PEDIATRIC RHEUMATOLOGY

MEETING ABSTRACT Open Access

OR7-003 – MEFV genotype, IL1B and role of NLRP3 in FMF

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Introduction

Familial Mediterranean fever (FMF) is the most common of the hereditary autoinflammatory disorders. FMF is caused by mutations of *MEFV* gene which encodes for pyrin. It has been recently reported that frequency of FMF-like symptoms decreases from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation. The effectiveness of interleukin (IL)-1b blockers has suggested that IL-1b may play a role in the pathophysiology of the disease. However, evidence of dysregulated IL-1b secretion in FMF patients is so far missing. Moreover, the role of NLRP3 has never been directly examined in FMF patients.

Objectives

To define in patients affected by Familial Mediterranean Fever (FMF), whether or not interleukin (IL)-1β secretion (1) is enhanced, (2) correlates with the type of MEFV mutation and (3) is mediated by NLRP3.

Methods

Freshly isolated monocytes from 20 FMF patients (12 homozygous and 8 heterozygous), 14 MEFV healthy carriers (HC) and 30 healthy donors (HD), unstimulated or after LPS-induced activation, were analyzed for redox state (reactive oxygen species (ROS) production and antioxidant responses), and for IL-1β and IL-1Receptor antagonist (IL-1Ra) secretion. NLRP3 down-modulation was induced by NLRP3 *in vitro* silencing.

Results

LPS-stimulated monocytes from FMF patients displayed enhanced IL-1β secretion which correlated with the number and penetrance of MEFV mutations. Silencing of NLRP3 consistently inhibited IL-1β secretion. As in other autoinflammatory diseases, MEFV mutated monocytes produced more ROS than genetically negative controls. However, contrary to CAPS, they were featured by a conserved and sustained antioxidant response. Consistent with this finding, MEFV mutated monocytes did not exhibit the functional indicators of oxidative stress observed in CAPS, including accelerated IL-1β secretion and deficient IL-1Ra production.

Conclusion

MEFV mutated monocytes display enhanced IL-1β secretion which correlates with the number of high-penetrance mutations and level of endogenous ROS. Unlike NLRP3 mutated cells, monocytes carrying MEFV mutations withstand oxidative stress and preserve IL-1Ra production, thereby limiting inflammation. Finally, in contrast to what found in the animal model, the increased secretion of IL-1β by LPS-stimulated FMF monocytes is NLRP3-dependent.

Disclosure of interest

None declared.

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