Enzymatically inactive Caspase-1 initiates TNF dependent inflammation *in vivo*

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Introduction

Results

Casp1 C284A^g induces RIP2 dependent inflammation *in vivo*.

A: Change of body temperature upon endotoxin shock. Injection of 10 μ g/g LPS i.p. induces a strong hypothermia - a surrogate of inflammation. Casp1 C284A^g mice show a significantly increased hypothermia compared to Casp1 KO mice. Rip2 deficiency abrogates this phenotype. However, Casp1 WT revealed the strongest hypothermia. **B:** Analysis of cytokine concentrations in serum 24 hours post LPS injection. IL-6 and TNF- α levels are significantly increased in C284A^g mice compared to Casp1 KO mice while IL-1 levels are on comparable low level due to the lack of an enzymatically active caspase-1. RIP2 deficiency reduces IL-6 and TNF- α levels of C284A^g mice to levels of Casp1 KO.

TNF- α inhibition blocks Casp1 C284A^g dependent inflammation.

C: Injection of 20mg/kg Etanercept 1h prior to LPS injection blocks Casp1 C284A^g mediated hypothermia. **D:** Analysis of cytokine concentrations in serum 24 hours post LPS injection. Following TNF- α inhibition, expression of IL-6 and TNF- α are reduced in C284A^g mice to levels of Casp1 KO mice.

NLRP3 activation is not involved in Casp1 C284A^g signaling.

E: Injection of 50mg/kg MCC950 2h prior to LPS injection does not block Casp1 C284A^g mediated hypothermia. **F:** Analysis of cytokine concentrations in serum 24 hours post LPS injection. Application of MCC950 did not reduce IL-6 and TNF- α serum levels compared to PBS control in C284A mice. Strong reduction of IL-1 β in MCC950 treated wild type mice proved the functionality of administered MCC950.

Conclusion

- Enzymatically inactive Casp1 C284A initiates inflammation *in vivo*
- Casp1 C284A induced inflammation is RIP2 dependent and TNF α mediated
- Casp1 C284A induced inflammation is independent of NLRP3 activity
- Severity of Casp1 C284A mediated inflammation seems to depend on the stimulus (i.e. systemic vs. local inflammation)
- Patients heterozygous for Casp1 WT and Casp1 mutant may benefit from combined IL-1 and TNF directed therapy

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