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REVIEW ARTICLE

MODULATION OF THE IMMUNE-RESPONSE FOR TREATMENT OF SEPSIS

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ABSTRACT

Sepsis occurs when pathogenic infections become systemic, and the response itself leads to both morbidity and mortality. Here I propose, that the immune response is a "localized" response, evolved to isolate infections and to prevent them from spreading when our epithelium is damaged, that goes into overdrive when pathogens do break through the "barrier" and invade the body in a systemic manner. A multi-pronged "early" approach modulating the immune response is likely the best way to prevent sepsis from developing fully and to limit its damaging effects on the micro-vascular systems of the body's organs.

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INTRODUCTION

Sepsis accounts for a staggering number of deaths and is among the leading causes of death in intensive care units. Furthermore, those who survive are frequently marked for life, having suffered damage to their organs blood-supply. No treatment has yet been found that can prevent sepsis and this syndrome's detrimental effects. Sepsis occurs when bacterial or viral infections becomes systemic and consists of two phase: firstly, a hyper-immune response occurs, activating immune-cells and causing blood clothing of micro-capillaries in organelles; secondly, a suppression of the immune response occurs involving the apoptotic death of immune cells, and thus, the possible appearance of secondary infections. Death can occur both during the initial hyper-immune response (multiple organ failures), and as a consequence of the secondary infections, and for those who survive the affected organs will have sustained damage to the micro-capillaries. In order to understand what underlies sepsis one has to look at how the body generally prevents and combats infections. Our first and foremost barrier against infections is our epithelium that acts as a physical barrier against both bacteria and viruses. When we are wounded, this barrier is broken, and pathogens have an opportunity to infect. The initial response we all know is the clotting of blood that seals the blood vessels, preventing excessive blood loss. However, this initial response is likely to have an additional function: it prevents pathogens entering the bloodstream and becoming systemic. Indeed, there is likely to be an immune response that initiates blood clotting when bacteria are detected in the micro-capillary of the epithelium, most likely mediated by NK-, B- and/or T-cells. This immune response is also most likely underlying the activation of dendritic cells and macrophages that are able to move through the infected tissue and engulf and neutralize pathogens. The described immune response probably occurs thousands of times during our life, protecting us against serious systemic infections. However, what we observe as sepsis is what happens when infections do become systemic, and the immune response described above is initiated when bacteria/viruses are encountered in the micro-capillary blood vessels of our organs throughout our bodies. Sepsis is the consequence of an encoded response evolved to be local, preventing infection from spreading, occurring in a systemic manner, thus inadvertently leading to mortality and morbidity. Interestingly, the characteristics of sepsis suggest that immune cells are capable of sensing where they are in the body –thus affecting the way they respond to a given pathogen: blood clotting during sepsis only occurs in the micro-capillary and not in the larger blood vessels. This sensing could potentially involve detection of surrounding oxygen levels, as oxygen levels decrease in the capillary blood vessels.

Interestingly, the secondary shutdown of the immune response observed during the later stages of sepsis, where apoptosis of immune cells is induced, must have evolved as a mechanism to limit the sepsis-induced organ damage, and thus, increase survival. The downside of this response is, of course, that if pathogens still are present secondary infections kicks in.

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The question is how to prevent sepsis. It is important to realize that we currently have antibiotics that inhibit bacterial growth or viral replication. Thus, partial or complete inhibition of the "sepsis" immune-response when bacterial infections become systemic, will not necessarily lead to lower survival. Indeed the opposite is likely to be the case. One proposed treatment involves the administration of granulocyte-macrophage colony stimulating factor for the activation of immune cells (Mathias *et al*., 2015). This treatment is likely to limit the systemic spreading of pathogens and thus also limit the sepsis response. However, while there are some clinical benefits of this treatment, there is no increase in the 28-day survival in the adult population (reviewed by Mathias *et al*., 2015). Another suggested treatment is the use of carbon monoxide (CO) at sub-lethal levels (Nakahira and Choi, 2015). In animal models, this treatment also activates macrophages, increasing autophagy and phagocytosis. However, this treatment might have another beneficial effect; it slows down the metabolism by limiting ATP production. By slowing down the metabolic rate, combined with antibiotics or antiviral drugs, it might be possible to partially inhibit the cascade of events leading to sepsis. One possible alternative to CO is hydrogen sulfide (H_2S). H_2S could be a more natural, and less dangerous, way of modulating the "sepsis" immune-response; CO is an inhibitor of ATP synthesis, while H_2S is an alternative substrate for ATP synthesis. In either case, early intervention is likely to be crucial, as once the systemic activation of the immune response described above has occurred, damage of the organs will also occur. Thus, drugs preventing blood coagulation are likely to be beneficial in preventing organ damage, but could also potentially increase the risk of internal bleeding associated with the infection. Thus, it would be attractive to identify what immune response leads to blood clotting in the capillary vessels, as specific inhibition of this response might allow general blood clotting to occur while protecting the micro-capillaries. In support of this motion, in murine studies, administration of a drug named cSN50, which reduces the nuclear translocation of transcription factors, attenuates the responses underlying micro-vascular injury, significantly increases survival of a "lethal endo-toxic shock" used to mimic sepsis (DiGiandomenico *et al*., 2014). In concluding remark, like with many other diseases a multi-pronged approach is most likely best for prevention of sepsis: early intervention with i) antibiotics or antiviral drugs, ii) administration of factors for the activation of macrophages and dendritic cells, iii) lowering the metabolic rate potentially using CO or H_2S, and iv) an inhibition of the response that underlies blood-clotting in the micro-vessels is probably the best approach for dealing with systemic infections and avoiding sepsis.

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