IL17A switches from a pathogenic to a protective function in experimental autoimmune myocarditis in the absence of IFNγ

Jobert G. Barin, G. Christian Baldeviano, Monica V. Talor, Dongfeng Zheng, Daniela Čiháková, Noel R. Rose

Deviation to autoaggressive Th17 responses has been reported to account for the protective effect of IFNγ in certain animal models of autoimmune disease. Building on our previous findings that IL17 signaling was critical for the progression of experimental autoimmune myocarditis (EAM) to dilative heart failure, we sought to address the question of whether IL17 mediated the severe form of EAM observed in IFNγ-deficient mice. To our surprise, we found that IFNγ−/−IL17A−/− double-knockout (DKO) mice had greater mortality compared to IFNγ−/− mice, starting at day 14 and reaching 50% by day 21 of EAM. DKO hearts were severely infiltrated, indicating acute inflammatory heart failure as the mode of death in these mice. We have found evidence of aberrant eosinophilic Th2-deviated infiltration in DKO mice, implicating eosinophils in mediating the enhanced morbidity. Production of IL5 by CD4+ cells was increased in DKO hearts, as well as cardiac production of CCL11/eotaxin. Heart-infiltrating DKO CD4+ cells showed evidence of Th2 deviation. These data point to a novel collaboration between IFNγ and IL17A in controlling eosinophil recruitment by autoaggressive Th2 cells. Moreover, they indicate that myocarditis is not restricted to a single CD4+ subset – but instead reflects redundancy among Th1, Th2, and Th17 populations to elicit qualitative and quantitative variations in disease phenotype and progression.