TOLL-LIKE RECEPTOR ENGAGEMENT CONVERTS INNATE DYSREGULATION INTO OVERT CYTOKINE STORM AND PROMOTES AUTOIMMUNITY IN MURINE MODEL OF LEAKY SCID

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Introduction. Recombination Activating Gene *(RAGs)* are key elements of early events in V(D)J recombination. Impairment of these enzymes results in severe restriction of T and B cell repertoire. The clinical phenotype among patients with primary immunodeficiency (PID) secondary to *RAG* mutations spans from early severe infections to late onset autoimmune manifestations. Susceptibility and high mortality with viral infections are contributed to the absence of proper infection-specific adaptive responses. The role of innate response in this process has not been fully investigated.
Objectives. To evaluate innate response and autoimmunity during acute and chronic viral infections in a murine model of rag deficiency.
Methods. We utilized homozygous *rag1*$^{S723C/S723C}$ (*mut/mut*) mouse model of leaky SCID. To recapitulate acute and chronic viral infections, we administered high dose intravenous or prolonged low dose intraperitoneal Poly(I:C), respectively. Cytokine and autoantibody levels were measured.
Results. High dose i.v. Poly(I:C) treatment within 10 hours was fatal in 100% of *mut/mut* mice. Serum TNFα and IL-6 remained highly elevated and did not decline with time, compared to control wild-type mice. Genearray of splenic dendritic cells from *mut/mut* mice revealed skewed activation of TLR3 associated pathways. Prolonged low dose i.p. stimulation augmented and broadened the spectrum of autoantibodies in *mut/mut* mice.
Conclusions. In our murine model high and low dose TLR3 stimulation resulted in cytokine storm and increased autoantibody production, respectively. Dysregulation of innate immune system after acute or chronic infection may contribute to the increased mortality and autoimmune phenotype of patients with RAG-dependent PID.