[PS1.31]

The Epstein-Barr virus-induced gene 3 (EBI3) regulates inflammatory immune responses during infection with *Trypanosoma cruzi*

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The Epstein-Barr virus-induced gene 3 (EBI3) is a member of the interleukin (IL)-12-family and acts as a soluble component structurally related to the subunit p40 of IL-12. Through a non-covalent association, EBI3 forms a heterodimer with the p28 subunit to IL-27 as well as the p35 subunit to IL-35. IL-27 is secreted by antigen presenting cells whereas IL-35 appears to be produced mainly by regulatory T cells. Both cytokines negatively regulate inflammation and suppress the outcome of inflammatory diseases. We analysed the inhibitory role of EBI3 during infection of EBI3-deficient ($^{-/-}$) mice with the intracellular parasite *Trypanosoma cruzi*, the causative agent of Chagas disease in Central and South America. Compared to C57BL/6 wildtype mice, EBI3$^{-/-}$ mice showed a higher parasitemia and an increased mortality rate accompanied with liver necrosis. EBI3$^{-/-}$ mice displayed an increased inflammatory immune response with elevated T helper (Th) type 1, Th type 2 and Th type 17 immune responses. The exacerbated production of the Th17 cytokine IL-17A might be responsible for the extended immunopathology in *T. cruzi*-infected EBI3$^{-/-}$ mice, whereas the increased Th2 immune response and the subsequent induction of arginase-1 (arg-1)-expressing alternatively activated macrophages appears to have overridden the otherwise protective Th1 immune response. Because increased arg-1 activity decreases the production of reactive nitrogen intermediates and favours polyamine synthesis EBI3-deficiency may favour parasite growth within macrophages. So far, our results demonstrate that EBI3 is an essential general regulator of inflammatory immune response in experimental Chagas disease. Further studies have to dissect the underlying mechanisms and clarify whether EBI3 associated with IL-27 or/and IL-35 account for its anti-inflammatory character.

Keywords: IL-35, IL-27, T helper type 1/2/17, Trypanosoma cruzi