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Regulation of Schistosomal Immunopathology by Dendritic Cells

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Editorial

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Dendritic cells (DCs) represent a very important link between innate and adaptive immunity [1]. In order to exert their function, DCs are able to respond rapidly to external stimuli, including pathogen derived components. DCs function involves two components that develop in sequence: a presentation step of antigens (Ags) and a sensitization step in which DC acquire the capacity to induce polarization of naive T cells [2]. This response is reflected by expression of co-stimulatory molecules and production of cytokines, such as IL-10 and IL-12, thus influencing the activation, differentiation and function of antigen-specific T cells [3, 4].

DCs are potent antigen presenting cells (APCs) that sense foreign antigens through pathogen recognition receptors (PRRs) and induce the differentiation of naive CD4+ T cells into various effector T cell populations example Th1, Th2, Th17, or T regulatory (Treg) cells [5-8].

Schistosomal eggs lodged in the liver and intestines resulted in tissue injury that is mediated and orchestrated by CD4+ T cells specific for egg Ags [9]. Immune responses to schistosomal Ags manifest a striking shift from an early pro inflammatory Th1 to a Th2-dominated response at the onset of egg laying around 5–6 weeks post infection [10]. In the context of schistosome infection, DCs are necessary for the induction of the Th1, Th2 and even the modulated immune response [11]. Moreover, schistosome ligand-activated DCs can initiate the differentiation of pro inflammatory Th17 cells that play a major role in the development of the severe egg-induced immunopathology [10, 12].

DCs can make cytokines such as IL-12 that drive T cell activation and proliferation and promote an early pro inflammatory Th1 response [13]. The excretory/ secretory products released from schistosomula stimulates DC that in turn drive strong Th2 responses [14] likely resulting from its capacity to limit the maturation of the DC population [15]. Two *Schistosoma* egg-derived components, the glycolipid lysophosphatidylserine and the carbohydrate determinant lacto-N-fucopentaose III, have been shown to activate TLRs example TLR2, TLR3 and TLR4. TLR activation by pathogens is one of the main pathways through which DCs become activated during infections, thus induce a transcriptional program in DCs that culminates in the production of many inflammatory gene products example TNF-α [16-18]. Moreover, egg lipopolysaccharides promote classical activation of macrophages and NO and other inflammatory mediators made by these cells that contribute significantly to fatal liver pathology [19, 20].

Chronic schistosomiasis is characterized by hyporesponsiveness of the effector T cell responses due to some modifications of DCs function [21]. DCs are central players in the regulation of T cell responses and suppression of the host immune responses by *schistosomes*. *S. mansoni* products were found to induce immunorgulatory cytokines production example IL-10, which has a direct anti-inflammatory effect on DCs by controlling TLR ligand-induced DC maturation [22]. They regulate immune responses through other potential mechanisms, such as suppression of pro-inflammatory mediator production (example IL-12, TNF-α and IL-6), or increased differentiation of Treg [3]. Everts et al. [23] found that DCs isolated from patients with schistosomiasis have an impaired capacity to respond to TLR ligands and to prime T cell responses by restricting IL-12 production. IL-10 producing DCs (regulatory DCs) can regulate T cell function both directly and indirectly, by altering the activation and cytokine production of antigen presenting cells. In the context of IL-17 induction, IL-10 inhibits Th17 cells by direct signaling and via the heightened

activation of Treg cells [24, 25]. Many other cell types are capable of secreting IL-10 including mast cells, neutrophils and natural killer cells, all of which can interact with DCs and contribute to T cell polarization [26].

Lastly, chronic schistosomiasis has also been shown to negatively affect the nutritional status of the host [27]. Under-nutrition can lead to an impaired function of DCs resulting in a diminished induction of adaptive immune responses [28].

In conclusion, during the course of schistosomal infection, DCs develop an early Th1 immune response followed by a Th2-polarized immune response that coincides with the onset of schistosomal egg production. Meanwhile, DCs produce a host-protective effect through IL-10, Treg cells and other regulatory mechanisms to regulate the development of potentially life threatening inflammation. Understanding the role of DCs in schistosomiasis is a fundamental issue that determines the immunologic outcome of this infectious disease and could be exploited for therapeutic manipulation of the immune system.

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