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FORCE IN LONG TERM IMMUNO_SUPPRESSION

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Extended Abstract

Sepsis is defined as the host inflammatory response to severe, life-threatening infection, with the presence of biochemical abnormalities and organ dysfunction. It is a major healthcare problem, affecting millions of people around the world every year. Its incidence is increasing owing to the ageing population, immuno-senescence and the resulting impaired immunity. Moreover, it is the most frequent cause of mortality in most intensive care units (ICUs), especially if not recognized and treated promptly [1]. Despite its worldwide importance and being considered a public health concern, accounting for more than $20 billion (5.2%) of total US hospital costs in 2011 [2] public awareness of sepsis is poor. The short-term mortality of sepsis is 10-40% and even higher for septic shock (30-60%). Most clinical studies examining patients with sepsis have used 28 day mortality as a clinical end point, and although only a few studies on long-term mortality exist, they indicate that long-term mortality is also increased among patients who had survived the acute episode of severe sepsis septic event, even after accounting for their underlying medical comorbidities. Recent data demonstrate that survivors have poor quality of life, frequently develop cognitive and functional disability, and require substantial ongoing acute and long term care [5]. In addition, higher long term mortality has been reported in patients with community-acquired severe sepsis or septic shock, as compared to individuals of similar age, sex and comorbidities [6]. Possible causes for the long-term impairments observed include hypoperfusion, toxins, maximal stress response (cytokines), exposure to treatments (such as steroids), immobility, development of complications such as acute lung injury or combinations of these and other factors. The current paradigm regarding the host immune response to sepsis is under debate [7-11]. Some theories are being considered in order to explain the nefarious consequences of sepsis on the survivors. The most recent and accepted theory states that sepsis consists on an initial hyper-inflammatory phase which can produce “early” deaths during the first 24 h-48 h (e.g. in the toxic shock). Two other theories, based on the immune response, try to explain the morbi-mortality and “late deaths” induced by sepsis few days after hyper-inflammatory phase. The first relies on a persistent activation of innate immunity that would lead to hyperinflammation, which in turn may cause multiple organ dysfunctions [12]. The second theory - and most widely supported - proposes that after an initial phase of hyper-inflammatory response, a failure or exhaustion of adaptive immunity (T-lymphocytes) occurs, that produces immuno-paralysis or immunosuppression (Figure 1). This phase of immunosuppression produces late deaths due to the exhausted immune response and the apparition of new opportunistic or recurrent infections [8]. The hypothesis that patients enter in a phase of “immune paralysis or immunosuppression” after sepsis or septic shock episodes come from the clinical observation that a considerable proportion of survivors developed both viral reactivation (commonly herpes simplex virus and cytomegalo virus) and secondary nosocomial infections by Candida sp., Acinetobacter sp., Stenotrophomonas sp. [7, 13], etc. Pneumonia also complicates the disease in the late phase of immunosuppression in 10-30% of patients in ICUs, who are treated with mechanical ventilation [14]. An episode of sepsis or septic shock also seems to raise morbidity and mortality in a late stage in successive years producing "longterm" deaths. However, confirmatory studies demonstrating the clinical significance of the “long-term” phase in sepsis are largely missing. The few studies available suggest that the “longterm” phase of sepsis is associated with significant re-increase of positive blood culture results, especially opportunistic bacteria and fungi [15], and patients who survived sepsis remained the strongest predictor of recurrent infections post-discharge, rehospitalizations for infection, and post-discharge mortality [16]. At the present time, it is completely unclear whether patients who acquire sepsis are simply inherently at risk for infection complications, or whether sepsis imposes additional susceptibility for subsequent infections. It is accepted that, during sepsis, increased apoptosis causes the depletion of immune cells, including both innate immune cells (dendritic cells, follicular dendritic cells, natural killer cells, and myeloid-derived suppressor cells) and adaptive immune cells (CD4+ T and CD8+ T cells and B cells). Among others, circulating histones mediate the apoptosis of these immune cells, therefore compromising the immune defenses and contributing to immunosuppression after septic shock, hence producing late deaths. Furthermore, the efficacy of the immune response requires coordinated mechanisms involved in the activation of a large number of genes participating in the innate immune system [17], which in turn depends on the accessibility of the transcription factors to the chromatin, histone post-translational modifications, and DNA methylation. In this regard, active genes in immune cells are associated with nucleosomes enriched for open-chromatin marks such as trimethylated histone H3 at Lys 4 (H3K4me3) and acetylated histones H3 and H4 [18]. In contrast, H3K9me2 and H3K27me3 are involved in gene silencing in immune

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cells [18, 19]. Furthermore, the high stress imparted on the immune system during a sepsis or septic shock episode affects seriously the function of myeloid cells, which has important effects on epigenetic signatures in these cells. Therefore, differentiation and maturation of immune cells, together with key genetic programs, are severely affected, thus producing fatal consequences in the innate immune response and increasing the risk of survivors for long-term deaths [20]. As we review in this work, intricate epigenetic mechanisms mediate immune responses during sepsis, demonstrating that epigenetics is an important driving force during immunosuppression, offering a more complex and plausible explanation to the compromised immune response after a septic episode, producing “late deaths” and “long-term deaths”.

Sepsis, a Severe Inflammatory Response and Life-Threatening Infection with Organ Dysfunction: The first definitions proposed in 1991 for the sepsis syndrome were based on the presence of presumed infection and at least two out of four Systemic Inflammatory Response Syndrome (SIRS) criteria. Moreover, severe sepsis was considered when acute organ dysfunction secondary to documented or suspected infection concurred; and septic shock (SS), if there was hemodynamic instability that required vasoactive support despite adequate fluid resuscitation [21]. A 2001 Task Force, recognizing limitations within these initial definitions, included an expanded list of both clinical and laboratory abnormalities, yet without offering any alternative due to the absence of new evidence [22]. However, in the last fifteen years increased knowledge of the etiology and pathobiology of sepsis, such as changes in organ function, morphology, cell biology, biochemistry, immunology, and growing evidence of poor clinical and epidemiological utility of previous definitions, have highlighted the need for new terms. In this regard, a new Task Force with expertise in sepsis was recently convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine [23-25]. They considered some limitations from previous definitions, as an excessive focus on inflammation, an inadequate specificity and sensitivity of the SIRS, and the misleading model that sepsis follows a continuum, through severe sepsis to shock. It was concluded that the term “severe sepsis” was redundant, and recommended the elimination of the terms “sepsis syndrome”, “septicemia” and “severe sepsis”. Besides, the Task sought to differentiate sepsis from uncomplicated infection. Finally, they defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, and SS was defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities were associated with a greater risk of hospital mortality than with sepsis alone (>40% vs. >10%). The organ dysfunction in sepsis may occur at different time in different patients (before, during and after infection is recognized), establishing a time window including both short (6 h) and long (72 h) around the onset of infection. New definitions were designated SEPSIS-3, emphasizing the need for future iterations (Table 1). Like for many syndromes, there is no gold standard diagnostic test for sepsis. Thus, clinical criteria were evaluated and established by the Task [23]. They recommended the use of an acute change of SOFA (Sequential Organ Failure Assessment) score of two points or more, consequent to infection, as criteria for sepsis in the ICU setting; and the use of qSOFA (quick evaluation of three parameters: systolic blood pressure <=100 mm Hg, respiratory rate >=22/min, and alteration in mental status) in the non-ICU settings to consider the possibility of sepsis. These scores were chosen based on their significantly higher predictive validity for in-hospital mortality in the different settings. On the other hand, SS could be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater, and by the presence of serum lactate level greater than 2 mmol/L in the absence of hypovolemia [24]. The adjusted odds ratio (OR) for hospital mortality increases linearly with increasing of serum lactate level, positioning it as a proxy for a cellular metabolic abnormality. Although not specific for sepsis, it should face validity given the lack of a superior available alternative. The epidemiologic strengths of the new consensus definitions SEPSIS-3 are counteracted by weakness in their ability to be used in the treatment of individual patients. Given the heterogeneity of molecular and cellular responses associated with septic condition, development of new biomarkers which allow identification of specific patterns may be helpful for categorization of this kind of critically ill patients, and could contribute to future SEPSIS-4

definitions, establishment of new treatment targets, to design of new therapeutic approaches and to predict future outcomes in survivors. In addition, sepsis is a syndrome that encompasses a stilluncertain physiopathology. It is characterized by a complex systemic biphasic immunological response to a microbial pathogen. The presence of pathogens in the bloodstream causes an innate immune response characterized by the stimulation of monocytes and neutrophils and release of pro-inflammatory cytokines like TNF?, and a counter regulatory anti-inflammatory reaction (i.e., mediated by IL-10) as negative feedback on the inflammation. The intensity of the initial inflammatory response varies in individual patients depending on multiple factors, including pathogen load and virulence, patient comorbidities and host genetic factors. Simultaneously, it results in an activation of a medley of different immune pathways (major expression of tissue factors, which activates coagulation, and an increase in nitric oxide synthesis, which induces vasodilatation), and usually determines the destruction of the pathogen. Tolllike receptors (a group of transmembrane proteins) act as innate immune system sensors through the recognition of highly conserved components of a variety of microorganisms. Under some circumstances, many of these beneficial components of inflammation can be deleterious, causing cell and tissue damage and hence multiple organ failure [26]. It can promptly occur due to a hyperinflammatory ‘cytokine storm’ response with fever, refractory shock, acidosis and hypercatabolism. However most patients have a restoration of innate and adaptive immunity and survive the infection. Nowadays, understanding of the immune

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response to sepsis is controversial. Although immunosupression, as a marked compensatory anti-inflammatory response, seems to justify late-deaths, less is known about the etiology of long-term deaths, being epigenetics hypothesized as the main conductor. Despite critically ill patients receive care for a large variety of disease states, the leading causes of death in the ICU are multiorgan failure, cardiovascular failure, and sepsis [27]. Multi-organ failure has a mortality rate of up to 65% when more than one organ system fails [28] new-onset renal failure has a mortality rate of up to 61%, and severe respiratory failure has a mortality rate ranging from 20% to 50%. Sepsis, the second leading cause of death in non-coronary ICUs, has a mortality rate of up to 45%. In patients who are diagnosed with sepsis, up to 51% develop acute renal failure, and up to 20% have acute respiratory failure requiring mechanical ventilatory support. Importantly, septic ICU patients have significantly higher mortality when compared to nonseptic critically ill patients [55% vs. 19.3%, OR=2.21 (1.65-2.97)]. Acute tubular necrosis and oliguria in septic patients, as well as cardiovascular failure (by SOFA score) in non-septic, have been identified as independent risk factors for mortality [26]. Overall, mortality rates in patients admitted to adult ICUs average 10% to 29%, depending on age and severity of illness. The mortality rate for patients who have been admitted to the ICU is greater for the following 10 years after they leave the ICU compared to patients of the same age who have never been admitted to the ICU [29]. These intriguing data suggest that some kind of "fingerprint" may occur in ICU patients after a critical health situation, which may depend on the severity of the pathology.

Epigenetic Changes Can Explain the Molecular Causes of Long-Term Immunosuppression: Epigenetics is a rapidly growing field of research which studies the heritable changes (in the progeny cells or of individuals) in the gene activity and expression that do not involve changes in the nucleotide sequence, and also stable, long-term alterations in the transcription of genes that are not necessarily heritable [30]. Epigenetic gene regulation refers to how a specific structural and chemical configuration of chromatin (mediated mainly by posttranslational modifications in histones, PTMs) translates into a defined outcome on its transcriptional status. Overwhelming inflammation reactions in response to microorganisms exposure and microbial products are conducted by the innate immune system cells (i.e., monocytes and neutrophils), which release high levels of pro-inflammatory cytokines and can produce early deaths in a septic process. Most patients survive to this critical scenario and can restore their innate and adaptive immunity. However, in some cases in which sepsis persists, patients can enter in a process called immunosuppression, immuno-paralysis or post-septic immunosuppression [8], which makes patients more susceptible to infections because hematopoietic cells result to be hyporesponsive to stimuli. Epigenetics, and especially chromatin remodeling, might act as driving forces involved in the short-term and long-term immunosuppression observed after sepsis episodes. In the phenomena of immunosuppression, several observations reinforce this hypothesis: 1) Early findings demonstrate lower levels of H3K9me2 at inflammatory gene promoters in innate immune cells, as compared with non-immune cells [31] and a rapid demethylation of H3K9me2 occurs at promoters of these genes after lipopolysaccharide (LPS) challenge [32] 2) Repetitive or sustained LPS challenge produces TNF- and IL1- repression - mediated after the recruitment of repressive HMT G9a, heterochromatin protein 1 (HP1) and DNMT3A/B - and a subsequent increase of H3K9me2 and DNA hypermethylation at the promoters of inflammatory genes [33] 3) Epigenetic mechanisms participate in the regulation of key specific genes and also in the maturation, development and regulation of the adaptive immune cells.

Sepsis and the Immune System: Epigenetic Regulation of the Innate and Adaptive Immune Cells: Importantly, the mortality rate for patients who have been admitted to the ICU is greater for the following 10 years after they leave the ICU compared to patients of the same age who have never been admitted to the ICU [29]. In those cases, immunosuppression due to defective innate and adaptive immune responses underlies this late effect. Expression arrays from pediatric patients who died of sepsis also showed altered gene expression profiles indicating immunosuppression [34]. Furthermore, gene expression studies performed in children with septic shock showed that genes participating in the modulation of the innate immunity were upregulated, whereas transcription of genes participating in the adaptive immunity were downregulated [34], confirming a compensatory anti-inflammatory response underlying the process of immunosuppression. Regarding these results, it should be clarified that the levels of epigenetic changes that occur in hematopoietic cells make progenitors in the bone marrow inefficient to restore the immune system, and therefore affect the ability of the host to initiate an immune response throughout the expression of key genes. It is known that apoptosis of immune cells may also contribute to immuno-paralysis. In this regard, immune cells such as CD4+ and CD8+ T cells, B cells, and dendritic cells showed high apoptosis with serious consequences for the immunity of the patients who survived [8], a phenomenon observed in all age groups during sepsis. However, other immune cells such as neutrophils (in the innate immune system) and T regulatory (TReg) cells, are resistant to apoptosis. In fact, TReg and myeloid derived suppressor cells (MDSCs), which are considered immunosuppressive cells, are increased in sepsis [35-37]. Beyond the apoptosis of immune cells, the drastic changes observed in the expression of genes involved in the innate and adaptive responses suggest the intervention of epigenetic reprograming at their promoter regions, which could condition the response of the immune system. Proof of that premise is that DNA methylation regulates gene expression programs of related pathways which establish the cellular identity of the immune cells in the immune system [38]. On the other hand, immune cells harvested from the spleen or lungs of patients with sepsis showed markedly decreased expression of anti- and pro-

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inflammatory genes [39], which may respond to intricate epigenetic reprogramming in immune cells and contribute to the apparition of new opportunistic infections [13-15]. As we describe in this section, sepsis has an important impact in the function of all types of immune cells in both innate and adaptive immune systems. Here, we summarize some of the consequences of sepsis on the immune cells and the possible role of epigenetics: In the innate immune cells.

Conclusion:

The immune landscape of sepsis is complex, although it seems to be orchestrated by molecular pathways and epigenetic forces that control both “pro-inflammatory” and “anti-inflammatory” phases, thus mediating the immunosuppression of patients after a sepsis episode. Both phases occur steeply throughout the progression of sepsis, with the early phase of sepsis evolving with an important participation of pro-inflammatory pathways, and the latter phase of sepsis characterized by immunosuppression, which conduces to development of secondary infections or virus reactivation, increasing the probability of late-deaths. It is still not clarified the impact of immunosuppression over the long-term prognosis but everything points to a key role. In these processes, epigenetic mechanisms are the conductors of specific chromatin signatures and transcriptional programs in immune cells, therefore conditioning the pro-inflammatory and anti-inflammatory responses in septic patients. Epigenetic imprinting may not only occur in differentiated innate and adaptive immune cells, which may explain late immunosuppressive process, but also in progenitor cells in the bone marrow and in other immune tissues like spleen and thymus during sepsis, which could contribute to long-term immunosuppression and long-term deaths of survivors from sepsis. Many questions on the cytotoxic effect of histones and the particular role of histone types and PTMs that condition immunosuppression make it extremely difficult to develop precise and effective biomarker and therapeutic strategies. The comprehension of epigenetic mechanisms and specifically the role of diverse histone types and PTMs will help to clarify the epigenetic control of genes participating in the pro-inflammatory and anti-inflammatory phases orchestrating immunosuppression, and hence will allow developing precise and effective diagnostic and prognostic biomarkers. There exists a perception that the recovery or preservation of the host immune function would contribute to improve survival in sepsis, especially in late deaths produced by immunosuppression. Therefore, therapeutic strategies that enhance the immune system may clearly contribute to the management of septic patients and probably improve the physiological state of patients affected by long-term immunosuppression. In this regard, epigenetic drugs and their regulative effect on the expression of key immune genes should play a pivotal role for future investigations and clinical trials.

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