CELLULAR RESPONSES TO *BRUGIA* INFECTIONS IN *MERIONES UNGUICULATUS*

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Lymphatic filariasis caused by nematode parasites *Wuchereria bancrofti* or *Brugia malayi* is a spectral disease and produce a wide range of immune mediated inflammatory responses which have been associated with either parasites and their products or parasite induced host factors. Mongolian jirds (*Meriones unguiculatus*) have been the permissive hosts for infection with *Brugia* species and have been widely used to maintain the life cycle and chemotherapeutic experiments. Further, jirds chronically infected with *Brugia* develop an immune hyporesponsive state which may be similar to that observed in microfilaraemic human subjects, and therefore can also be considered as a useful model to dissect the immunological events associated with the disease. However, immunological studies on this model have been hampered by the limited availability of specific reagents which can be used to define the specific mechanisms involved in disease pathogenesis. The pathological changes in the *B. pahangi* infected lymphatics were well characterized by the formation of granulomatous intralymphatic thrombi, lymphatic dilation, and granulomatous lymphadenitis and enlargement of renal lymph nodes which drain the infected lymphatics. These studies indicated that the onset of these changes is immunologically mediated and can be correlated to the periods of parasite development. In infected jirds, these lesions have been shown down regulated as they become chronic microfilaraemic state. Examination of cellular immune responses during the premicrofilaraemic phases of infection indicated an early, intense cell-mediated inflammatory immune response and that this response was rapidly down regulated before the onset of microfilaraemia. These results suggest that the microfilariae are not required to maintain the hyporesponsive condition and stages other than microfilariae can induce this condition. This early

induction of cellular response appears to be compartmentalized in lymphoid tissues especially in renal lymph nodes that drain the infected lymphatics but not in spleens. Inflammatory responses as determined by macrophage activation also indicated that their function was down modulated during filarial infection suggesting that the mechanisms involved in macrophage inactivation may be related to those that induce down modulation of granulomatous inflammatory response. Cytokines have been shown to play a central role in the regulation of immune responses to filarial agents. In order to measure changes in the cytokine profiles of lymphoid tissues of infected jirds, our laboratory has cloned and sequenced a cDNA encoding the entire cytokines IL2 and IFN γ (Th1 type), IL4, IL5, and IL 10 (Th2 type). Using the sequence information for the jird cytokines, we have developed methods to quantitate cytokine specific m-RNA expression in lymphoid tissues. This method uses the PCR amplified products in a ELISA format or Q-PCR 5000 system (Perkin Elmer, CA) with which zeptomolar levels of cytokine mRNA were detected. Increasing levels of IL4 were detected from day 1 post infection in both spleen and renal lymph node cells. Levels of IL10 were higher during the early periods of infection and an increase at 56 DPI. Increase in IL5 levels were also observed at 28 DPI in spleens and at 28 and 56 DPI in renal lymph node cells. Although INF γ levels were unchanged, levels of IL2 were low in both spleens and renal lymph nodes. These results suggest that jirds with primary *B. pahangi* infection, develop a rapid polarization of Th2 type response that corresponds to an increase in lymphatic granulomas and a long lasting hyporesponsive microfilaraemic state. Experiments by measuring the cellular responses and their cytokine profiles are in progress to determine their changes in chemotherapeutically abbreviated infections and in vaccinated animals.