CAMs)</td>
<td>Fever</td>
</tr>
<tr>
<td>Migration of neutrophils to inflamed area</td>
<td>Activation of hypothalamo-pituitary-adrenal axis</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>Coagulation</td>
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The exact mechanism behind blood transfusion induced immunosuppression remains a subject of debate; however, it is conceived to be mediated through the production of anti-inflammatory cytokines (Th2 response). The reported clinical risks of TRIM support judicious transfusion guidelines and the use of leukocyte-reduced blood when possible (3, 4, 7, 11, 15).

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Beyond the stress of surgery, additional variable factors, such as blood transfusions, pain, and hyperglycemia result in perioperative immunomodulation. Transfusion of allogenic blood reduces the patients’ cellular immune response—known as transfusion-associated immunomodulation (TRIM). The clinical impact of TRIM can be either beneficial or deleterious (Table 4).

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Activation of the neuroendocrine axis by perioperative pain contributes to post-surgical immune changes. Adequate postoperative pain management may reduce the extent of surgery-induced immunosuppression and inflammation. During surgery, pain signals are transmitted through a combination of neurons (i.e. small myelinated (A-δ) and unmyelinated (C) sensory afferent fibers) and algic factors (cytokins, histamine, prostaglandins). These nociceptive signals activate the neuroendocrine system and its release of...
catecholamines and glucocorticoids, substances known to drive the Th2 response. Continuous feedback between the neural and immune systems, creates a positive feedback loop whereby increased production of pro-inflammatory cytokines contributes to more severe pain, and vice versa. Patients who experience adequate analgesia, demonstrate decreased levels of pro-inflammatory cytokines and increased lymphocyte activity (17). The propagation of this upregulatory neural-immune cascade has been implicated in the development of chronic or neuropathic pain (Figure 2). Drugs, such as local anesthetics, clonidine, and β-blockers represent pharmacologic immune protection by effectively attenuating the nociceptive signals and neuroendocrine response to surgical stress (Table 5) (4, 7, 16).

**ANESTHESIA AND THE IMMUNE RESPONSE**

Volatile and intravenous anesthetics have a suppressive effect on components of the immune system (Table 6). Inhibition of the cellular components of the immune system is both time and dose dependent (3, 11).

**Figure 6**

Table 5: Immune Effect of perioperative drugs that diminish the ‘surgical stress’ response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Immune Effect</th>
</tr>
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<tbody>
<tr>
<td>Local anesthetics</td>
<td>• Different neural blockade reduces neuroendocrine response → abating dominant Th2 reaction</td>
</tr>
</tbody>
</table>
| Clonidine | • Intravenous use reduces catecholamine levels → diminishing Th2 response  
             • Decreases B and TH responses and lowers myocardial ischemia |
| β-blockers | • Reduces the hyperadrenergic reaction in the presence of elevated catecholamine levels during surgery  
             • By manipulating the stress signals during surgery, β-blockers indirectly provide immune protection by breaking the positive feedback loop between increased stress reaction and an anti-inflammatory cytokine profile |

The use of synthetic opioids during surgery is advantageous as they do not intensify the postoperative immune modulation and the potential co-morbidities. They do not bind to the \( \mu \) receptor; therefore, are immunologically benign. Morphine, on the other hand, acts on the \( \mu \) receptor present on immunocompetent cells to depress their function and weaken host defense against infection (3, 16).

The immune protection afforded by local anesthetics is mediated through decreased activation of the neuroendocrine system by afferent nerve blockade (1). Patients who receive only regional anesthesia, versus general, have decreased serum cortisol levels, and as a result, preservation of lymphocyte proliferation, Th1/Th2 balance, and NK cell function (3).
CLINICAL IMPLICATIONS

Anesthesiologists, in choosing an anesthetic, should carefully consider its clinical impact on the patients’ immune function. Volatile anesthetics have a more profound immunosuppressive effect than total intravenous anesthesia (TIVA) and regional anesthetics. Thus, anesthesiologists should regard TIVA and/or extradural anesthesia as important tools in alleviating postoperative immunosuppression (1). Special consideration should be given to the immunocompromised patient population where further insult to their fragile immune states could possibly result in overwhelming infection or tumor recurrence (2). Anesthetic management should additionally attempt to attenuate the surgical stress response which may lead to preferential Th2 development and defective cell immunity (i.e. use of β-blockers and clonidine) (3). Potentially, determination of an increase in Th2 cytokines postoperatively may aid physicians in predicting those patients who are vulnerable to suffer certain post-operative complications such as cognitive impairment, infection, and cancer progression/recurrence (2).

IMMUNE RESPONSE AND COGNITION

Inflammatory processes have been implicated in the pathogenesis of delirium and postoperative cognitive decline. There has been emerging research suggesting the role of inflammatory cytokines, especially IL-6 and IL-8, in the development of delirium. It is proposed that peripheral immune stimulation (e.g. surgery, infection) leads to brain inflammation. Patients with delirium have been found to have higher levels of IL-6 compared to nondelirious patients. However, not every patient with increased IL-6 and IL-8 levels develop delirium. It appears that patients most susceptible to developing delirium have a diminished cognitive reserve (e.g. dementia, elderly brain) rendering them unable to compensate for additional CNS inflammation (18).

Postoperative cognitive dysfunction (POCD) is a significant contributor to post-surgical morbidity and mortality, especially in the elderly. Although the pathogenesis of POCD is not established, extensive research suggests that it may be rooted in the neurological inflammatory response triggered by surgery (19). The acute peripheral cytokine storm produced during surgery, especially IL-6, IL-1, and TNF-α, gain entry to the CNS via the relatively permeable blood-brain barrier in the periventricular regions (20, 21). Microglia cells, in response to these cytokines, secrete additional cytokines creating a central inflammatory state (21). Specifically, inflammatory processes within the hippocampus is conceived to be responsible for the memory interference and cognitive decline following surgery. In addition, vagal afferents, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), nitric oxide, and genetics (presence of apolipoprotein ε4) contribute to progression of POCD (22). Research into preventing POCD focuses on inhibiting the neuroinflammatory processes within the hippocampus after surgery and improving the identification of vulnerable patients.

POSTSURGICAL INCREASED SUSCEPTIBILITY TO INFECTION

Wound infection and the associated morbidity is a major complication of surgery. The excessive inflammatory response followed by depression in cellular immunity is a significant underlying factor (2). Because the magnitude of the stress response corresponds to the degree of surgical injury there should be conscientious efforts to employ minimally invasive technique when clinically feasible.

The postoperative immunoinflammatory response is multifactorial and chronological. Almost immediately following surgical incision, there is a surge in inflammatory Th1 cytokines (IL-6, and TNF-α) and corticosteroids. However, as early as two hours after surgery, these Th1 cytokines begin to decline with a simultaneous increase of Th2 cytokines (IL-10 and TGF-β). Dysregulation of the cytokine balance is a major contributor to the cellular immunity derangement and susceptibility to infection (2, 15). It has been demonstrated that postoperative increases in IL-10 serum levels correlate with sepsis and MOF (23, 24).

Additionally, the number of T lymphocytes is decreased following surgery. The magnitude of the reduction correlates with the duration of the surgery and volume of blood loss. Moreover, they exhibit decreased mitogenic activity, cytokine secretion, and proliferation. Patients who exhibit anergy, either pre- or postoperatively, and those with highly severe depression of T lymphocyte proliferative responses are most susceptible to developing sepsis (15, 23, 24).

Interventions that counteract T-cell immunosuppression and unbalanced cytokine levels may reduce the rate of postoperative infection.

Depressed antigen presentation by macrophages following surgery is another important risk factor for increased morbidity from sepsis. The release of prostaglandins, nitric oxide, and anti-inflammatory cytokines during surgery are believed to be responsible for this inhibition (2, 5, 24).
A functioning immune system is ultimately the host’s greatest protection against postoperative infection. Therefore, surgeons and anesthesiologists should strive to minimize unfavorable changes in patients’ pre- and postoperative immune function. Such interventions include minimally invasive surgical techniques, enteral nutrition, reduced blood transfusions, and avoidance of immunosuppressive drugs (9, 15).

**POSTOPERATIVE TUMOR PROGRESSION**

Surgery is successful in treating cancer in many patients; however, occasionally radical surgery accelerates growth and dissemination of residual malignant cells. The combination of increased age, surgery, neuroendocrine response, and analgesics, especially opioids, depress natural killer (NK) cell activity (3, 11, 17, 25, 26). NK cells are an important component of the innate immune system and are paramount in identifying and lysing viral and tumor infected cells; they act as ‘tumor surveillance’ cells. Enhanced tumor progression following surgery is thought to be largely mediated by NK cell suppression (3, 26, 27, 28, 29, 30).

Animal studies indicate that the majority of anesthetics have a profound suppressive effect on NK cells and increased tumor metastasis and retention. The anesthetics ketamine, thiopental, and halothane, but not propofol, reduced the number and activity of NK cells and promoted lung tumor metastases, with ketamine exerting the largest effects. It was observed that only the transfer of NK cells, versus other leukocytes, restored host defense against metastasis. In addition, it was show that administration of substances that boost NK cell activity, i.e. immunostimulators, decrease metastases. On the other hand, impediments to NK cell function (e.g. prolonged hypothermia, alcohol ingestion, and stress) increase cancer progression (25).

A balanced Th1/Th2 ratio is important for anticancer immunity. The characteristic dominant Th2-type immune response after surgery is associated with depressed cellular immunity and tumor surveillance (27). It has been shown that a prevailing Th2 status develops in patients with digestive tract malignancy.

Increased serum levels of IL-6 and immunosuppressive acidic protein (IAP) are thought to be markers for decreased antitumor immunity. IAP was originally purified from cancer ascites. It stimulates tumor growth and exhibits potent suppression of cellular immunity. Elevated levels of IAP have been associated with inflammation and cancer. Interfering with the production of these inflammatory mediators has the potential to preserve antitumor immunity (31).

In summary, surgical manipulation results in shedding of tumor cells and release of growth and angiogenic factors (e.g. vascular endothelial growth factor: VEGF) to the circulation which feed tumor growth (25, 29). Reduced preoperative NK activity correlates with increased oncological morbidity and mortality in patients with colorectal, breast, lung, and head and neck cancer. It is well documented that oncology patients who endure multiple surgeries, versus one, suffer worse prognosis despite comparable tumor stage at presentation (28). It is likely that cancer patients cannot compensate for multiple surgical insults to their already fragile immune states. During this high risk perioperative period for metastasis or growth of primary tumor, immune status becomes critical for long-term oncological outcome (28, 30). As surgery is a valuable piece of cancer treatment, anesthetics that are less immunosuppressive may be beneficial in preventing metastasis formation after primary tumor resection.

**CONCLUSION**

Perioperative management should consider the potential clinical significance of the postoperative stress response and immunoinflammatory changes. Using minimally invasive techniques, when clinically warranted, is probably the most effective way to decrease the surgical induced immune depression. It has been shown that laparoscopic surgery attenuates the usual postoperative cytokine cascade, release of acute phase reactants, decrease in lymphocytes, and shift towards a Th2 cytokine profile which is associated with shortened hospitalization periods and faster recovery (7, 12, 15). Additionally, anesthesiologists, in understanding how potential postoperative immunosuppression could be detrimental to the immune states of selected patients, i.e. immunocompromised, may opt to use anesthetics/drugs that control the intraoperative ‘stress’ response and are the least immunosuppressive (4). Regional analgesia is very effective in inhibiting the stress response to surgery by interfering with afferent neural input to the central nervous system, and as a result, decreasing the postoperative susceptibility to infection and metastasis (7, 8, 27, 28).

Clonidine and β-blockers can be additional pharmacological tools in attenuating the patients’ perception of surgical stress (4, 8, 9, 16). Additionally, it has been shown that total intravenous anesthesia compared with balanced inhalation anesthesia is more immunologically favorable. For example,
patients receiving propofol appear to have stronger cellular immunity (Th1 response), negligible effects on NK cells, decreased postoperative catecholamine, IL-6, and cortisol levels, and smaller reductions in number of T and B-cells compared with patients receiving isoflurane anesthesia (3, 14, 32). Also, synthetic opioids, like fentanyl, appear to increase NK cell function and number (32). Use of these anesthetics, if clinically feasible, may be significant, especially in managing oncological surgery and these patients’ vulnerability to metastasis and infectious complications.

References
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