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A significant role for tumor necrosis factor in *Nlrp3* inflammasomeopathies

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Introduction

The NLRP3 inflammasome is a protein complex responsible for caspase-1 dependent maturation of the pro-inflammatory cytokines IL-1β and IL-18. Gain of function missense mutations in NLRP3 cause the disease spectrum known as cryopyrin-associated periodic syndromes (CAPS).

Objective

To elucidate systemic autoinflammatory disease mechanisms involved NLRP3 inflammasomeopathies other than IL-1β and IL-18.

Materials and methods

Knock-in *Nlrp3*$^{L351P/+}$*/CreL/Il1b-/-/Il18-/-*mice (*FCAS Il1b*$^{-/-}$*Il18-/-*), *Nlrp3*$^{L351P/+}$*/CreL/* Casp1$^{-/-}$, (*FCAS Casp1*$^{-/-}$), *Nlrp3*$^{A350V/+}$*/CreL (MWS)* and *Nlrp3*$^{A350V/+}$*/CreL/Tnf*$^{-/-}$ *(MWS Tnf*$^{-/-}$*)* were generated in which Cre-mediated expression is limited to the myeloid cell lineage.

Results

Nearly all *FCAS Il1b*$^{-/-}$*Il18-/-*mice survived and grew normally until adulthood however, investigation of mice at > 6 months of age showed marked splenomegaly and elevated numbers of white blood cells as compared to *FCAS Casp1*$^{-/-}$ mice and non-mutant *Il1b*$^{-/-}$*Il18-/-*littermates, suggesting a caspase-1 dependent phenotype independent of IL-1β and IL-18. To examine other potential inflammatory mediators, non-lethal *in vivo* LPS (5 ug/g) stimulation of FCAS Il1b$^{-/-}$ Il18$^{-/-}$mice revealed significantly elevated levels of serum TNF at both 2 and 6 hours post induction when compared to *FCAS Casp1*$^{-/-}$mice and non-mutant *Il1b*$^{-/-}$*Il18-/-*controls. To further investigate the role of TNF in *Nlrp3* inflammasomeopathies, *MWS* mice (which die within two weeks of birth) were bred on a TNF knockout background. MWS Tnf$^{-/-}$ pups were indistinguishable from non-mutant controls with all animals surviving to adulthood with normalization of both body and spleen/body weight comparisons. Serum analysis of *MWS Tnf*$^{-/-}$ pups showed attenuation of NLRP3 inflammsome related cytokines when compared to intact *MWS* pups. The skin of intact *MWS* pups exhibited strong neutrophilic and inflammatory macrophage infiltrations, which were normalized in *MWS Tnf*$^{-/-}$ animals. Interestingly, *MWS Tnf* $^{+/-}$ pups also showed an intermediate protective effect on all of the aforementioned comparisons. To determine if TNF ablation could be recapitulated with therapeutic intervention, *MWS* pups were treated with recombinant soluble TNF receptor (Etanercept 400ug/g sc EOD). Treatment provided similar phenotypic rescue and extended survival for an average of 22 days after cessation of treatment. Adult *MWS Tnf*$^{-/-}$mice at > 6 months of age were found to have splenomegaly and elevated numbers of white blood cells when compared to non-mutant *Tnf* $^{-/-}$littermates, implicating a role for other inflammatory mechanisms as mice age.

Conclusion

TNF plays an unexpected and significant role in murine inflammasomeopathies, which may have therapeutic implications for CAPS patients with incomplete responses to IL-1 targeted therapies.

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