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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-1β 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 than those formed in cells expressing fluorophore-tagged WT procaspase-1. We could confirm our results by adding the caspase-1 inhibitor YVAD-CMK to Casp1-WT macrophages: the pyroptosomes became larger, more intense and more stable over time. Furthermore, life-cell-imaging detected for the first time, that pyroptosomes of enzymatically inactive procaspase-1 were spread by cell division.

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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