FROM SEPSIS TO A PARALYSED IMMUNE SYSTEM

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Brief message

Hi everyone! I am Kavita, and I am currently pursuing my master's in Medical Biology. The past academic year, I got the pleasure to be part of RAMS as the chair of the editorial board. Working with an enthusiastic and motivated team of editors, with different interests, was truly amazing. During my bachelor's, I followed several courses regarding the immune system and cancer. Whereas my main topic of interest is mostly cancer, I thought of exploring another part of immunology when writing this brief message. This is when I decided to write about another fascinating topic, namely sepsis and its role in immunoparalysis.

According to the World Health Organization, 49 million people are affected by sepsis yearly, leading to 11 million deaths each year [1]. In short, sepsis can be described as a life-threatening organ dysfunction due to a dysregulation in the host immune response caused by an infection [2]. This dysfunction is characterised by the presence of a pro- and anti-inflammatory cytokine storm [2]. Nowadays, due to the advances in medical healthcare, a major part of septic patients can survive this disease. Remarkably, the cytokine storm, which can be seen as an over-activation of the immune system, can also result in a long-term immune dysfunction called immunoparalysis [2,5,9]. These immunoparalysed patients have an increased susceptibility to secondary infections and viral reactivation, resulting in an attenuated five-year survival compared to individuals who never had sepsis [3,4]. But how does immunoparalysis occur, and what is its long-term effect on sepsis treatment?

During the septic stage, an unstable shift in specific immune cell subsets' representation and function occurs, contributing to the ongoing septic response and the later immunodeficiency [5]. The proposed mechanism of immunoparalysis is the apoptosis of B-lymphocytes, CD4 T-lymphocytes, and follicular dendritic cells in septic patients, resulting in decreased numbers of circulating lymphocytes and dendritic cells [5]. Furthermore, the presence of apoptotic lymphocytes increases the production of anti-inflammatory cytokines and impairs the release of pro-inflammatory cytokines [5,6]. Lastly, these apoptotic cells can also increase the tolerance of lymphocytes to pathogens [5]. Overall, the combination of these pathways lead to the induction of paralysis of the immune system.

Now we know how immunoparalysis occurs, it is also essential to look at the implications of these findings for long-term treatment of sepsis. New insights have led to the emergence and possible implementation of a new, promising treatment option for sepsis, known as personalised healthcare. In order to make this treatment possible, patients are endotyped, which means that you divide the patient into various subgroups based on specific differences such as gender, age, genetics, and environment [7].

Personalised approaches can be applied when a patient is admitted to the hospital. During this treatment stage, they can be subjected to supportive therapies and samples are taken for laboratory analyses [8]. With some of these relatively simple methods like clinical scales, mediator concentrations, or the activation of immune cells, you can stratify the patient in a specific category [8]. Hereafter, a threshold is

applied to decide if a patient is a suitable candidate for a particular therapy. This approach is already used in some clinical trials and for some measurable biological characteristics, known as biomarkers, feasible at the bedside [7,8]. For sepsis, some biomarkers are already established, including measuring the number of cytokines produced by leukocytes [7].

Application of suitable biomarkers for patients will aid in a personalised treatment, as the biomarker gives you a better understanding of the patient's immune status. Although sepsis is now easier to treat than before with the medical advances, it concerns critically ill patients, and the mortality remains high. Therefore, the application of a personalised treatment approach is a promising option to decrease the vast number of deaths related to sepsis and its later consequences, including immunoparalysis.

References

1. World Health Organization. WHO Sepsis. (2020) Retrieved from: https://www.who.int/health-topics/sepsis#tab=tab_1 (Accessed: 13-12-2020)
2. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA,* **315**, 801-810 (2016)
3. Donnelly, JP. *et al.* Unplanned readmissions after hospitalisation for severe sepsis at academic medical center-affiliated hospitals. *Crit Care Med,* **43**, 1916–1927 (2015)
4. Walton, AH. *et al.* reactivation of multiple viruses in patients with sepsis. *PLoS ONE*, **9**, e98819 (2014)
5. Martin, MD. *et al.* CD4 T Cell Responses and the Sepsis-Induced Immunoparalysis State. *Front. Immunol*, **11**, 1364 (2020)
6. Voll, RE. *et al.* Immunosuppressive effects of apoptotic cells. *Nature,* **390**, 350-351 (1997)
7. Landelle, C. *et al.* Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock. *Intensive Care Med,* **36**, 1859-1866 (2010)
8. Cavaillon. JM. *et al.* Sepsis therapies: learning from 30 years of failure of translational research to propose new leads. *EMBO Mol Med,* **12**, e10128 (2020)
9. Gaieski, DF. *et al.* Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*, **41**, 1916–1927 (2013)

EXAM QUESTION

Question 1

Practise your knowledge regarding the topic of this brief message. Do you know the answer?

What could be a treatment strategy for patients with a decreased function of the immune system during sepsis?

A. Blocking TNF-alpha
B. Vaccination with BCG
C. Block PD1-PD1L interaction
D. Stem Cell Transplantation

The answer to this question can be found on page 33 in this journal.