## **ORAL PRESENTATION**



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# Enzymatically inactive procaspase-1 stabilizes the ASC-pyroptosome

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### Introduction

Caspase-1 (or interleukin-1 converting enzyme, ICE) plays an important role in mediating proinflammatory innate immune responses, especially by activation of pro-IL-1ß within inflammasomes. Some patients with recurrent febrile episodes and systemic inflammation of yet unknown origin harbor *CASP1*-mutations with incomplete penetrance. These *CASP1*-variants cause reduced enzymatic activity of procaspase-1 and less IL-1ß secretion.

### **Objectives**

The paradox of reduced IL-1 $\beta$  secretion but increased inflammation led to the hypothesis, that *CASP1*-variants have different protein interaction clusters and thus enhance alternative signaling pathways.

#### **Material and methods**

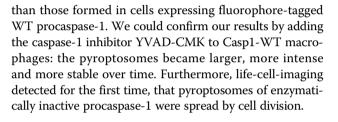
We established an in vitro model of transduced immortalized murine macrophages, expressing either wild type (WT) or enzymatically inactive (C284A) procaspase-1 fusion-reporter proteins and characterized them after NLRP3-inflammasome stimulation.

#### Results

As expected, variant procaspase-1 (C284A) macrophages did not secret IL-1ß and pyroptosis was reduced. In addition, the usage of fluorophore-tagged fusion proteins revealed a longer and more intense interaction of the enzymatically inactive procaspase-1 (C284A) with ASC (apoptosis-associated speck-like protein containing a CARD) compared to WT. Variant procaspase-1 (C284A) and ASC formed macromolecular complexes in the cytosol (so called pyroptosomes), that were significantly larger

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#### Conclusion

Variant procaspase-1 stabilizes inflammasome/pyroptosome formation. This may enhance inflammation via two IL-1ß-independent mechanisms: The pyroptosome causes a proinflammatory stimulus through increased recruitment and interaction of further proinflammatory proteins (e.g. RIP2, receptor interacting protein 2). Moreover, this stimulus might be amplified via pyroptosome- and cell division.

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