Title:

CD209a Expression on Dendritic Cells is Critical for the Development of Pathogenic Th17 Cell Responses in Murine Schistosomiasis

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Abstract:

In murine schistosomiasis, immunopathology and cytokine production in response to schistosome eggs is uneven and strain dependent. Infected CBA mice develop severe hepatic egg-induced granulomatous inflammation associated with prominent Th17 and Th1 cytokine responses, whereas in BL/6 mice milder lesions develop in a Th2-dominant cytokine environment. The pathogenic Th17 response in CBA mice is largely dependent on IL-1β and IL-23 produced by schistosome egg-stimulated dendritic cells (DC); by comparison, this pro-inflammatory cytokine pathway fails to materialize in low-pathology BL/6 mice. The requirements for Th17 cell differentiation induced by CBA DC have been elucidated; however, the reason for strain-dependent difference in APC reactivity to live eggs is not known. Initial gene profiling disclosed a significant difference in C-type lectin receptor (CLR) expression between CBA and BL/6 bone marrow derived DC (BMDC). CLR are pattern recognition receptors capable of binding carbohydrates, including those secreted by schistosome eggs. A dramatic increase in CD209a, a murine homologue of human DC-specific ICAM-3-grabbing non-integrin (DC-SIGN), was documented by real-time PCR and flow cytometry on tissues from infected CBA mice, including liver, spleen and granuloma cells. Functional assays determined that CBA DC, but not macrophages, B cells, or granulocytes, elicit Th17 cell differentiation in response to schistosome eggs. Gene silencing in CBA DC, and over-expression in BL/6 DC, demonstrated CD209a to be essential for IL-1β and IL-23 production and subsequent Th17 cell differentiation. These findings reveal a novel role for CD209a in mediating pathogenic pro-inflammatory Th17 responses in helminthic disease.