Acta Anaesthesiologica Taiwanica 53 (2015) 23–28

Contents lists available at ScienceDirect

Acta Anaesthesiologica Taiwanica

journal homepage: www.e-aat.com

Review Article

Clinical implication of perioperative inflammatory cytokine alteration

Chung-Hsi Hsing [1, 2, 3 *], Jhi-Joung Wang [1, 2]

[1] Department of Medical Research, Chi-Mei Medical Center, Tainan, Taiwan
[2] Department of Anesthesiology, Chi-Mei Medical Center, Tainan, Taiwan
[3] Department of Anesthesiology, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 2 February 2015
Accepted 6 March 2015

Key words:
anesthesia;
cytokines;
immunosuppression;
surgery;
systemic inflammation

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.

1. Introduction

Inflammation after surgical injury is characterized by increased blood flow and vascular permeability, accumulation of leukocytes, and upregulation of inflammatory mediators.[1] Cytokines are key modulators of inflammation and play both inflammatory and anti-inflammatory roles.[1,2] 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.[2,3] 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.[4–6] 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.[7] 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.[7] 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 glycogenolysis which enhances hepatic mediated gluconeogenesis. Glucagon is released by pancreatic islet cells which increases hepatic glucose production from a substrate that arises

Conflicts of interest: The authors have declared that no competing interests exist.

* Corresponding author. Department of Anesthesiology, Chi-Mei Medical Center, Tainan, Taiwan.
E-mail address: hsing@seed.net.tw (C.-H. Hsing).

http://dx.doi.org/10.1016/j.aat.2015.03.002

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.[7] 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.[8] Surgery is a major traumatic element in postoperative immunodepression in normal people.[9] Damage of the immune response could increase perioperative morbidity and mortality rates from infection in exposed patients.[10] Both humoral and cellular immunity are dampened by surgery injury. A higher degree of surgical trauma determines greater immunodepression.[11]

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, interferons, interleukins, lymphokines, and tumor necrosis factor. 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.[12] 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 over exuberant 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] 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 pathogen-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.[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).[16] 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.[17] The receptor dedicated to the different effects of HMBG1 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.[18,19] 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-1 β, and interferon-r.[19]

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 syndromes (SIRS) or multiple organ failure (MOF) and late death.[21] 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.[23] 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,[31,32] IL-1β,[32] IL-6, IL-8,[33,34] and IL-19[35] 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.[36,37] 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.[38,39]

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.[41] 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