[PS1.9]
Cellular Host-Pathogen Interactions

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Abstract

Leishmania is the prototypical model of the T helper 1/T helper 2 (Th1/Th2) dichotomy of the immune response. These two extremes in response to infection have been best characterized in mouse models and lead to the control and elimination of pathology in case of Th1 and in uncontrolled infection and tissue damage in the case of Th2. Because Leishmania has been shown to utilize complement receptor 3 (CR3) to enter host cells and CR3 has been reported to downregulate Th1 responses, the role of CR3 in in vivo infection was characterized in part-2. My studies reveal that CR3 deficiency leads to heightened, albeit not complete, resistance to Leishmania major on a susceptible Balb/c background.

A growing body of evidence indicates that Leishmania and other intracellular pathogens do not passively infect their hosts. Rather, many pathogens manipulate their hosts in such a way as to make them more hospitable to infection. In part-3, I examine how CR3 affects host cell responses to L. major and how infection may act to modulate macrophage cell signaling events that would lead to appropriate activation and parasite killing. This includes looking at the activation of mitogen activated protein kinases (MAPK), the translocation of transcription factors into cell nuclei, and the production of effector molecules like nitric oxide (NO).

Part-4 presents my investigation of CR3 and Leishmania infection in resistant C57BL/6 mice. This part will outline our results examining parasite phagocytosis, production of Th1-driving interleukin-12 (IL-12), and mitogen-activated protein kinases (MAPK) and interferon-gamma (IFN-γ)-mediated cell signaling.

The last part draws on my research and the extensive body of literature that dissects Leishmania-host immune interactions to attempt to build a framework wherein I can begin to unravel the often contradictory mechanisms involved in Leishmania infection. In addition, I will consider future directions for research.

Keywords: leishmaniasis, macrophage, complement receptor 3