Doctoral Thesis

The role of the cytokines osteopontin and interleukin-1 delta during immune responses

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The Role of the Cytokines Osteopontin and Interleukin-1 delta during Immune Responses

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Summary

The capacity of the immune system to react rapidly to invading microorganisms or inflammatory insults is critical for the survival of the host. To mount an effective response, the pathogen must be immediately identified so that the appropriate action can ensue. The earliest recognition event occurs when the microbial signature molecules, Toll ligands interact with the evolutionarily conserved Toll-like receptors expressed on antigen-presenting cells (APC) of the immune system. This signal is interpreted intracellularly by the APC, and sets in motion the message that will be conveyed to the naïve cognate Th cell, including engagement of the T cell receptor via the peptide/MHC complex, co-stimulatory signals, and the cytokine microenvironment. Deciphering these multiple signals by the naïve CD4 Th cell leads to activation, differentiation and ultimately clonal expansion. The cytokine osteopontin (OPN) is released early after CD4 Th cell activation, and is alleged to induce Th1 differentiation and mediate an important role in the cell-mediated immune responses against *listeria monocytogenes* and herpes simplex virus-type 1. Gaining further insight into the effect of OPN on anti-viral immunity and CD4 Th cell differentiation is the subject of the first part of this thesis. Unexpectedly, we observed that OPN is not required to mount an effective immune response against influenza and vaccinia viruses, as expansion of specific effector CD4 and CD8 T cells, CTL-mediated lysis of infected targets, and virus clearance was uncompromised in the absence of OPN. Furthermore, using a cognate antigen co-culture system, it was demonstrated that endogenous OPN is dispensable for the polarization of naïve CD4 T cells to IFNγ+ Th1 cells.

Since OPN was also implicated in the induction of autoimmune diseases such as arthritis and multiple sclerosis, we investigated the influence of OPN and one of its receptors, CD44v6/v7 on the development of experimental autoimmune myocarditis, a mouse model of human cardiomyopathy. The findings from these studies form the second part of this thesis, and demonstrate that both OPN and CD44v6/v7 are not required for the development of autoimmune myocarditis, as indicated by histological scoring of heart sections.

The final part of this thesis is concerned with the role of the novel cytokine, interleukin-1 delta (IL-1δ) in immune responses. IL-1δ is a member of the ever-expanding IL-1 family, and bears close similarity to the IL-1R antagonist (IL-1Ra). Preliminary findings indicate that IL-
18−/−mice display an increased CD4 T cell compartment in the periphery, and an augmented marginal zone B (MZB) cell population. Analysis of the humoral response revealed a hyper-IgE syndrome in naïve IL-1β−/−mice, and immunization with either the virus-like particle, Qβ or UV-inactivated vesicular stomatitis virus (VSV), lead to dramatically enhanced antibody titers. However, infection with live VSV resulted in a more comparable humoral response, suggesting that some replicating viruses may overcome the effects of IL-1β in vivo. Interestingly, IL-1β−/−mice were exceptionally susceptible to infection with influenza virus, however the underlying reasons for this hypersensitivity remain to be elucidated. In summary, the findings from this thesis question the initial importance placed on OPN in anti-viral immunity and autoimmunity, and may provide new insights into the potential function of IL-1β in immune responses.