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Review

Targeting macrophage immunometabolism: Dawn in the darkness of sepsis

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ABSTRACT

Sepsis is known since the time (470 BC) of great Greek physician, Hippocrates. Advancement in modern medicine and establishment of separate branches of medical science dealing with sepsis research have improved its outcome. However, mortality associated with sepsis still remains higher (25–30%) that further increases to 40–50% in the presence of septic shock. For example, sepsis-associated deaths account more in comparison to deaths-associated with myocardial-infarction and certain cancers (i.e. breast and colorectal cancer). However, it is now well established that profound activation of innate immune cells including macrophages play a very important role in the immunopathogenesis of sepsis. Macrophages are sentinel cells of the innate immune system with their location varying from peripheral blood to various target organs including lungs, liver, brain, kidneys, skin, testes, vascular endothelium etc. Thus, profound and dysregulated activation of these cells during sepsis can directly impact the outcome of sepsis. However, the emergence of the concept of immunometabolism as a major controller of immune response has raised a new hope for identifying new targets for immunomodulatory therapeutic approaches. Thus this present review starts with an introduction of sepsis as a major medical problem worldwide and signifies the role of dysregulated innate immune response including macrophages in its immunopathogenesis. Thereafter, subsequent sections describe changes in immunometabolic stage of macrophages (both M1 and M2) during sepsis. The article ends with the discussion of novel macrophage-specific therapeutic targets targeting their immunometabolism during sepsis and epigenetic regulation of macrophage immunometabolism and vice versa.

1. Introduction

Sepsis is a life-threatening condition associated with multi-organ dysfunction originating due to the dysregulated innate immune response against pathogenic infections [1]. According to the third consensus on sepsis or sepsis-3 it is defined as a life-threatening condition of organ dysfunction caused by a dysregulated host's immune response to an infection [1] It may develop in any age group of patients but in a certain group of patients that is neonates, children and old age population it is more prevalent and proves detrimental [2,3]. Even depending on gender, its prevalence is more common in males as compared to females independent of age [4]. The incidence of sepsis worldwide is very high [5–7]. For example, a tentative extrapolation from the data obtained from high-income countries has indicated that globally 31.5 million cases of sepsis and 19.4 million cases of severe sepsis occur annually [8]. This is further associated with the death of potentially 5.3 million people every year [8]. The mortality-associated with severe sepsis and septic shock varies from 25-30% and 40-50% that is very high [9,10]. Additionally, the management of sepsis is very costly and seems to be both economic as well as humanistic burden [11].

Severe sepsis is the phenotype of sepsis that exists with hypotension, hypoperfusion or organ dysfunction [12]. The pathophysiological abnormalities observed during severe sepsis include lactic acidosis, oliguria, acute respiratory distress syndrome (ARDS) along with an acute alteration in mental status [12]. While septic shock is similar to severe sepsis but hypotension persists during volume resuscitation and requires the use of vasopressors (i.e. epinephrine, norepinephrine, isoproterenol, and dobutamine etc.) [7,12,13]. The third consensus on sepsis or Sepsis-3 defines septic shock as a pathophysiologic condition observed during sepsis with particularly profound circulatory, cellular, and metabolic abnormalities causing a greater risk of mortality than with sepsis/severe sepsis alone [14]. The immunopathogenesis of sepsis is a very complex process that involves both overactivation and suppression of immune response [15,16]. The later phase of immunosuppression observed during sepsis proves detrimental to host and

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makes them susceptible to acquires secondary infections [17–19]. Various nice reviews are available describing the role of innate immune system in the pathogenesis of sepsis, its outcome and therapeutic targeting [7,20–26].

Macrophages are important innate immune cells and due to their immunoregulatory function and ubiquitous presence play an important role in immune homeostasis and inflammatory process [27–31]. This immunoregulatory function of macrophages is controlled by their metabolic stage that varies depending on their stage of activation. Thus the activation of macrophages with various pathogen-associated molecular patterns (PMAPs), death or damage-associated molecular patterns (DAMPs), cytokines, and alarmins can impact their pro-inflammatory or anti-inflammatory stage via affecting their metabolic stage called macrophage immunometabolism. This change in the immunometabolic stage of macrophages proves detrimental to the host due to its direct impact on macrophage phenotype and function.

Immunometabolism can be defined as an interdisciplinary field that is derived from a combination of classical immunology and metabolism, employing experimental advancements and paradigms of both the fields [32]. This can further be categorized into two main branches: (1) Cellular immunometabolism dealing with the study of changes in immune cell metabolism determining their fate under diverse conditions [33–35], and (2) Tissue immunometabolism mainly focuses on the effect of immune cells on tissue and systemic metabolism supporting the adaptation of an individual to an organism to environmental changes [32]. Immunometabolism exerts its regulatory role on the immune system and associated diseases including infections, cancer, and autoimmunity [36–38]. Hence, metabolomics has also attracted its attention towards sepsis research and associated health outcomes [39]. The present review is focussed on the role of macrophages and their immunometabolic stages in sepsis immunopathogenesis, the impact of immunometabolic changes on epigenetic control of macrophages, and targeting of macrophage immunometabolism as a future therapeutic approach for sepsis.

2. Monocytes and macrophages during sepsis

Monocytes and macrophages play an essential role in the host defense against a variety of pathogens and generation of inflammatory immune response during sepsis [40,41]. Furthermore, the inflammatory function of macrophages is increased by interferon (IFN)-γ via enhancing the release of pro-inflammatory cytokines [41]. This increase in the release of pro-inflammatory mediators from macrophages occurs through IFN/STAT1 (Signal transducer and activator of transcription 1) signaling pathway in sepsis [42,43]. The later stage of sepsis is accompanied by immunosuppression or immunoparalysis that is mainly due to the apoptotic cell death of conventional T cells and upregulation of regulatory T cells (Tregs) [44,45]. However, macrophages also play an important role in this immunosuppression/immunoparalysis [46–49]. The macrophages isolated from patients with lethal sepsis do not respond properly to LPS stimulation and exhibit endotoxin tolerance [16,50–52]. This endotoxin tolerance exhibited by macrophages as a result of the shift towards M2 macrophage or alternatively activated macrophage (AAM) phenotype contributes to the immunosuppression observed during later stages of sepsis [16,50,52,53]. IFN-γ therapy has been proven beneficial for reversing this immunosuppressive stage of macrophages during sepsis [54,55].

The metabolic pathways regulating function of these myeloid cells are also affected during the process [56,57]. Thus it becomes essential to study the metabolic stage of the macrophages during sepsis. For example, the metabolism of glucose to drive oxidative phosphorylation (OXPHOS) in the mitochondria, and alternative metabolism of glucose to lactate via anaerobic glycolysis or aerobic glycolysis are emerging as key immune-metabolic axis [58,59]. This immune-metabolic axis is influenced by the type of injury/infection and its duration that further determines the function of immune cells controlling exaggerated inflammation and the pathogenesis of sepsis [58,59].

3. Normal and altered immunometabolism of macrophages during sepsis

Under normal physiologic conditions, macrophages use oxidative phosphorylation (OXPHOS) as a major metabolic pathway to utilize glucose for their energy requirement [60,61]. This process of OXPHOS is carried out in mitochondria via activation of electron transport chain (ETC) [61,62]. The process requires NADH (Nicotinamide adenine dinucleotide-reduced form) and FADH (Flavin adenine dinucleotide-reduced also called semiquinone) generated by Krebs or Tricarboxylic Acid (TCA) cycle [60–62]. However, an encounter of macrophages with pathogens or potential inflammogens that are lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN) and certain cytokines (i.e. TNF-α, IL-1, IL-4, IL-10 etc.) induce the phenomenon of metabolic reprogramming [60,63]. This causes a shift from OXPHOS to glycolysis to synthesize ATP molecules to meet the increased energy demand required to counteract pathogens/inflammogens [58,61]. This is called Warburg effect and was first observed in tumor cells [64–66]. Although only two ATP molecules are produced per molecule of glucose during glycolysis this ATP production is faster than OXPHOS [67]. Thus both processes including a shift from OXPHOS to glycolysis and mitochondrial metabolism exert a great impact on immune response generated by macrophages via regulating genes associated with their activation [61,68–70]. For example, an early adaptation of ETC of macrophage mitochondria upon an encounter with live bacteria impacts its immune function via affecting immune-metabolic axis [68]. An *in vivo* inhibition of ETC complex II (CII) in a mouse model of sepsis increased the bacterial burden in the spleen of the mice due to a significant decrease in serum IL-1β accompanied by higher serum levels of anti-inflammatory cytokine IL-10 [68]. Thus the inhibition of CII in macrophages impairs their bactericidal activity and potential to secrete pro-inflammatory cytokines [68].

The change in metabolic stage of macrophages was observed more than 50 years back by Rossi and Zatti in 1964 during the process of phagocytosis [71,72]. Even the switch from OXPHOS to the glycolysis in peritoneal macrophages during the process of phagocytosis was known as early as in 1963 [73]. It is important to note that alveolar macrophages from guinea pigs use OXPHOS as an energy source during the process of phagocytosis [73]. An increase in glycolysis during LPS mediated stimulation of macrophages is supported by an increased expression of glucose transporter 1 (GLUT1) (Fig. 1) [74]. The increased surface expression of GLUT1 helps to overcome the increased glucose demand required to shift cellular metabolism from OXPHOS to glycolysis [74] (Fig. 1). This metabolic shift to glycolysis is further supported by an increased generation of nitric oxide (NO) [75,76]. An increased generation of intracellular NO by macrophages for more than twelve hours damages their mitochondrial ETC [75,76]. Thus this metabolic shift in macrophages during prolonged inflammatory conditions like sepsis is a requirement for their survival [77]. A shift from OXPHOS to glycolysis and increased fatty acid synthesis (FAS) leads to the induction of pro-inflammatory phenotypes of macrophages that is M1 macrophages [78–80] (Fig. 1). Thus this metabolic reprogramming (i.e. a shift from OXPHOS to glycolysis) alongside changes into lipid and amino acid metabolism during sepsis impacts genes determining their pro-inflammatory and anti-inflammatory function [81–83].

3.1. Classically activated macrophages (CAMs) or M1 macrophages in sepsis, shift in their immunometabolic stage and its regulation

The acute inflammatory immune response generated in response to infections causes transformation of uncommitted monocytes/macrophages (M0) into CAMs/M1 macrophages where they play a significant role in the progression of the sepsis [84–86]. These M1 macrophages secrete plethora of pro-inflammatory molecules including cytokines, chemokines, and reactive oxygen/nitrogen species (ROS/RNS) responsible for clearing pathogens and generating inflammatory immune