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Review

Dendritic cells in sepsis: Potential immunoregulatory cells with therapeutic potential

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ABSTRACT

Sepsis is a disease of dysfunctional immune response against the pathogen causing a profound immune-mediated damage to the vital organs and death of the patient in most cases. However, when sepsis is described much attention is given to monocytes/macrophages, complement system, neutrophils, cytokine storm, and T cells. Dendritic cells (DCs) get less attention in this scenario despite comprising the major immune cell population. Therefore the present review is designed to highlight the importance of DCs in the pathogenesis of sepsis, sepsis-associated immunosuppression, and organ damage. The article starts with an introduction of sepsis as a major medical problem needing an urgent therapeutic targeting. Thereafter it provides a brief information regarding classical and plasmacytoid DCs and their role in the maintenance of immune homeostasis. The subsequent sections describe the role of DCs in the immunopathogenesis of sepsis via immunoregulation, impact of sepsis on DCs including their immunometabolic changes, and their therapeutic targeting during sepsis.

1. Introduction

Sepsis is a life-threatening condition to host developed due to the dysregulated immune response against a pathogen (that may vary from bacteria to viruses including fungi and parasites) causing organ damage. Although a significant development is seen in the field of medicine in last 100 years including the immunology and host-pathogen interaction, molecular biology, and development of omics (i.e. proteomics, metabolomics etc.). Still, we are struggling for the identification of a specific therapeutic target for the management of sepsis in the clinics and intensive care units (ICUs) around the world. For example, data obtained from high-income countries shows that every year 31.5 million cases of sepsis and 19.4 million cases of severe sepsis are observed worldwide causing the death of approximately 5.3 million people every year (Fleischmann et al., 2016a, b). For example, the TLR4 antagonist called Eritoran (synthetic lipid A antagonist) developed to target sepsis failed in a clinical trial (Opal et al., 2013). However, another drug called Drotorecogin-alpha activated (DAA), a recombinant form of activated protein C (APC) developed by Eli Lily, USA and sold under the trade name Xigris, also did not show any protective effect to patients and failed in clinics with severe side effects including increased hemorrhage (Ranieri et al., 2012; Lai and Thompson, 2013; Annane et al., 2013). The drug was withdrawn from the market in 2011 (Lai and Thompson, 2013; Marti-Carvajal et al., 2012). Thus to develop better immunomodulatory agents synthetic or biologics we need to understand the immunopathogenesis of the sepsis in detail.

Dendritic cells (DCs) are the potential innate immune cells that play an important role in the recognition of the pathogen, regulation of immune response and inflammation (Lewis and Reizis, 2012; Reizis et al., 2011a; Qian and Cao, 2018). DCs can be classified into two major categories: (1) classical or conventional DCs (cDCs), previously called myeloid DCs (mDCs), and (2) plasmacytoid DCs (pDCs) or interferon-producing cells (IPCs) (Lewis and Reizis, 2012; Guilliams et al., 2014). Both the classes of DCs share important functions including very efficient pathogen recognition required to clear the pathogen without exhibiting any direct effector function along with their novel capacity to mobilize and activating various components of both the innate immune and adaptive immunity (Lewis and Reizis, 2012). Thus the present review is designed to highlight the role of DCs in the pathogenesis of sepsis and their immunometabolic regulation during infection/sepsis.

2. Dendritic cells as controller of immune response

DCs were first described as by the Nobel Prize winner Ralph

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Steinman and Zanvil Cohen in the late 1970 s as cells that functionally differ from macrophages and other lymphocytes (Steinman and Cohn, 1974, 1973). These cell do not express surface lymphocyte differentiation markers and lack the process of endocytosis exhibited by macrophages (Steinman and Cohn, 1974). Now after almost 45 years of their discovery they are well known for their role in the process of host defense against different pathogens and toxins, very potent and robust antigen processing cells (APCs) required to activate adaptive immune response, and an induction of immunologic tolerance to self-antigens (Merad et al., 2013; Mbongue et al., 2014). As mentioned DCs can be categorized into classical or conventional DCs (cDCs) and plasmacytoid DCs (pDCs). These cDCs can be further divided into different subtypes depending on their location, ontogeny, and function (Merad et al., 2013). For example, epidermal Langerhans cells (LCs) present in the epidermis of the skin, tissue migratory DCs present in the peripheral lymph nodes, lymphoid organ-resident DCs, mucosal DCs comprise different subtypes of cDCs where they play essential role in host defense against invading pathogens and induction of immunologic tolerance (Iwasaki, 2007; Chang et al., 2014; Niedergang et al., 2004; Merad et al., 2008). All three subtypes of DCs in humans express higher levels of MHC class II (HLA-DR) with the absence of typical lineage markers CD3 (T cell), CD19/20 (B cell) and CD56 (natural killer cell) (Ziegler-Heitbrock et al., 2010). For example, pDCs are $CD303^+$, and two subtypes of cDCs are $CD1c^+$, and $CD141^+$ (Ziegler-Heitbrock et al., 2010). The cDCs are further divided into two subtypes called cDC1 or classical type 1 DCs ($CD8\alpha^+$ and $CD103^+$ DCs), and classical type 2 DCs ($CD11b^+$ and $CD172a^+$ DC) on the basis of their distinct developmental pathway (Guilliams et al., 2014).

2.1. cDCs in immune homeostasis

The cDCs are originated in the bone marrow from clonogenic common DC progenitor (CDP) that undergoes terminal differentiation in the peripheral lymphoid organs or tissues (Naik et al., 2007; Onai et al., 2007; Reizis, 2012). The deletion of the transcription factor called Zbtb46 (BTBD4) did not impair murine DC development but impair expression of several lineage-specific genes in cDCs and its overexpression facilitates cDCs development (Satpathy et al., 2012). The cDCs are present at different organs including liver, lungs, kidneys, skin, and intestine here these cells provide protection against invading pathogens (Fig. 1). For example, LCs present in the epidermis of the skin provide protection against HIV-1 infection, and play an important role in contact hypersensitivity (Kaplan et al., 2005; Matsuzawa et al., 2017; Mayr et al., 2017; de Witte et al., 2007). While, cDCs present in lungs provide protection against viral infections via promoting $CD8^+$ T cell immune response (Pascual et al., 2008; del Rio et al., 2007). Whereas intestinal cDCs are shown to promote the expression of gut-homing receptor chemokine receptor 9 (CCR9) on $CD8^+$ T cells required for their homing to the intestine and maintain intestinal immune homeostasis (Johansson-Lindbom et al., 2005). These intestinal lamina propria cDCs also recognize pathogenic gut bacteria (i.e. *Salmonella typhimurium*) via TLR5 and mice lacking TLR5 exhibit an impaired transport of the pathogen from the intestine to the mesenteric lymph node (MLN) (Uematsu et al., 2006; Bogunovic et al., 2009). Furthermore the deficiency of $CD103^+$cDCs increases the severity of colitis in mice as these cells are required for regulatory T (Treg)-cell differentiation under steady-state conditions via transforming growth factor-β and retinoic acid-based mechanisms (Varol et al., 2009; Coombes et al., 2007; Shiokawa et al., 2017; Scott et al., 2011). The intestinal epithelial cell (IEC) and cDC interaction via thymic stromal lymphopoietin (TSLP) is also involved in the maintenance of intestinal homeostasis as these cDC release IL-10 and IL-6 but no IL-2 that promotes the polarization of T cells towards classical non-inflammatory TH2 cell phenotype and function (Rimoldi et al., 2005). This regulatory interaction between cDCs and IECs is seemed to lose in Crohn's Disease (CD) or inflammatory bowel disease (IBD) (Rimoldi et al., 2005). While the cDCs present in the kidneys play important role in mediating tolerance during kidney allograft transplantation and secrete IL-10 and their removal causes a profound kidney damage during toxic nephritis (Degauque et al., 2006; Scholz et al., 2008). The protective effect of cDC during renal damage is mediated by the expression of ICOS-L (inducible costimulatory ligand) that stimulates the release of IL-10 (Scholz et al., 2008). While the $CD8^+$ cDCs present in the lymph nodes and spleen are involved in providing protection against intracellular pathogens and play important role in the induction of tolerance to self-antigens (Shortman and Heath, 2010). Furthermore these DCs also exert a positive impact on $CD4^+$ T cells for the generation of $CD8^+$ cytotoxic T cells during viral infections in a cognate and antigen-specific manner via a process called licensing under the conditions where DCs are poorly licensed by pathogen-derived signals (Smith et al., 2004). Thus cytotoxic T cell immune response is heavily dependent on the process called cognate DC licensing. The IL-12 produced by DCs during intracellular pathogen infections causes the generation of Th1 immune response and the generation of IFN-γ from $CD8^+$ T cells (Henry et al., 2008). IL-12 further increases the duration of conjugation event between $CD8^+$ T cells and DCs that increase the production of CCL1 and CCL17 from DCs. Both these chemokines help in the priming of naïve $CD8^+$ T cells (Henry et al., 2008). Whereas the pre-treatment of $CD4^+$ T cells with IL-12 increases the TCR-induced IFN-γ, TNF-α, IL-13, IL-4 and IL-10 production via increasing the AKT, p38, and LCK (Lymphocyte-specific protein tyrosine kinase) phosphorylation without altering other TCR signaling molecules (Vacaflores et al., 2016). IL-12 further increases the oxidative metabolism of CD4 + T cells via increasing the mitochondrial respiration to further increase the production of cytokines that are not transcriptionally regulated including IFN-γ, TNF-α, and IL-10 (Vacaflores et al., 2016). The presence of Oligomycin and 2-deoxygluocose (2-DG, an inhibitor of glycolysis) inhibited the effect of IL-12 on oxidative metabolism and thus the generation of IFN-γ, TNF-α, IL-4, and IL-10 (Vacaflores et al., 2016). This IL-12 and type I interferon signaling is also required for the prolonged the division of activated $CD8^+$ T cells *in vivo* via maintaining the maintaining high-affinity IL-2 signaling through sustaining the expression of CD25 and the high-affinity IL-2 receptor on $CD8^+$ T cells via activating PI3K pathway and the expression of FoxM1, a positive regulator of cell cycle progression genes (Starbeck-Miller et al., 2014; Marchingo et al., 2014).

2.2. pDCs in immune homeostasis

pDCs are nonconventional DCs that originate from both common DC progenitors (CDPs) and common lymphoid progenitors (CLPs) but differ from cDCs in a way that these cells produce higher amount of type 1 IFNs in response to viral infections (Liu et al., 2009; Kushwah and Hu, 2011). However, pDCs predominantly originate from $IL\text{-}7R^+$ lymphoid progenitor cells and the expression of Siglec H (Sialic acid binding receptor H, that acts as an endocytic receptor) and Ly6D (Lymphocyte antigen 6 family member D) define pDC lineage commitment along the lymphoid progenitor cells expressing higher levels of IRF8 (interferon regulatory factor 8) or interferon consensus sequence-binding protein (ICSBP) transcription factor (Rodrigues et al., 2018; Zhang et al., 2006; Murphy et al., 2016). The pDCs are identified by the presence and expression of TCF4 (Transcription factor 4) or immunoglobulin transcription factor 2 (ITF-2) that will bind to immunoglobulin enhancer mu-E5/kappa-E2 motif to the Ephrussi-box or E-box present in the SSTR2-INR to activate transcription (Rodrigues et al., 2018; Manz, 2018). Mature pDCs generated from CDPs and $IL\text{-}7R^+$ lymphoid progenitors show heterogeneity although both secrete type 1 IFNs but only myeloid-derived pDCs exhibit similar ability of antigen processing and presentation as compared to cDCs (Rodrigues et al., 2018). These pDCs were first discovered in humans and thereafter their mouse equivalents were identified (Hochrein et al., 2002). The mouse pDCs express very low levels of CD11c, while human pDCs do not express CD11c instead express B cell marker B220/CD45RA (Hochrein et al., 2002; Reizis