



MEETING ABSTRACT

Open Access

PW03-024 - A transgenic mouse model for variant procaspase-1

A Hermisdorf^{1*}, F Pessler², H Luksch¹, S Winkler¹, R Naumann³, J Roesler¹, A Roers⁴, A Rösen-Wolff¹

From 7th Congress of International Society of Systemic Auto-Inflammatory Diseases (ISSAID) Lausanne, Switzerland. 22-26 May 2013

Introduction

We have detected several genetic variants of *CASP1* in patients suffering from unexplained recurrent febrile episodes. Paradoxically, *in vitro* and *in vivo* analyses of patients' cells revealed decreased enzymatic activity of these caspase-1 variants leading to impaired cytokine production despite the proinflammatory phenotype of the patients. The pathophysiological processes associated with *CASP1* variants are still under investigation.

Objectives

In order to recapitulate the effects of the *CASP1* mutations found in the patients we tried to establish a bacterial artificial chromosome (BAC) transgenic mouse line expressing enzymatically inactive *Casp1*^{C284A} under the control of the own promoter.

Methods

The purified BAC fragment containing Flag-tagged *Casp1*^{C284A} (*Casp1*^{C284AFlag}) was injected into the pronuclei of fertilized C57Bl6 mouse oocytes, followed by transfer of these oocytes to pseudopregnant foster mothers. Pups born from these mothers were analyzed for the presence of full-length *Casp1*^{C284AFlag} by screening with sequence specific PCR, Southern blot, and sequencing of the transgene. *Casp1*^{C284AFlag} transgenic mice were crossed to conventional *Casp1* knock-out (KO) mice and the immunological phenotype of the progeny was analyzed by *in vitro* stimulation of BMDCs. Expression levels of the *Casp1*^{C284AFlag} transgene were quantified by qRT-PCR and Western blots. Released cytokine levels were determined by cytometric bead arrays.

Results

From two independent pronucleus injections we received 180 pups. Only three of them harbored transgene sequences and only one female animal proved to harbor the complete *Casp1*^{C284AFlag} transgene (TG). Crossing to *Casp1* KO mice yielded the following genotypes: *Casp1*WT/WT/TG, *Casp1*WT/KO/TG, and *Casp1*KO/KO/TG. qRT-PCR analyses revealed that unstimulated *Casp1*^{C284AFlag} transcription was reduced to 0.1% of wild-type *Casp1*. Hence, protein expression could not be detected in unstimulated cells. However, stimulation with LPS upregulated transcription and low-level translation of *Casp1*^{C284AFlag} in BMDCs. Determination of released cytokines after LPS/ATP stimulation revealed increased release of IL-6 and TNF- α from *Casp1*WT/KO/TG mice with proven *Casp1*^{C284AFlag} expression.

Conclusion

These data indicate that even tiny amounts of *Casp1*^{C284AFlag} induced release of other proinflammatory cytokines and that this might contribute to the proinflammatory phenotype observed in our patients. Baseline expression of enzymatically inactive *Casp1*^{C284AFlag} may be embryonically lethal in mice since not a single mouse could be generated which expressed the transgene under unstimulated conditions. Hence, a conditional *Casp1*^{C284AFlag} knock-in mouse model is being established.

This study was supported by the Federal Ministry of Education and Research (BMBF; Deutsches Netzwerk für Primäre Immundefekte PID-NET) and by EU Marie Curie International Reintegration grant no. GA-2007-224894 (F.P.).

Disclosure of interest

None declared.

¹Department of Pediatrics, University Clinic Carl Gustav Carus, TU Dresden, Dresden, Germany

Full list of author information is available at the end of the article

Authors' details

¹Department of Pediatrics, University Clinic Carl Gustav Carus, TU Dresden, Dresden, Germany. ²TWINCORE Center for Clinical and Experimental Infection Research, Hannover, Germany. ³Max Planck Institute of Molecular Cell Biology and Genetics, Germany. ⁴Institute of Immunology, TU Dresden, Dresden, Germany.

Published: 8 November 2013

doi:10.1186/1546-0096-11-S1-A250

Cite this article as: Hermsdorf *et al.*: PW03-024 - A transgenic mouse model for variant procaspase-1. *Pediatric Rheumatology* 2013 **11**(Suppl 1): A250.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

