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MEETING ABSTRACT Open Access

# PW03-025 - Procaspase-1 contributes to inflammation via NF-KB

M Heymann[1*], S Winkler[1], S Özen[2], E Yilmaz[2], T Kallinich[3], A Rösen-Wolff[1], J Roesler[1], S Hofmann[1]

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## Introduction

Caspase-1 is a pro-inflammatory enzyme which gets activated by autoprocessing following the assembly of multiprotein complexes called inflammasomes. Mature caspase-1 is responsible for the activation of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Luksch and colleagues reported naturally occurring *CASP1* genetic variants in patients suffering from unexplained recurrent febrile episodes. Paradoxically, in vitro and in vivo analyses revealed decreased enzymatic activity of these caspase-1 variants leading to impaired cytokine production. A study of Lamkanfi and colleagues provides a possible explanation by indicating a link between enzymatically inactive procaspase-1 and activation of NF-κB, a pro-inflammatory transcription factor.

## Objectives

We tried to solve the indicated paradox by analyzing NF-κB activation in the presence of the procaspase-1 variants found.

## Methods

NF-κB activity was determined using a luciferase reporter assay system in transfected HEK 293T cells. RIP2 cleavage and ubiquitination studies were also performed in these cells. Protein/protein interactions of RIP2 and procaspase-1 were investigated in THP-1 cells by co-immunoprecipitation and in human monocyte derived macrophages by confocal fluorescence microscopy.

## Results

Procaspase-1 variants with reduced enzymatic activity increased NF-κB activation by interacting with RIP2 (receptor interacting protein kinase 2). In contrast, wild-type (wt) procaspase-1 reduced NF-κB activity by cleaving RIP2 and decreasing RIP2 ubiquitination which is essential for NF-κB activation. In addition to transfection experiments, we showed RIP2/procaspase-1 interaction in the human monocyte cell line THP-1 and in human monocyte derived macrophages after stimulation with LPS in a time dependent manner.

## Conclusion

Our results support the hypothesis that procaspase-1 variants with reduced enzymatic activity bind to RIP2 and thereby increase NF-κB activitation. This may contribute to pro-inflammatory signalling and thereby contribute to unexplained recurrent febrile episodes in the patients.

## Disclosure of interest

None declared.

**Authors' details**
[1]Dept of Pediatrics, University Hospital Dresden, Dresden, Germany. [2]Faculty of Medicine Ankara, Hacettepe University, Ankara, Turkey. [3]Dept for Pediatric Pneumology & Immunology, Charité Medical University of Berlin, Berlin, Germany.

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[1]Dept of Pediatrics, University Hospital Dresden, Dresden, Germany
Full list of author information is available at the end of the article