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The role of dendritic cell alterations in susceptibility to hospital-acquired infections during critical-illness related immunosuppression

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ABSTRACT

Systemic inflammatory response syndrome (SIRS) is a common condition in critically ill patients. SIRS is characterized by alteration of both innate and adaptive immunity and causes protracted immunosuppression, exposing the patients to severe secondary infections. Dendritic cells (DCs), which play a pivotal role bridging innate and T cell-dependent immunity, exhibit prolonged alterations after SIRS. In an early phase, SIRS causes depletion or systemic activation of immature DCs in parenchymal tissues and lymphoid organs, leading to impaired pathogen detection and presentation. Later on, newly formed DCs acquire a poorly immunogenic phenotype, with poor capacity to capture, process and/or present antigens and to stimulate T cells. Here, we review the studies that describe alterations in DC function post-SIRS. Knowledge about the molecular mechanisms involved are still scarce but their understanding might open new therapeutic avenues to prevent or reduce protracted immunosuppression in critically-ill patients.

1. Introduction

Patients suffering from critical diseases such as sepsis, severe trauma or brain-injuries are hospitalized in intensive care units (ICUs) because of their high risk of death. Improvements in the standard of care of these patients has progressed enormously, resulting in significant reductions in morbidity and mortality rates (Kaukonen et al., 2014). However, ICU patients remain at high risk of death from hospital-acquired complications, secondary to the initial cause of hospitalization. Nosocomial (airways) infections are a particular cause of morbidity and mortality, and their management in ICUs exacts high costs on the health system. Since bacterial colonization precedes the establishment of infection, numerous preventive strategies aimed at reducing the exposure of ICU patients to bacteria have been tested. However, a recent meta-analysis has shown that the only preventive strategy that has demonstrated effectiveness at reducing mortality consists of digestive decontamination accompanied with systemic antimicrobial therapy (Roquilly et al., 2015). As clinicians are facing a reduction in the efficiency of antimicrobial therapy due to the emergence of bacterial resistance, this strategy is becoming increasingly difficult to apply successfully. Furthermore, this meta-analysis suggests that bacterial colonization might be a first symptom and not the cause of nosocomial infections (Roquilly et al., 2015). Interest has thus been redirected to characterize the mechanisms that prevent ICU patients from responding adequately to secondary infections. Recent studies have revealed profound, long-term alterations in both the innate and adaptive arms of the immune system which increase the susceptibility of ICU patients to infections and that together are responsible for critical-illness related immunosuppression (CIRI). For example, patients who died following sepsis showed clear alterations in number and function of T cells and antigen presenting cells in lymphoid organs (Boomer et al., 2011). As dendritic cells (DCs) combine the capacity to detect environmental changes with the ability to communicate with T cells and innate lymphocytes, they might play a key role in CIRI. In this review we summarize recent studies describing profound alterations to the life cycle and functional properties of DC that likely contribute to CIRI, increasing the susceptibility to infection in critically ill patients.

2. Systemic inflammatory response syndrome is a common characteristic of critical illness

Systemic inflammatory response syndrome (SIRS) is a clinical condition commonly associated with critical diseases such as

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severe infection (sepsis) or trauma. SIRS has an internationally recognized definition consisting of the concomitant presence of two signs among abnormal temperature, increased heart rate, increased respiratory rate, and abnormal white-cell count (ACCP/SCCM, 1992). Mechanistically, SIRS is the clinical expression of a systemic inflammatory response to pathogen- or tissue damage ("danger")-associated molecular patterns (PAMPs and DAMPs, respectively) (Zelenay and Reis e Sousa, 2013). The PAMPs, their receptors, the signal cascades they trigger, and the functional consequences of their detection by cells of the immune system, are well characterized and have been extensively reviewed (Zelenay and Reis e Sousa, 2013). Many DAMPs have also been identified, although their receptors and functional outcomes of their recognition are not so well understood (Zelenay and Reis e Sousa, 2013). Nevertheless, there appears to be extensive overlap in receptor usage and detection outcomes between PAMPs and DAMPs. This probably explains why SIRS induced by severe sepsis, major surgery, multiple trauma or acute brain injury share many features and increase the susceptibility of patients to similar complications early (organ failure) and late (opportunistic infections) after encounter of these different SIRS triggers.

3. DC life cycle, antigen presentation function and response to SIRS

DCs are the chief antigen presenting cells for the initiation and regulation of T cell-dependent immune responses. DC precursors constantly leave the bone marrow and seed peripheral tissues and secondary lymphoid organs, where they develop into immature DCs (Merad et al., 2013). The term steady-state DCs refers to the DCs present in the periphery and lymphoid organs in the absence of inflammation. Steady-state DCs express low levels of two types of molecules required for activation of naive T cells, namely major histocompatibility complex (MHC) molecules, which present antigenic peptides recognized by T cell receptors, and co-stimulatory molecules required for T cell activation (e.g., CD40, CD86). It is widely accepted that steady-state DCs are tolerogenic because if T cells recognize antigens presented by immature DCs they die, lose the capacity to become effector (immunogenic) T cells, or become regulatory T cells dedicated to dampening rather than promoting immune responses. In the absence of SIRS, the DCs die in the immature state, with a turn-over rate of less than a week in lymphoid organs, and a more variable but also fast turn-over rate in peripheral tissues (Kamath et al., 2002).

The maturation of DCs can be induced either by the detection of PAMPs/DAMPs (direct activation) or by stimulation with pro-inflammatory cytokines released during an inflammatory response (indirect or bystander activation) (Spörri and Reis e Sousa, 2005) (Vega-Ramos et al., 2014). DCs that mature in response to direct activation are characterized by high plasma membrane expression of MHC and T cell co-stimulatory molecules and secretion of cytokines for T cell polarization. They down-regulate their capacity to capture and present new antigens (Wilson et al., 2006), but are highly efficient at presenting antigens captured at the time of activation and are immunogenic. Indirectly activated, mature DC are phenotypically similar to their directly activated counterparts, but they do not secrete cytokines and retain the capacity to present new antigens, and are not immunogenic (Spörri and Reis e Sousa, 2005) (Vega-Ramos et al., 2014). Indirectly activated DCs are not covered in this review because most of the DC that mature in response to SIRS probably do so via direct activation. The lifespan of mature DCs is not significantly different to that of immature ones, and new DCs continue to be produced after the onset of SIRS with similar rates as before SIRS (Kamath et al., 2002).

4. Protracted impairment of antigen presentation in DCs of ICU patients

Signs of CIRI are present for weeks after the onset of SIRS in critically ill patients, but it is useful to distinguish two periods: an early stage during which inflammation is evident, and a late one lasting several weeks after resolution of SIRS characterized by an apparent return to basal conditions (Fig. 1). The mechanisms of DC impairment appear distinct at these two periods, an important consideration when devising strategies for therapeutic restoration of immunocompetence.

4.1. Early period: decreased number of immature DCs

Reduced numbers of circulating DCs have been observed in septic (Grimaldi et al., 2011) or brain-injured ICU patients (Roquilly et al., 2013). Lymphoid organs also present reductions in the resident DC pool (Boomer et al., 2011). Apoptosis of immune cells is a well-known feature of response to severe sepsis (Hotchkiss et al., 2000), and DC apoptosis has been observed in bacterial sepsis (Raffray et al., 2015), malaria infection (Pinzon-Charry et al., 2013) and severe trauma and brain injuries (Roquilly et al., 2013). Interleukin 10 (IL-10), has been demonstrated to play a role. During chronic HIV infection, IL-10 induces elimination of mature DCs, resulting in accumulation of immature cells (Alter et al., 2010). IL-10 is immunosuppressive and probably contributes to terminate the immune response after clearance of infections, but excessive IL-10 production during systemic infection become deleterious and increases the susceptibility to secondary infections (Perona-Wright et al., 2009). To compensate for DC elimination, numerous clinical studies have investigated the effects of inoculating growth factors such as GM-CSF to hasten the formation of new cells. However, the results have been disappointing (Bo et al., 2011), suggesting that the decreased number of cells is only a contributor, and perhaps not the most important, to overall immunosuppression.

Indeed, a distinctive feature of directly activated DCs is that while they are highly adept at presenting a long-lived 'snapshot' of antigens acquired at the time of activation, they lose their ability to present newly encountered antigens (Wilson et al., 2006; Young et al., 2007) (Fig. 1). Down-regulation of presentation of new antigens by directly activated DCs is not normally deleterious during most infections because few DCs encounter the infecting pathogen and those that do not can respond to a subsequent challenge. However, systemic circulation of PAMPs or DAMPs during severe sepsis or trauma cause widespread DC activation in the local affected tissue or even in the whole body. These events reduce the number of immature DC capable of presenting pathogen antigens encountered subsequently, impairing the ability of the immune system to mount T cell responses against new infections (Wilson et al., 2006) (Young et al., 2007) (Fig. 1). Direct activation of an excessive number of DC during SIRS can thus be immunosuppressive.

4.2. Long-term alteration of DC functions after SIRS resolution

Given the fast turn-over of DCs (Kamath et al., 2002), it would be expected that the impairment in T cell immunity caused by systemic DC activation should only last until the activating stimulus that triggered SIRS disappears and new immature DCs replace the activated ones. However, CIRI continues for weeks after the onset of SIRS, and DC impairment appears to play a major cause. We showed that a single injection of CpG in mice causes impaired DC function for up to 21 days (Wilson et al., 2006), long after disappearance of CpG activity. The causes of the long-term impairment of DC function following systemic infection or inflammation have not been thoroughly investigated. An attractive hypothesis is that SIRS induces an altered differentiation program on DC precursors

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