Host Immune Responses to Trypanosomes

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The mammalian host's innate and adaptive immune systems are both key to successfully resisting or controlling trypanosomosis. When trypanosomes are inoculated into the mammalian hosts by a blood-feeding insect such as a tsetse fly, the first contact between the trypanosome and host occurs in the skin. Here, a chancre often develops at the dermal inoculation site. Intense innate immune reactions, cellular reactions, and edema formation accompany these chancres. Thereafter, parasites start to circulate through the blood or lymph, invading lymphatic tissues and various organs. There, the trypanosomes again encounter various innate immune components before being confronted with the adaptive immune system. Once entered into the circulation stage of infection, trypanosomes are going to encounter responses from macrophages and B cells, as well as the T helper compartment that links these two.

Keywords: immunity ; organ ; transcriptomics

1. Macrophages and Their Cytokines

The secreted types and roles of cytokines in the pathogenesis of AT vary depending on the production quantity and the phase of infection. AT affects the host in different ways, with susceptibility and resistance to the disease determined by the host's cytokine balance during infection. Various studies have shown that African trypanosomes induce many cytokines in mammalian hosts. Dominant cytokine producers are macrophages, the primary cells contributing to innate immunity that phagocytose pathogens [1]. Macrophages are innate antigen-presenting cells that are essential in T-cell activation [2] and, hence, are indirectly involved in adaptive immune responses. This transition function is mediated through the secretion of effector molecules, including cytokines [3], that are also involved in immunosuppression and immunopathology.

Activated macrophages can be largely classified into (i) classically activated macrophages that secrete proinflammatory cytokines such as IL-1, IL-6, and TNF, and produce nitric oxide synthase, an enzyme necessary to deliver nitric oxide, or (ii) alternatively activated macrophages, that produce anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 [3]. Classically activated macrophages are typically recruited to fight pathogens by promoting inflammation in early infections. To counterbalance this activity, alternatively activated macrophage induction is a hallmark of chronic infections, as these cells have an immunosuppressive function, reduce inflammation, and prevent and repair tissue damage [3].

During trypanosome infections, macrophages are activated by a number of parasite compounds, including the VSG-GPI anchor and unmethylated trypanosomal DNA, released from dead trypanosomes. Activation is enhanced by interferon-gamma (IFN-γ) produced by T-helper (Th) 1 cells. Activated macrophages play a significant role in controlling the parasitemia peak by secreting proinflammatory cytokines such as TNF, IL-12, and nitric oxide [4][5], as well as parasite phagocytosis [6][7][8]. Interestingly, TNF is not only involved in the inflammatory response in the early phase of trypanosomosis but is also involved in the induction of chronic anemia and the neurologic signs in the late phase of infection [9]. The role of TNF in the inflammation of the central nervous system lesions, found in chronic *T. b. brucei*-infected mice, has been known for a long time [10]. It is, however, only much more recently that scRNA-seq analysis has provided a detailed view of overall mechanisms that drive brain pathology in experimental models for AT. This new data has indicated a possible role of microglia cells, the primary immune cells of the central nervous system that are similar to peripheral macrophages, in driving pathology [11]. These new findings indicate changes in innate and adaptive immunity, the type I interferon response, neurotransmission, synaptic plasticity, pleiotropic signaling, circadian activity, and vascular permeability, all correlating with early central nervous system (CNS) symptoms during the encephalitic stage [12]. Furthermore, immune alterations through interactions between microglia and other immune cells were discovered, exemplified by the crosstalk between microglia and $CD138^+$ plasma cells. Here, homeostatic microglia actively support $CD138^+$ plasma cell survival via B cell activating factor (BAFF), and reciprocally, $CD138^+$ plasma cells produce IL-10 to mitigate inflammatory responses in microglia during *T. brucei* infection [11].

Alternatively activated macrophages secrete anti-inflammatory cytokines IL-4, IL-13, and thymic stromal lymphopoietin (TSLP), a key cytokine that promotes Th2 response [13][14]. In mice, IL-4 was required or prolonged survival of *T. b.*

gambiense infected mice [15]. Likewise, TSLPR$^{-/-}$ mice were susceptible to *T. congolense* infection by failing to control parasitemia compared to wild-type control. The latter is attributed to impaired activation of alternatively activated macrophages and overproduction of proinflammatory cytokines, including IFN-γ and TNF [14]. Meanwhile, one of the key anti-inflammatory cytokines that regulate African trypanosome infection is IL-10. It reduces the effector activities of T cells and macrophages which produce inflammatory cytokines after initiating a trypanosome infection [16]. In the absence of IL-10, *T. b. brucei*-infected mice maintain an inflammatory response and succumb early [17].

2. T Cells

Like macrophages, T cells also control AT by secreting cytokines. CD4$^+$ T cells regulate inflammatory responses by producing cytokines and assisting B cells with effective isotype class-switching and specific antibody responses to parasite antigens [18]. It has been shown that during *T. congolense* infections, IgG2a, IFN-γ, and IL-10 production were all impaired in CD4$^+$ T cell-deficient mice [19]. In addition, CD8$^+$ T cells can kill pathogens by secreting cytokines, even in the case of extracellular pathogens such as salivarian trypanosomes. Trypanosome lymphocyte-triggering factor (TLTF), a trypanosome component located in the flagellar pocket, is known to modulate the cytokine network of the host immune system by activating CD8$^+$ T cells and inducing the production of IFN-γ [20]. In the early infection stage, the TLTF level increases for interaction with the host. However, continuous release of this molecule over-stimulates the host immune system. This is ultimately unfavorable for the parasite, so the level of TLTF decreases as the host produces anti-TLTF antibodies, blocking the effect of this trypanosome molecule through neutralization in the late stage of infection [21].

In mice infected with *T. b. brucei*, natural killer (NK) and NK-T cells first produced IFN-γ, followed by CD8$^+$ and subsequently CD4$^+$ T cells. IFN-γ not only participates in the early inflammatory reaction but also activates phagocytosis of red blood cells by recruiting erythrophagocytic myeloid cells, causing anemia, the main hallmark of AT. Hence, the absence of NK, NK-T, and CD8$^+$ T cells showed a reduced anemic phenotype during trypanosomosis through cell depletion and neutralization experiments. This observation was confirmed using IFN-γR$^{-/-}$ mice [22]. When progressing into the later stages of infection, CD4$^+$ T cells become the main produced IFN-γ [23]. Interestingly, however, CD4$^+$ T cells are also crucial producers of IL-10 at this stage, needed for the anti-inflammatory cytokine context alongside *T. brucei*-induced alternatively activated macrophages [24]. As it will be outlined in detail below, the most recent scRNA-seq data has provided new insights into the cellular source of both IFN-γ and IL-10, showing that a unique population of CD4$^+$ T cells is capable of producing both ‘counteracting’ cytokines simultaneously [25].

3. B Cells

As African trypanosomes are extracellular bloodstream parasites continuously exposed to the host’s humoral immune response, they are expected to be targeted by antibodies, and hence activating B lymphocytes. Interestingly, DNA from *T. b. brucei* can induce B cell proliferation [4]. On the B cell side itself, the lymphocyte adapter protein Bam32, important for B cell activation and cell survival, is crucial during trypanosomosis. Indeed, in Bam32$^{-/-}$ mice, the germinal center response associated with the anti-trypanosome IgG antibody response was abrogated, resulting in a worsened control of *T. congolense* infection [26].

As mentioned in the introduction section, trypanosomes use a system of antigenic variation to construct their glycoprotein coat, using a single VSG at any given time [27]. Since trypanosomes can produce antigenically distinguishable VSGs, they force the host to trail the VSG switching with the switching of antibody responses. When specific antibodies against the specific epitopes of the VSG are generated, opsonized parasites, VSG-coated trypanosomes, are mainly phagocytosed by liver resident macrophages, i.e., Kupffer cells [7], thereby clearing successive parasitemia waves [28][29]. In theory, the removal of trypanosomes should be accomplished by a combination of antibody-dependent phagocytosis and complement-mediated lysis, guaranteed by the presence of anti-VSG antibodies. Initially, immunoglobulin levels, especially IgM, increase dramatically in mammalian hosts infected with trypanosomes. When IgMs against the specific VSG are produced, they should be able to fix complement and assist in the assembly of the various complement components on the parasite’s surface, leading to the destruction of the latter [30]. However, a wealth of data has been generated over the years, indicating that trypanosomes can efficiently block the complement cascade from reaching the final membrane attack complex [31].

Activated B cells initiate germinal center formation with the help of follicular CD4$^+$ T helper cells and produce various antibody isotypes through class-switching recombination, including IgGs that generally have an increased antigen binding affinity compared to the primary IgMs [18][32]. Hence, IgGs should play an important role in the phagocytosis of trypanosomes by macrophages [33]. However, the exact role of various antibody classes is not clear-cut. Indeed, in a study using a *T. b. brucei* model, IgG was shown to have a dominant role over IgM, when it comes to parasite clearance

[34]. In contrast, IgMs were found to play a dominant role when studied in a model system of experimental *T. (b.) evansi* infections in mice [35][36]. Important to mention, however, is that trypanosomes have adopted an efficient mechanism to remove antibodies from their surface, ensuring that immune-mediated elimination never reaches a level of complete parasitemia clearance prior to the switching of the coat by the mechanism of antigenic variation [37]. Hence, while highly specific anti-VSG antibodies can eliminate trypanosomes in a VSG-dependent manner, a small population of trypanosomes that manages to escape an anti-VSG host attack will perpetuate the infection. In order to try and counteract immune escape, the host is triggered into excessively activating antibody-producing B cells, resulting in hypergammaglobulinemia [38] and polyclonal B cell activation [39] This increases the level of polyspecific and non-specific antibodies, including autoantibodies in the serum, in addition to trypanosome-specific antibodies [40]. Trypanosome DNA and VSG appear to contribute to host non-specific B cell activation [41]. Simultaneously, specific antibody response to trypanosome antigens decreases. Therefore, while in the early stages of infection, trypanosome-specific antibodies are mainly involved in parasite clearance, as the infection progresses, a significant portion of antibodies will become polyspecific, and the fraction of autoantibodies against nucleic acids and even red blood cell surface proteins increases [42][43]. Recently, it was confirmed that B cells from *T. brucei*-infected murine meninges produce high-affinity autoantibodies that can recognize mouse brain antigens, including myelin basic protein, which are associated with cortical demyelination and brain pathology [44][45].

During the late stages of trypanosome infection, the B cell compartment becomes suppressed or even depleted. This process involves the rapid disappearance of immature B cells in the bone marrow and transitional and marginal zone B cells in the spleen, followed by the gradual disappearance of follicular B cells in the spleen [46][47][48]. These damaged and missing B cells cannot effectively produce antibodies against new VSG variants. Therefore, IgM and IgG responses are significantly reduced or eliminated [34]. Additionally, a decrease in anti-VSG recall responses to previously encountered VSG variants may allow the re-emergence of previously encountered trypanosome variants and allow the accumulation of mosaic VSG variants [49]. In addition, infection-associated B cell depletion will ultimately reduce the efficacy of vaccines unrelated to trypanosomosis [46][50]. While in the past, events related to the infection-associated abrogation of B cell functionality have been mainly described in a phenotypic and functional cellular context, most recent data has now come from scRNA-seq approaches [36][51][52].

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