Leishmania-Host Interaction and Survival Strategies "A Review"

Dr. Heena Sachdeva, Dr. Manish Sharma

Abstract- *In order to develop a successful parasitic relationship with its host, Leishmania parasites use to interact and infect a number of host cell types viz. macrophages and dendritic cells for the successful parasitic relationship with its host. During the initial stage of the infection, both neutrophils and macrophages are recruited at the site and these acts as intermediate hosts to be used by parasites to enter macrophages.*

I. INTRODUCTION

The uptake of Leishmania promastigotes by host cells is a classical receptor-mediated process that initiates phagocytosis. The complement receptors (CR)1, CR3 (Mac-1) fibronectin receptor and mannose-fucose receptor on the surface of macrophages play important roles in promastigote binding [1]. The surface lipophosphoglycan (LPG), GP63 and proteoglycans on L. major promastigotes are also important determinants in the initiation of phagocytosis and intracellular survival of parasites [2,3].

Macrophages are the major effector cells responsible for destruction of the parasites. Macrophages can be activated by different signals and their activation is generally divided into classical and alternative types. Classical activation is mediated by the products of Th1 and NK cells, in particular, IFN-gamma. IFN-gamma stimulates macrophages to produce inducible nitric oxide synthase (iNOS), an enzyme which catalyzes L-arginine to generate nitric oxide [4]. NO is a toxic molecule that plays a major role in killing intracellular parasites, including Leishmania [5].

In contrast to classical activation, alternative macrophage activation is induced by Th2 cytokines such as IL-4 and IL-13 [6]. It has been found that IL-4 induced polyamine biosynthesis (via upregulation of arginase) favours L. major parasite survival in macrophages [7]. This finding reinforced the notion that Leishmania encoded arginase is a virulent factor and its expression functions to preferentially enhance alternative macrophage activation leading to parasite survival [8,9]. Several reports show a central role of dendritic cells (DC) in generating immune responses against Leishmaniasis [10]. The skin contains three DC populations that consist of epidermal langerhan cells and two migratory dermal DC subsets. Previous studies showed that epidermal langerhan cells phagocytose L. major in vivo and migrate to draining lymph nodes for presentation to antigen specific T cells [11]. Interaction of DC with Leishmania results in IL-12p70 production [12]. Moreover, different DC subsets are differentially permissive to Leishmania parasites and thus seem to be inversely correlated with the ability of infected cells to produce IL-12p70 [13]. The production of IL-12 by DC's initiates Th1 response and protective immunity by promoting early NK cell activities (including IFN-gamma production and cytotoxicity) [14].

Leishmania may impair host macrophage signaling pathways to disrupt cellular functions. Impaired responsiveness to IFN-gamma, lipopolysaccharide (LPS), and activators of protein kinase C (PKC) have been seen in Leishmania infections [15]. Altering signal transduction through the disruption of cellular phosphorylation, either by an alteration of cellular kinases and phosphatases or by Leishmania expressing its own phosphatases that act on macrophage proteins, is used by Leishmania to enhance survival [16]. L. donovani has been shown to impair tyrosine phosphorylation and activation of JAK1, JAK2, and STAT1 in response to IFN-gamma, possibly involving the activation of the cellular protein tyrosine phosphatase SHP-1 [17,18].

Macrophages produce nitric oxide through the induction of iNOS, in response to extracellular signals, including IFN-gamma and LPS [19]. GIPLs (Glycosylinositol phospholipids) on the amastigote surface can inhibit NO production, thus, reducing leishmanicidal activity [20]. The repeating units of LPG may also protect promastigotes from toxic oxygen metabolites generated during the macrophage oxidative burst by scavenging hydroxyl radicals and superoxide anions [21]. LPG protects the parasites by attenuation of the PKC-mediated induction of the oxidative burst [22]. Gp63 has also been associated with suppression of the oxidative burst [23]. Leishmania parasites may also survive by modulating macrophage cytokine production. Both promastigotes and amastigotes have been shown to downregulate macrophage IL-12 production, which is necessary for the Th1 response [24].

Leishmania are a diverse group of intracellular pathogens that have efficiently developed adaptive measures

to ensure their survival. Not only have they developed strategies to survive inside the sand fly vector, but the parasites have also established means to survive in the vertebrate bloodstream. Leishmania effectively use the immune response of the host to target themselves for engulfment into macrophages.Once phagocytised, they manipulate the harsh environment through the inhibition of hydrolytic enzymes, toxic metabolic products, cell signaling, cytokine production, and other events. These strategies allow Leishmania to successfully undermine the host innate and acquired immune responses and promote parasite survival [25].

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