



MEETING ABSTRACT

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# PW03-025 - Procaspase-1 contributes to inflammation via NF- $\kappa$ B

M Heymann<sup>1\*</sup>, S Winkler<sup>1</sup>, S Özen<sup>2</sup>, E Yilmaz<sup>2</sup>, T Kallinich<sup>3</sup>, A Rösen-Wolff<sup>1</sup>, J Roesler<sup>1</sup>, S Hofmann<sup>1</sup>

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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)-1 $\beta$  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- $\kappa$ B, a pro-inflammatory transcription factor.

## Objectives

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

## Methods

NF- $\kappa$ B 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- $\kappa$ B activation by interacting with RIP2 (receptor interacting protein kinase 2). In contrast, wild-type (wt) procaspase-1 reduced NF- $\kappa$ B activity by

cleaving RIP2 and decreasing RIP2 ubiquitination which is essential for NF- $\kappa$ B 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- $\kappa$ B activation. 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

<sup>1</sup>Dept of Pediatrics, University Hospital Dresden, Dresden, Germany. <sup>2</sup>Faculty of Medicine Ankara, Hacettepe University, Ankara, Turkey. <sup>3</sup>Dept for Pediatric Pneumology & Immunology, Charité Medical University of Berlin, Berlin, Germany.

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<sup>1</sup>Dept of Pediatrics, University Hospital Dresden, Dresden, Germany  
Full list of author information is available at the end of the article