Clinical implication of perioperative inflammatory cytokine alteration

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ABSTRACT

Cytokines are key modulators of inflammatory responses, and play an important role in the defense and repair mechanisms following trauma. After traumatic injury, an immuno-inflammatory response is initiated immediately, and cytokines rapidly appear and function as a regulator of immunity. In pathologic conditions, imbalanced cytokines may provide systemic inflammatory responses or immunosuppression. Expression of perioperative cytokines vary by different intensities of surgical trauma and types of anesthesia and anesthetic agents. Inflammatory cytokines play important roles in postoperative organ dysfunction including central nervous system, cardiovascular, lung, liver, and kidney injury. Inhibition of cytokines could protect against traumatic injury in some circumstances, therefore cytokine inhibitors or antagonists might have the potential for reducing postoperative tissue/organ dysfunction. Cytokines are also involved in wound healing and post-traumatic pain. Application of cytokines for the improvement of surgical wound healing has been reported. Anesthesia-related immune response adjustment might reduce perioperative morbidity because it reduces proinflammatory cytokine expression; however, the overall effects of anesthetics on postoperative immune-inflammatory responses needs to be further investigated.

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1. Introduction

Inflammation after surgical injury is characterized by increased blood flow and vascular permeability, accumulation of leukocytes, and upregulation of inflammatory mediators. Cytokines are key modulators of inflammation and play both inflammatory and anti-inflammatory roles. Over recent decades, cytokines have gained more attention in the understanding of physiological changes after trauma or surgery. Cytokines participate in acute and chronic inflammation in a complex network of interactions. Under physiologic conditions, pro- and anti-inflammatory cytokines serve as immunomodulatory elements that limit potential injury or excess inflammatory reactions. Under pathologic conditions, imbalanced cytokines may provide systemic inflammatory responses or immunosuppression. A dynamic and balanced shift exists between pro- and anti-inflammatory cytokines which affects organ dysfunction, immunity and infection, as well as wound healing and pain after surgery. In this review, we discuss the functions and changes of cytokines and the potential clinical implication of cytokine/anticytokine therapy in the perioperative period.

2. Immuno-inflammatory responses following surgical injury

Patients with surgical injury induce endogenous mediators that alter hemodynamic, metabolic, and immune responses. This immuno-inflammatory response is initiated immediately following traumatic injury. After surgical injury, polymorphonuclear leukocytes (PMNs), endothelial cells, macrophages, and lymphocytes all become activated by the secretion of various mediators including cytokines and other molecules such as reactive oxygen species, nitric oxide, platelet activating factor, growth factors, and eicosanoids. Furthermore, several physiological events occur to sustain the injury: the release of adrenaline suppresses insulin secretion but stimulates secretion of growth hormone and rennin, proteolysis and glycoenolysis which enhances hepatic mediated gluconeogenesis. Glucagon is released by pancreatic islet cells which increases hepatic glucose production from a substrate that arises.

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from tissue catabolism. The liver synthesizes a group of acute phase reactants such as C-reactive protein (CRP), protease inhibitors, and fibrinogen. Complement is also activated, resulting in limiting hemorrhage and enhanced immunity. Cytokines are the key mediators in the immuno-inflammatory responses. The inflammatory response to surgical injury involves a complex crosstalk between several hormones such as catecholamines, adrenocorticotropic hormone (ACTH), cortisol, glucagons, eicosanoids, and cytokines. Exposure to anesthesia and major surgery affects many of the functions of the immune-inflammatory system, and most likely damages the immune response. Surgery is a major traumatic element in postoperative immunodepression in normal people. Damage of the immune response could increase perioperative morbidity and mortality rates from infection in exposed patients. Both humoral and cellular immunity are dampened by surgery injury. A higher degree of surgical trauma determines greater immunodepression.33

3. Types and functions of cytokines

Cytokines are a broad and loose category of heterogeneous low molecular polypeptides or glycoproteins (8–25 kDa) including chemokines, interleukins (ILs), HMGB1, and tumor necrosis factors. They act on specific cell-surface receptors that activate intracellular JAK-STAT signals.12 Cytokines are secreted proteins whose function is communication between cells predominantly in autocrine and paracrine mechanisms.12 The functions of cytokines include cell differentiation, proliferation, survival, or even apoptosis/cell death, and inducing cytokine production and regulating immune responses.15 Cytokines are produced by immune cells (macrophages, lymphocytes, and mast cells) and nonimmune cells (endothelial cells, fibroblasts, and various stromal cells).12,13 One cytokine may be produced by more than one type of cell. Cytokines play an important role in the defense and repair mechanisms following trauma, but this highly controlled system may become overexuberant after severe injuries to the host.14

Application of recombinant cytokines such as TNF-α in animal models can evoke systemic inflammatory response syndrome (SIRS), and blocking it can have beneficial effects on diseases.6,10 TNF-α, IL-1β, IL-6, IL-8, IL-12, and IFN-γ are probably the most important and well-studied proinflammatory cytokines after trauma.14

Another category of cytokines called alarmins that are present in systemic inflammation without evidence of a bacterial focus, suggests the presence of endogenous triggers in immune activation after trauma. Alarmins are characterized as groups of pattern-associated molecular pattern (PAMPs) and damage-associated molecular pattern (DAMPs), which are released either after non-programmed cell death, excluding apoptosis, or produced and released by cells of the immune system.5,15 Alarmins include high mobility group box 1 (HMGB1), heat shock proteins (HSPs), defensins, cathelicidin, eosinophil-derived neurotoxin (EDN) as well as others. These structurally diverse proteins serve as endogenous mediators of innate immunity as chemoattractants and activators of antigen presenting cells (APCs).15 Defensins, cathelicidin, and EDN are rapidly released from storage compartments triggered by either PAMP/DAMP recognition or proinflammatory cytokines, and then trigger immune responses. HMGB1 is a nuclear protein released by injured cells, which not only influences nuclear transactions, but also plays an important role in signaling after tissue damage.1 The receptor dedicated to the different effects of HMGB1 is the receptor for advanced glycation end product (RAGE). It is released by necrotic but not apoptotic cells, as well as secreted by activated immune cells, macrophages, mature myeloid dendritic cells (DCs), and activated NK cells without using the Golgi apparatus pathway.9,15 The active secretion of HMGB1 after lipopolysaccharide stimulation

seems to be partially dependent on the TLR4-CD14 complex and TGF-beta, and is triggered by cytokines as TNF-α, IL-1β, and interferon-γ.18

4. Cytokines function as a regulator of immunity after injury

Cytokines rapid appearance after injury reflects active gene transcription and translation. They bind to specific cellular receptors resulting in activation of intracellular signaling pathways that regulate gene expressions.20 Cytokines can regulate the production and activity of other cytokines, and then either augment (proinflammatory) or attenuate (anti-inflammatory) the immuno-inflammatory response. There are significant overlaps in bioactivity among different cytokines. The capacity of cytokines to activate diverse cell types and responses, highlights the pleiotropism of these inflammatory mediators. Cytokines direct the inflammatory response to sites of injury and infection, and are essential for proper wound healing processes.21 However, dysregulation of cytokine expression such as excess production of proinflammatory cytokines can induce hemodynamic instability, metabolic derangements, or even muscle wasting. In severe injuries, persistently exaggerated proinflammatory cytokine responses may contribute to systemic inflammatory response syndrome (SIRS) or multiple organ failure (MOF) and late death.22 There is now a general agreement that SIRS are accompanied by the inability to regulate the inflammatory response.22 The overproduction of inflammatory cytokines generates a systemic activation that can lead to tissue necrosis and eventually to MOF and death.22 Proinflammatory cytokines incite the production of reactive oxygen species (ROS) from various cells. Excess production of ROS causes cellular damage in vital organs seen in septic shock.24–26 Severe sepsis and SIRS also induce apoptosis, which contributes to multiple organ dysfunction.27–30 Notably, the production of anti-inflammatory cytokines in these periods may attenuate the exaggerated responses. However, excessive anti-inflammatory cytokine production compromises immunity and can lead to overwhelming infectious morbidity.21

5. The effects of cytokines on tissue injury

Inflammatory cytokines play important roles in postoperative organ dysfunction. In major surgery such as cardiac surgery with cardiopulmonary bypass (CPB) that induces the release of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and IL-19, which has been involved in the inflammatory cascade. Post-CPB induced acute systemic inflammation is a typical SIRS in surgical patients. This inflammatory cascade contributes to the development of postoperative complications, including respiratory failure, renal dysfunction, bleeding disorders, neurologic dysfunction, altered liver function, and ultimately, multiple organ failure.26,37 It has been shown that an anti-inflammatory response may also be initiated during and after CPB. IL-10, an anti-inflammatory cytokine is likely to be induced after CPB and may play an important role in limiting post-CPB complications.38–40

5.1. Cytokines and central nervous system injury

After traumatic brain injury, there is rapid activation of glial cells and additional recruitment of granulocytes, T-cells and monocytes/macrophages from the blood stream triggered by the upregulation of cell adhesion molecules, chemokines, and cytokines.40 A cascade of inflammatory mediators is produced, and contributes to the pathological consequences of central nervous system (CNS) injury.42 Cytokines and inflammatory cells are mediators in the common pathways associated with perinatal brain injury induced by a variety of insults, such as hypoxic–ischemic injury, reperfusion
injury, toxin-mediated injury, and infection.\textsuperscript{42} Neuroinflammation can cause neuronal damage, but also confers neuroprotection.\textsuperscript{43} After focal cerebral ischemia, neurotoxic mediators released by microglia such as the cytokines IL-1β and TNF-α are upregulated, which contributes to secondary infarct growth. Cytokine induction from ischemic lesions involves NMDA-mediated signaling pathways and confers neuroprotection.\textsuperscript{50} There is increasing evidence that neuroinflammation represents a double-edged sword. The opposing neurotoxic and neuroprotective properties of neuroinflammation during CNS injury provide currently unexplored research problems.\textsuperscript{60}

### 5.2. Cytokines and cardiovascular injury

Current evidence indicates that cytokines are contributors in myocardial dysfunction and cardiomyocyte necrosis in ischemia-reperfusion (I/R) injury.\textsuperscript{61} Increase in the production TNF-α, IL-1β, and IL-6 contribute to the pathology of myocardial infarction and cardiopulmonary bypass surgery.\textsuperscript{62} Besides, recent studies have showed TNF-α and IL-1β link TLR4 signaling in post-ischemic cardiac dysfunction.\textsuperscript{53} In acute and chronic heart failure, elevated proinflammatory cytokines released by immune cells play a pathogenetic role in myocardial dysfunction. Cytokines also have a regenerative capacity of the myocardium and its blood vessels.\textsuperscript{66} The cytokines granulocyte colony-stimulating factor (CSF) and erythropoietin may stimulate cell regeneration under normal physiologic conditions and in patients with myocardial injury. In experimental cardiac injury models, the addition of cytokines has been shown to improve myocardial function.\textsuperscript{55} In vascular injury, increased expression of adhesion molecules by endothelial cells and recruitment of inflammatory cells, growth factors, and cytokines have consequent effects on vessel injury.\textsuperscript{69} Circulating TNF-α, IL-1β, and IL-8 interact with specific receptors on endothelial cells that activate JAK-STAT, nuclear factor (NF)-κB, and Smad signaling pathways leading to induced cell adhesion, apoptosis, and permeability.\textsuperscript{68} Cytokines also interact with integrins and matrix metalloproteinases (MMPs) and modify extracellular matrix composition. Persistent increase of cytokines is associated with vascular dysfunctions such as atherosclerosis, aneurysm, and hypertension.

### 5.3. Cytokines and acute lung injury

Cytokine networks on cells of the alveolar—capillary membrane are necessary for cellular communication during pulmonary inflammation, and the subsequent events of these interactions are pivotal to the immuno-inflammatory responses leading to acute lung injury (ALI).\textsuperscript{65} Proinflammatory cytokines are known to play roles in ischemia—reperfusion injury of the lung.\textsuperscript{50} The dysregulated expression of cytokines and growth factors in response to infectious or harmful insults can provoke deleterious lung inflammation. Early response cytokines, adhesion molecules, and the chemokine IL-8 could promote the recruitment of neutrophils into lung tissue. TNF-α or IL-1β activate microvascular endothelium leading to the expression of endothelial cell-derived E- and P-selectins and ICAM-1, and then recruits leukocytes. These activated leukocytes can release reactive oxygen metabolites, proteolytic enzymes, and additional cytokines and then induce ALI. Recent studies further demonstrated that TNF-α plays a central role in the development of pulmonary edema in ALI through activation of TNF receptor p55-mediated caspase 8 death signaling.\textsuperscript{51}

### 5.4. Cytokines and hepatic injury

Proinflammatory cytokines causes activation and priming of neutrophils for reactive oxygen formation and recruits them into the vascular beds of the liver and induce hepatic injury.\textsuperscript{32} The phenomenon is similar to cytokine-related lung injury. Cytokines as chemotactic signals from the parenchyma will trigger extravasation of leukocytes and attack hepatocytes. Leukocyte adhesion induces degranulation with release of proteases and formation of reactive oxygen species, which diffuse into hepatocytes and induce an intracellular oxidant stress and mitochondrial dysfunction and then cell death.\textsuperscript{60} In addition, necrotic cells release mediators such as high-mobility group box-1 (HMGB-1), which further promotes neutrophilic hepatitis and tissue damage.

### 5.5. Cytokines and acute kidney injury

Cytokines have been implicated in the pathobiology of acute kidney injury (AKI). Intravenous administration of TNF-α decreased glomerular filtration ratio (GFR) and led to damage of the glomerular endothelial surface, which is an important determinant of acute kidney injury in sepsis.\textsuperscript{33} In addition, IL-1β-mediated neutrophil recruitment is likely to be a key process in AKI.\textsuperscript{65} Recently, the effects of IL-6 on AKI were confirmed.\textsuperscript{55} IL-6-deficient mice were resistant to HgCl2-induced AKI and neutrophil infiltration. Renal IL-6 expression and STAT3 activation in renal tubular epithelial cells were significantly increased during the development of kidney injury and correlate with the onset and severity of AKI.\textsuperscript{55} It is now believed that the IL-6/IL-6R axis plays a critical role in acute kidney injury.\textsuperscript{55} The recently discovered cytokine, IL-19 also mediates tissue damage in murine ischemic AKI.\textsuperscript{55}

### 6. Cytokines in wound healing

After surgical injury, wound healing is proceeded by hemostasis, inflammation, proliferation, and tissue remodeling.\textsuperscript{70} Cutaneous wound healing is an instant response to a wound, which repairs damaged lesions and restores dermal structure and functions.\textsuperscript{53} The extracellular matrix, growth factors, and inflammatory mediators, and cytokines are critical for cutaneous wound healing.\textsuperscript{60,61} Keratinocyte growth factor (KGF), a fibroblast growth factor (FGF) family of mitogens, is strongly upregulated in dermal fibroblasts after a skin injury\textsuperscript{63,64} and is essential for wound re-epithelialization.\textsuperscript{61,63} Cytokines can induce KGF expression in fibroblasts.\textsuperscript{64} IL-1β, IL-6, and TNF-α were identified as strong stimulators of KGF expression in fibroblasts.\textsuperscript{65,66} Moreover, the expression of these cytokines after an injury correlated with the time course of KGF expression.\textsuperscript{66} A recent report showed that wounds in IL-6-deficient mice showed delays in macrophage infiltration, fibrin clearance, and wound contraction.\textsuperscript{66} IL-6 modulates immune responses and is essential for the wound healing process.\textsuperscript{67} Recently it was identified that IL-19 directly regulates KGF expression during wound healing.\textsuperscript{59} IL-19 induced IL-1β, IL-6, TGF-β, MMP2, MMP9, and CXCR4 expression,\textsuperscript{69} which contribute to cutaneous wound healing. Furthermore, applied IL-19 protein on surgical wounds in mice can promote a cutaneous wound healing process.\textsuperscript{69} We thus should consider that in some circumstances, inflammatory cytokines may be applied as a therapeutic agent for the improvement of surgical wounds.

### 7. Cytokines in post-traumatic pain

Evidence has showed that TNF-α plays an important role in T-cell-mediated tissue injury, and targeting anti-inflammatory treatment can ameliorate injury-induced neuropathic pain.\textsuperscript{71} A recent study showed the positive effects of TNF-α antagonist etanercept on functional recovery and reducing hypersensitivity after peripheral nerve crush injury.\textsuperscript{75} It was suggested that etanercept...
optimizes the involvement of macrophages and the secretion of inflammatory mediators in pain. Dahl and Cohen showed that perineural injection of etanercept can treat postamputation pain. They used perineural etanercept in six traumatic amputees with postamputation pain. Three months after injections, five of the six patients showed significant improvements in residual limb pain and functional capacity. Etanercept also reduced acute sciatica secondary to lumbar disc herniation in a triple-blind randomized controlled trial. IL-1β also affects post-traumatic pain. Schafer et al. showed that IL-1β attenuated pain perception after surgery by promoting the release of β-endorphins from the pituitary gland and increasing the number of central opioid like receptors. Prostacyclin is an important mediator of peripheral pain sensation. Recently, Schuh et al. presented that early synthesis of prostacyclin is an important mediator of peripheral pain sensation.

Anesthetic techniques can reduce the immune functions by interferon-activating adrenergic receptors and the production of cytokines. Elevated activity. There is a positive correlation between the activity of adrenergic receptors and the production of cytokines. Elevated epinephrine concentrations can trigger TNF-α and IL-6 release by activating α2 and β2 adrenergic receptors in macrophages, respectively. The impact of volatile anesthetic on cytokine secretion could be related to intracellular calcium concentrations because Ca2+ is a vital step on cytokine regulation. The intracellular Ca2+ pools can be altered by volatile anesthetics. Previous studies showed that halothane restricted ATP-stimulated Ca2+-transients in endothelial cells. Thus, inhalational anesthetics reduce adrenergic activity, intracellular calcium concentration, inhibits inflammatory cytokine production and affects postoperative immunomodulatory responses. The intravenous anesthetic propofol is widely used for surgical anesthesia and patient sedation for intensive care. Propofol has anti-inflammatory effects on inhibition of stimuli-induced TNF-α, IL-1β, IL-6, IL-8, and IL-10 production. Propofol also suppresses inducible NO synthase/NO biosynthesis in endotoxin lipopolysaccharide (LPS)-activated macrophages. The molecular mechanisms for anti-inflammatory propofol include inhibiting NF-κB activation and decreasing mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) activation. Recent studies demonstrated that propofol can protect multiple organ injuries in sepsis by reducing inflammatory cytokines production. One may consider that anesthesia-related immune response adjustment could reduce perioperative morbidity by reducing pro-inflammatory cytokine production; however, the overall effects of anesthetics on postoperative pathophysiological responses especially in patients with pre-existing immunological disorders or malignancy needs to be further investigated.

9. Inhibit cytokines could protect traumatic injury

The implication of cytokine inhibitors in traumatic injury have been investigated, although the effects of cytokine inhibition on surgical injury needs to be further investigated. The TNF-α antagonist, etanercept, can be used to reduce traumatic brain injury (TBI) in rats. Cheong et al. showed that neurological and motor deficits, cerebral contusions, and increased brain TNF-α contents caused by TBI can be attenuated by etanercept therapy. They found that etanercept may penetrate directly into the contused brain tissues and improve outcomes of TBI by reducing brain TNF-α and stimulating neurogenesis. The TNF-α antagonist also reduces apoptosis of neurons and oligodendroglia in rat spinal cord injury (SCI). This positive effect of etanercept on spinal cord injury is probably attributable to the suppression of TNF-α, TNFR1, TNFR2, and activated caspase-3 and caspase-8 overexpressions. Anti-IL-6-receptor antibody also promotes repair of spinal cord injury in mice. Mukaino et al. used an anti-mouse IL-6-receptor antibody to improve motor function after SCI. This change was accompanied by reducing chemokines CCL2 and CCL5 recruitment and decreasing CXCL10 expression. In post-traumatic ischemic/reperfused hearts, etanercept markedly inhibited oxidative/nitrative stress and myocardial injury by reducing TNF-α. Inhibiting TNF-α could also improve bone formation following trauma. Previous studies also demonstrated that TNF-α negatively regulates bone formation at the injured growth plate in rats. TNF-α mediates p38 activation, influences osteoblast recruitment, proliferation and differentiation at the injured growth plate. HMGB1, released by injured cells, plays an important role in signaling after tissue damage. The HMGB1 inhibitor, glycyrrhizin can relieve the severity of traumatic pancreatitis in rats. Taken together, cytokine inhibitors or antagonists might reduce traumatic injury and has the potential for reducing postoperative tissue/organ dysfunction.

10. Conclusion

Surgical trauma may induce acute systemic inflammation which originally plays a role in immune defense from bacterial infection and in the wound healing process. Cytokines are major modulators of inflammatory responses; however, cytokine dysregulation may provide systemic inflammatory responses or immunosuppression leading to multiple organ dysfunction or infectious disorders. Inhibit cytokines could protect organ injury in some circumstances, therefore, cytokine inhibitors or antagonists might have the potential for reducing postoperative tissue/organ dysfunction. Anesthesia-related immune response adjustment might reduce pro-inflammatory cytokine production. The overall effects of anesthetics on perioperative cytokine production and pathophysiological responses needs to be further investigated.
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