FOXO3A DEFICIENCY PROTECTS FROM COXSACKIEVIRUS B3 MYOCARDITIS: ROLE OF NK CELL FUNCTION

Poster Contributions
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Background: Coxsackievirus B3 (CVB3) myocarditis can lead to dilative cardiomyopathy and heart failure. Cardiac injury is mediated by direct viral damage and host immune response. FOXO transcription factors play key roles in immunoregulation and stress resistance, including anti-inflammatory effects. We therefore investigated FOXO3a in CVB3 myocarditis.

Methods: CVB3 myocarditis was induced in WT and FOXO3a-/- mice. mRNA/miRNA expression, SNP analysis and viral load was assessed. Hearts were stained with hematoxylin/eosin and evaluated by inflammatory score. Natural killer (NK) cells were analyzed for cytotoxicity, IFN-γ production and activation markers by fluorescence activated cell sorting.

Results: FOXO3a-/- mice showed significantly lower viral titers compared to WT accompanied by a reduced inflammatory score and diminished expression of CD3+ T cells, CD14+ monocytes and NKp46+ cells. Expression of proinflammatory cytokines was reduced in FOXO3a-/- mice at 7d p.i.. Importantly, there was no difference in myocardial mRNA expression of CVB3 receptor. Interestingly, FOXO3a gene transfer in vitro had no effect on viral adhesion and entry but significantly inhibited CVB3 replication in cardiac myocytes. On day 3 p.i. FOXO3a-/- mice showed cardiac accumulation of activated NK cells as well as enhanced cardiac IFN-γ expression. Ex vivo, NKp46+ NK cells of FOXO3a-/- mice showed a higher activation status and enhanced cytotoxic activity with higher frequencies of activated CD69+ and CD27+CD11b+ effector NK cells as well as enhanced expression of IFN-γ accompanied by upregulation of miR-155. Analysis of healthy human donors for the gain of function FOXO3a SNP rs9400239 revealed a significantly reduced CD107a dependent degranulation activity and IFN-γ expression in donors homozygous for the allelic variant. In line with these findings, patients with CVB3 myocarditis exhibited a more severe course of the disease.

Conclusion: Our results implicate FOXO3a in the response to viral myocarditis confining inflammation. Increased NK cells function in FOXO3a-/- mice might play a crucial role in defense against CVB3 myocarditis while human carriers of a FOXO3a SNP have more severe disease.