Immune Response to Burn Injury: Hyperinflammation and Immunosuppression

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Abstract

Burn is an injury to the skin or other tissue. Mostly, it caused by contacting with hot liquids, solids, and flames. The important thing that should be consider in burn incident is the severity of burn and it based on the depth and area of the burn injury. The severity of burns will cause differences of pathophysiological responses. This was a literature review study. Various articles were collected from online database including reports, journals, and published in the last 10 years. The articles were from the scholar journals. The systemic inflammatory response in severe level of burns was not given good response to disappear of lesion burn and initiating tissue repair. Moreover, it was given an organ failure to the patient. The body responded to this incident by releasing antiinflammatory mediators. This response is very strong and prolonged, so it caused immunosuppression and increase the risk of secondary infection to the patients. Burns affects the patient's immune system. The ratio between pro and antiinflammatory mediators are determining the patient's subsequent status.

Keywords*: Immune response, Burn Injury, Hyperinflammation, Immunosuppression*

Introduction

Burn is an injury to the skin or other tissue caused from contacts with hot liquids, hot solids, flames, radiation, radioactivity, electricity, and friction or contact with chemicals[(1)]. Most of burns incidences are caused by hot fluids, solids, and flames [(2)]. The differences of causes of these burns will affects the pathophysiological response [(3)]. Moreover, the important note after the burn incident is the level of burn severity based on the on the depth and area of the wound.

The presence of tissue damage due to burns causes an immune response in body, the response is the inflammation form to disappear the lesion and initiate tissue repair[(4)]. The inflammatory reaction was driven by some cells who involved in innate immunity, such as neutrophil cells and macrophage cells. At earlier, the inflammatory response was to protect the host but the consequences of this process given an exacerbate injury. In severe burns cases, the inflammatory response is very strong and systemic or known as systemic inflammatory response syndrome (SIRS) which can lead to organ failure[(5)]. Therefore, the body responds by forming a counter antiinflammatory response syndrome (CARS) and it is expect to restore the homeostasis condition and control SIRS. Unfortunately, a prolonged antiinflammatory response not profitable response but now it causes an immunosuppressive condition and increases the risk of secondary infection for the patients [(6)].

Hyperinflammation reaction of Burn Injury

Burns have an effect on the immune system [(7)]. Burns also cause tissue damage because many endogenous molecules are released or called damage-associated molecular patterns (DAMPs) [(8)]. The molecules

come from neutrophil cells or cells who are necrosis. DAMPs molecules are include chromatin associated high-mobility group box 1 protein (HMGb1) [9], heat shock proteins (HSPs)[10], purine metabolites, such as ATP[11] and uric acid[12]. The molecules directly bound by immune cells through a receptor, and the receptor called pattern recognition receptors (PRRs)[13]. DAMPs will bind with pattern recognition receptors (PRRs) in the form of toll-like receptors (TLRs) on the surface of antigen presenting cells (APCs). The binding between DAMPs and TLRs will generate the signals in cells, initiated by Myddosome formation, it consists of myeloid differentiation primary response gene 88 (MyD88) and IL-1 receptor-associated kinases (IRAKs). During the formation stage, IRAK4 auto-phosphorylation occurs then phosphorylates and activates IRAK1, so IRAK1 is released from Myddosome complex and then joint with TNF receptor-associated factor 6 (TRAF6) to activate TGF-β-activated kinase (TAK1)[14]. After that, TAK1 activates two distinct signaling lines, namely IKK complex-NF-κB- pathway and –MAPK pathway. TAK1 binds with IKK complex via the ubiquitin chain, than inducing kappa kinase (IKK-) β inhibitor activity. After on active status, IKK-β will degrade the kappa inhibitor (IK-) β, so NF-κB is active. TAK1 can also activate mitogen-activated protein kinase (MAPK) then mediates the activation activator protein 1 (AP-1). Transcription factors of NF-kB and AP-1 will translocate in nucleus to induce the expression of various genes who encoding proinflammatory cytokines, such as tumor necrosis (TNF-) α, interleukin (IL-) 1β, and IL-6[15].

The production of proinflammatory cytokines by innate immune cells is regulated by a transcription factor, one of that is nuclear factor kappa-B (NF-κB). Nuclear factor kappa-B is a heterodimer protein that binds with cytosol inhibitor in an inactive state, especially in normal condition of the body. However, this protein will be released their inhibitor complex to be able to translocate to the nucleus and activate the transcription process of inflammatory mediators [16]. Based on the results of the study mentioned that in severe burns level, there was an excessive response of proinflammatory cytokines production in second stimulation, such as the exposure of lipopolysaccharide (LPS) which described the infection condition. This high production of proinflammatory cytokines were not depend on the degree of the second stimulant exposure, but it was due to the increasing of NF-κB activation [17].

Immunosuppression after Burn Injury Leading to Secondary Infection

The immune system consists of loops feedback series to restore homeostatic conditions. Thus, the presence of SIRS will accompanied with counter antiinflammatory response syndrome (CARS) which is characterized by the release of antiinflammatory cytokines, such as IL-10, TGF-β, and cytokine antagonists IL1-Rα. Furthermore, the ratio between pro and antiinflammatory mediators were determine whether the immune system can return to be homeostatic state or develop to be inflammation, immunosuppression, and catabolic syndromes, and this can increase the risk of organ failure and sepsis [18].

After trauma, epithelial cells produced Alarmins, such as Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. All of three can induce type 2 of innate lymphoid cells (ILCs) which plays an important role in the activation of type 2 immune response by producing IL-4, IL-5, IL-9, and IL-13. Hyperactive response of type 2 immune response can suppress the development of type 1 immune response who is protective toward pathogenic microorganisms, so the patients are high risk to occur un-control infection. The increasing numbers of type 2 ILCs were detected in the peripheral blood circulation of burn patients [19]. IL-4 and IL-13 activated the M2 phenotypic macrophage cells. This process called alternative macrophage activation. The active Macrophage cells produced IL-10 and TGF-β which they work to inhibit the development of TH1 cell function [15].

The description of cytokines balance who related with T cells helper, namely Th1 and Th2 cells are known as a cause of the decreasing body's ability to fight infection. Th1-related cytokines are IFN-γ, IL-12, and IL-2, whereas Th2-related cytokines are IL-10, IL-4, and IL-5 [20]. The cytokines were turn negatively regulate production. Thus, the ratio between two of cytokines will determine whether the immune system can effectively fight to the pathogen.

Previously, a study noted that the severe burn injury caused a systemic inflammatory response with a mediation by macrophage cells with releasing a number of proinflammatory cytokines, such as TNFα and IL-12. However, it was take place at a certain point, TNFα can regulate IL-12 production by inhibiting IL-12 gene expression as part of the cytokine feedback scheme and self-limiting modulations. This regulatory mechanism does not depend on the IL-10 barrier pathway (the main IL-12 inhibitor), NFκB (the main activator for IL-12 production as a response to LPS), or IRF-1 (the main activator for IL-12 production as a response to IFN-γ [21]. It was known in last several years that this regulatory mechanism occurred via TNFR-1 [22]. Thus, the incidence of SIRS was described by the hyperactive response of immune cells and it was caused the reduction of pathogens resistance.

Post-burn immunosuppression also occurred due to the production of microRNAs (miRNAs) after efferocytosis process (phagocytosis process of apoptotic cells by M1 macrophage cells to regulate inflammation), one of that is microRNA-21. MicroRNA (miR-) 21 is a noncoding RNA and consisting 21-23 nucleotides, it plays a role in RNA silencing and post-transcription regulation in gene expression [23].

MicroRNA (miR-) 21 was produced as a negative regulator to suppress the toxic effects of LPS. MicroRNA (miR-) 21 acts to inhibit the activation of PTEN as it known as facilitator to TNFα production in pathogenic LPS response. RNA silencing by miR-21 on the PDCD4 gene target supports c-Jun expression and AP-1 transactivation. This condition lead the macrophages to M2 phenotype [24]. M2 macrophage cells suppress the development of a type 1 immune response toward pathogens and his caused persistent infection with characterized by an increasing of IL-10 expression. Interleukin (IL-) 10 bound with heterodimer receptor subunits (IL-10R1 and IL10R2) and activated Jak and Tyk2 kinases, so there was an activation of STAT-3. This signaling pathway provides an inhibitory mechanism for IL-12 production in target cells.

Conclusion

Burns injury give an affect for the patients, especially in immune system. It begins with a series of inflammatory responses, which the aim of this is to eliminating the lesson of wound and initiating tissue repair. The inflammatory process in burns injury with severe damage should be controlled. When the inflammatory response becomes very strong in cases of severe burns, the body responds by forming an antiinflammatory mediators. the ratio between pro and antiinflammatory mediators are determine by immune system, it can return to be a homeostatic state or develop persistent inflammation, immunosuppression, and catabolic syndromes, which this can increase the risk of organ failure and sepsis in patients.

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