



MEETING ABSTRACT

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PW02-019 - Inflammatory pathways activation in TRAPS patients

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Introduction

Mutations in TNFRSF1A can result in the autosomal dominant TNF receptor-associated periodic syndrome

(TRAPS): a complex and heterogeneous systemic auto-inflammatory disorder. Misfolding, intracellular aggregation and ligand-independent signalling by mutant TNFR1 play central roles in disease pathophysiology.

Objectives

This work was conducted to study the intracellular signalling pathway activation elicited by mutant TNFR1.

Methods

To understand the complexity of intracellular signalling pathway perturbation in TRAPS, a prototypic mutant TNFR1 (C33Y), or wild-type TNFR1 (WT), were expressed at near physiological levels in an SK-Hep-1 cell model system. TNFR1-associated signalling pathway intermediates were examined under a range of conditions, employing reverse-phase protein microarray. Peripheral blood mononuclear cells (PBMC) from C33Y TRAPS patients and matched healthy controls were similarly examined.

Results

In comparison to cells expressing WT TNFR1 alone, expression of C33Y-TNFR1 in SK-Hep-1 cells and TRAPS patients' PBMCs revealed a subtle up-regulation of a wide spectrum of signalling intermediates and their phosphorylated forms. These were associated with a proinflammatory/ anti-apoptotic phenotype, including NF- κ B, p38, MEK/ERK and JNK MAP kinase pathways, Phosphoinositide 3 kinase, STAT3, JAK2/c-Src, Gsk-3 β and transcription factors (including ATF, Elk, Jun). Increased activated Jak2/STAT3 may contribute to an "IL6

amplifier" positive feedback loop that promotes and sustains a proinflammatory state.

Conclusion

The study thus reveals the pleiotropic effect of a TRAPS-associated mutant form of TNFR1 on multiple inflammatory signalling pathways.

Disclosure of interest

None declared.

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