Sepsis: What We Know and What We Don’t

Jyotika Sharma*
Department of Microbiology and Immunology, UND School of Medicine and Health Sciences, 501 N Columbia Road, Grand Forks, ND 58202-9037, USA

*Corresponding author: Jyotika sharma, PhD, Assistant professor, Department of Microbiology and Immunology, UND School of Medicine and Health Sciences, 501 N Columbia Road, Grand Forks, ND 58202-9037, USA; Tel: 701-777-2624; Fax: 701-777-2054; E-mail: jyotika.sharma@med.und.edu

Received September 28, 2012; Accepted September 30, 2012; Published October 02, 2012


Copyright: © 2012 Sharma J. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Sepsis is a complex immune disorder that results in 750,000 hospitalizations annually in the United States alone [1]. In addition to posing an immense health hazard with a mortality rate of 20-50%, it is also a huge economic healthcare burden with the patients consuming half of the ICU resources in the country. In October 2011, the only FDA approved drug for the treatment of sepsis (Xigiris) was withdrawn from market following the much anticipated results of the clinical trial (PROWESS-SHOCK) where it failed to show any survival benefit for severe sepsis and septic shock patients [2]. As a result we are now left with no effective preventive or treatment options for this deadly immune disorder, despite three decades of active research. Why has it been so hard to tackle sepsis? One obvious reason is the complexity of this disorder as it is thought to be interplay of multiple host immune pathways [3]. The second likely reason is that most of the research has been focused on initiation of inflammatory response when the need is to take into account factors responsible for exaggeration of ongoing inflammation as well as lack of negative regulatory mechanisms/resolution of inflammation/restoration of homeostasis.

Resolution of Inflammation: Return to Homeostasis

Once the pathogenic insult has been taken care of, it is imperative that the immune cells are cleared off the milieu, in order to restore the quiescent state of homeostasis. This is achieved by the process of efferocytosis, where the innate immune cells such as neutrophils, once they have completed their task of combating pathogens, start to undergo apoptosis and are eventually phagocytosed by professional phagocytes in the vicinity. Deregulation of this process can result in secondary necrosis of these apoptotic cells causing the release of host alarmins in the extracellular milieu which, we now know, play an important role in exaggeration of an ongoing inflammation. As sepsis is often characterized by massive cell death in systemic organs, it is tempting to speculate that a deregulation of efferocytosis process and turnover of neutrophils contributes to sepsis development. However, studies correlating these two processes with sepsis are surprisingly few. In addition to clearing dead cell carcasses, the process of efferocytosis also modifies the phenotype of phagocytic cells from inflammatory to anti-inflammatory nature resulting in production of host mediators such as TGF-beta and IL-10 that not only shut the inflammatory response but also inhibit further influx of immune cells [8]. All of these events constitute the complex process of resolution. How then, in the context of an inflammatory disorder such as sepsis, or for that matter any inflammatory disease condition, this regulated process of resolution is disrupted and progresses towards an accelerated and sustained condition of chronic inflammation? This is an area of investigation which may hold some key answers to queries regarding the mechanisms of sepsis development and how an otherwise beneficial host response turns to a harmful process of excessive inflammation and overt tissue destruction.

Conclusion

A lack of understanding of molecular mechanisms tipping the balance between a local, resolving inflammation to a systemic non-resolving inflammatory response has limited our efforts to find effective...
treatment options for sepsis. This knowledge likely holds the key to combating this deadly immune disorder.

References


