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Ecto-5'-nucleotidase (CD73) regulates host inflammatory responses and prolongs infection during murine Salmonellosis

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Abstract

Food-borne intracellular bacteria, Salmonella spp. are a principal cause of hospitalization and death. Adenosine is an important immune regulator of inflammation that limits tissue damage during infection. Surface enzymes CD39 (nucleoside triphosphate dephosphorylase) and CD73 (ecto-5'-nucleotidase) mediate the synthesis of extracellular adenosine that can regulate both innate and adaptive immune responses. We hypothesized that anti-inflammatory responses mediated by ecto-5'-nucleotidase (CD73) impair host defense against intracellular bacterial infection. We studied the expression of CD39 and CD73 in liver, spleen and Th cells after infection of C57BL/6 mice with Salmonella enterica serotype Typhimurium (ST) and evaluated the role of CD73 after infection of wildtype and CD73-deficeint mice, in regulating immune responses and bacterial burden. Liver and spleen cytokine mRNA expressions were tested by qRT-PCR. Cytokines were assayed by ELISA from cultured supernatant of activated splenocytes. Splenocyte-derived Th cells were tested for intracellular cytokines by flow cytometry. Inflammatory responses in infected CD73-deficeint mouse livers were assayed in the H&E tissue sections. Bacterial count was done from liver and spleen tissues. After Salmonella infection of wildtype mice, both CD39 and CD73 transcripts and protein levels declined in the spleen and liver tissues. Salmonella-infected wildtype mice became sicker and lost significantly more body-weight compared to the infected CD73-deficeint mice. Splenocytes from Salmonella-infected CD73-deficeint mice had significantly more IFN-γ and IL17A producing cells and greater expressions of IFN-γ, TNF-α, and iNOS mRNA in the liver when compared to wildtype mice. Both spleen and liver tissues from the infected CD73-deficeint mice showed significantly reduced expressions of anti-inflammatory cytokines, including, IL-10, IL-4 and TGFβ-1. Liver sections from the CD73-deficient mice showed a greater number of "inflammatory-foci" and a reduced liver bacterial burden than in the wildtype mice. CD73

expression contributes to adenosine accumulation that attenuates inflammatory responses during Salmonellosis, which may impair immunity to favor increased bacterial colonization and may prolong infection.