MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp
EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 3 No. 12 (Dec - 2023) EJMMP ISSN: 2795-921X

CHANGES IN CYTOKINE PROFILE AFTER SURGERY

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Abstract: The inflammatory response after surgery is associated with the patient's prognosis and depends on many factors: the patient's disease and condition, the type and extent of surgery, and the anesthetics and techniques used [1-3]. Therefore, it is important for the surgical team to understand the immunomodulation caused by intraoperative care and implement appropriate treatment to improve the patient's prognosis. Cytokines are key modulators of inflammatory responses and play an important role in mechanisms of protection and recovery after injury. After traumatic injury, an immune-inflammatory reaction is immediately initiated, and cytokines quickly appear that act as regulators of immunity. In pathological conditions, unbalanced cytokines can cause systemic inflammatory responses or immune-suppression. Expression of perioperative cytokines varies depending on the severity of surgical trauma, type of anesthesia, and anesthetic agents. Inflammatory cytokines play an important role in postoperative organ dysfunction, including damage to the central nervous system, cardiovascular system, lungs, liver, and kidneys. Cytokine inhibition may protect against traumatic injury in some circumstances, so cytokine inhibitors or antagonists may have the potential to reduce postoperative tissue/organ dysfunction. Cytokines are also involved in wound healing and post-traumatic pain. The use of cytokines has been reported to improve healing of surgical wounds. Anesthesia-related regulation of the immune response may reduce perioperative morbidity by reducing the expression of proinflammatory cytokines; however, the overall effect of anesthetics on postoperative immune-inflammatory responses requires further study.

Key words: cytokine, endogenous mediators, humoral and cellular immunity, inflammatory response, surgical trauma.

Introduction

Inflammation after surgical trauma is characterized by increased blood flow and vascular permeability, accumulation of leukocytes, and activation of inflammatory mediators. Cytokines are key modulators of inflammation and play both inflammatory and anti-inflammatory roles [2]. Over the past decades, cytokines have received increased attention in understanding physiological changes following injury or

surgery. Cytokines are involved in acute and chronic inflammation in a complex network of interactions. Under physiological conditions, pro- and anti-inflammatory cytokines serve as immunomodulatory elements that limit potential damage or excessive inflammatory responses. In pathological conditions, unbalanced cytokines can cause systemic inflammatory responses or immunosuppression. There is a dynamic and balanced shift between pro- and anti-inflammatory cytokines that influences organ dysfunction, immunity and infection, as well as wound healing and pain after surgery [4, 5, 6]. In this review, we discuss the functions and changes of cytokines and the potential clinical implications of cytokine/anti-cytokine therapy in the perioperative period.

2. Immune-inflammatory reactions after surgical trauma

In patients with surgical trauma, endogenous mediators are induced that alter hemodynamic, metabolic and immune responses. This immunoinflammatory response begins immediately after traumatic injury [7]. Following surgical injury, polymorphonuclear leukocytes (PMN), endothelial cells, macrophages, and lymphocytes are 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]. In addition, several physiological events occur to maintain the damage: epinephrine release suppresses insulin secretion but stimulates growth hormone and rennin secretion, proteolysis, and glycogenolysis, which enhance liver-mediated gluconeogenesis. Glucagon is released by pancreatic islet cells, which increases the production of glucose in the liver from substrate resulting 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, which leads to limited hemorrhage and increased immunity [7]. Cytokines are key mediators of immunoinflammatory responses. The inflammatory response to surgical injury involves a complex interaction between several hormones, such as catecholamines, adrenocorticotropic hormone (ACTH), cortisol, glucagons, eicosanoids, and cytokines. Exposure to anesthesia and major surgery affects many functions of the immune-inflammatory system and is likely to impair the immune response [8]. Surgery is the major traumatic element of postoperative immunosuppression in normal individuals [9]. Damage to the immune response may increase perioperative morbidity and mortality from infection in exposed patients [10]. Both humoral and cellular immunity are weakened by surgical trauma. A higher degree of surgical trauma determines greater immunosuppression [11].

Types and functions of cytokines

Cytokines are a broad and disparate category of heterogeneous small-molecule 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 to communicate between cells primarily through autocrine and paracrine mechanisms. The functions of cytokines include cell differentiation, proliferation, survival, or even apoptosis/cell death, as well as inducing cytokine production and regulating immune responses. Cytokines are produced by immune cells (macrophages, lymphocytes, and mast cells) and nonimmune cells (endothelial cells, fibroblasts, and various stromal cells) [12, 13]. A single cytokine can be produced by more than one cell type. Cytokines play an important role in defense mechanisms and recovery from injury, but this tightly controlled system can become overactive after severe host injury [14]. The use of recombinant cytokines such as TNF-α in animal models can induce systemic inflammatory response syndrome (SIRS), and blocking it may have beneficial effects on disease. 6 TNF-α, IL-1β, IL-6, IL-8, IL-12, and IFN-γ are likely the most important and well-studied pro-inflammatory cytokines following injury. Another category of cytokines, called alarmins, which are present in systemic inflammation without evidence of a bacterial focus, suggest the presence of endogenous triggers of immune activation after injury. Alarmins are characterized as pathogen-associated molecular pattern

(PAMP) and damage-associated molecular pattern (DAMP) groups that are released either after unprogrammed cell death, excluding apoptosis, or are 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, chemoattractant, 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 damaged cells that not only influences nuclear transactions but also plays an important role in signaling after tissue injury [17]. The receptor responsible for the various effects of HMBG1 is the receptor for advanced glycation end product (RAGE). It is released by necrotic but not apoptotic cells and is also secreted by activated immune cells, macrophages, mature myeloid dendritic cells (DCs), and activated NK cells without using the Golgi pathway [18,19]. Active secretion of HMGB1 following lipopolysaccharide stimulation appears to be partially dependent on the TLR4–CD14 complex and TGF-β and is triggered by cytokines such as TNF-α, IL-1 β and interferon-r.

Cytokines act as regulators of immunity after injury.

The rapid appearance of cytokines after injury reflects active gene transcription and translation. They bind to specific cellular receptors, which leads to the activation of intracellular signaling pathways that regulate gene expression [20]. Cytokines can regulate the production and activity of other cytokines and then either enhance (proinflammatory) or dampen (anti-inflammatory) the immunoinflammatory response. The biological activities of various cytokines overlap significantly. The ability of cytokines to activate different 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. However, dysregulation of cytokine expression, such as excess production of proinflammatory cytokines, can cause hemodynamic instability, metabolic abnormalities, or even muscle atrophy. In severe trauma, persistently elevated proinflammatory cytokine responses may contribute to the development of systemic inflammatory response syndromes (SIRS) or multiple organ failure (MOF) and late death. 21 There is now general agreement that SIRS is accompanied by a failure to regulate the inflammatory response. Overproduction of inflammatory cytokines causes systemic activation that can lead to tissue necrosis and ultimately MOF and death. 23 Proinflammatory cytokines stimulate the production of reactive oxygen species (ROS) by various cells. Excessive production of ROS causes the damage to cells of vital organs observed in septic shock [21,22,23]. Severe sepsis and SIRS also induce apoptosis, which contributes to multiorgan dysfunction. Notably, the production of anti-inflammatory cytokines during these periods may attenuate the exaggerated responses. However, excessive production of anti-inflammatory cytokines compromises immunity and can lead to enormous infectious morbidity.

Effect of cytokines on tissue damage

Inflammatory cytokines play an important role in postoperative organ dysfunction. During major surgical procedures such as cardiac surgery with cardiopulmonary bypass (CPB), which induces the release of proinflammatory cytokines such as TNF-α, 31, 32, IL-1β, 32 IL-6, IL-8, 33, 34 and IL- 19, which is involved in the inflammatory cascade. Acute systemic inflammation caused by post-CPB is a typical SIRS in surgical patients. This inflammatory cascade contributes to the development of postoperative complications, including respiratory failure, renal dysfunction, bleeding disorders, neurological dysfunction, changes in liver function, and ultimately multiple organ failure. It has been shown that an anti-inflammatory response can also be initiated during and after CPB. IL-10, an anti-inflammatory cytokine, is likely induced after CPB and may play an important role in limiting post-CPB complications [24,25].

Cytokines in wound healing

After surgical trauma, wound healing occurs through hemostasis, inflammation, proliferation and tissue remodeling. Skin wound healing is the immediate response to a wound that heals damaged areas and restores skin structure and function. 58 Extracellular matrix, growth factors, inflammatory mediators, and cytokines are critical for skin wound healing [26]. Keratinocyte growth factor (KGF), a family of fibroblast growth factor (FGF) mitogens, is highly activated in dermal fibroblasts after skin injury [27,28]. and is required for wound re-epithelialization. Cytokines can induce KGF expression in fibroblasts. IL-1β, IL-6, and TNF-α were identified as potent stimulators of KGF expression in fibroblasts. Moreover, the expression of these cytokines after injury correlates with the dynamics of KGF expression. A recent report showed that wounds in IL-6-deficient mice exhibit delayed macrophage infiltration, fibrin clearance, and wound contraction. IL-6 modulates immune responses and is essential for the wound healing process. Recently, IL-19 was found to directly regulate KGF expression during wound healing. IL-19 induced the expression of IL-1β, IL-6, TGF-β, MMP2, MMP9, and CXCR4, 70 which promote skin wound healing. In addition, application of IL-19 protein to surgical wounds in mice may promote the healing process of skin wounds. Thus, we must consider that in some circumstances, inflammatory cytokines may be used as a therapeutic agent to improve surgical wounds [29].

Cytokines in post-traumatic pain

Data have shown that TNF-α plays an important role in T cell-mediated tissue injury, and targeted anti-inflammatory treatment can alleviate injury-induced neuropathic pain. A recent study showed the beneficial effects of the TNF-α antagonist etanercept on functional recovery and reduction of hypersensitivity after peripheral nerve injury. Etanercept has been suggested to optimize macrophage participation and secretion of inflammatory mediators in pain. Dahl and Cohen showed that perineural injection of etanercept can relieve pain after amputation. They used perineural etanercept in six patients with traumatic limb amputees and post-amputation pain. Three months after the injections, five of the six patients had significant improvements in residual limb pain and functional ability. In a triple-blind randomized controlled trial, etanercept also reduced the incidence of acute sciatica caused by lumbar disc herniation. IL-1β also influences post-traumatic pain. Schafer [30] showed that IL-1β attenuates 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 sensitivity. Recently, Schuh presented that early prostacyclin synthesis at the injury site induces the accumulation of IL1β-expressing macrophages, which is a key step in neuropathic pain after traumatic injury. It is conceivable that inhibition or antagonism of inflammatory cytokines could be used to treat post-traumatic pain in the future [31].

Conclusion

Surgical trauma can cause acute systemic inflammation, which initially plays a role in immune defense against bacterial infection and in the wound healing process. Cytokines are major modulators of inflammatory responses; however, dysregulation of cytokines can cause systemic inflammatory responses or immunosuppression, leading to multiple organ dysfunction or infectious diseases. Cytokine inhibition may protect organ damage in some circumstances, so cytokine inhibitors or antagonists may have the potential to reduce postoperative tissue/organ dysfunction. Anesthesia-related regulation of the immune response may reduce the production of proinflammatory cytokines. Further study of the overall effects of anesthetics on perioperative cytokine production and pathophysiological responses is needed.

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