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Toll like receptor 2 is overexpressed in FMF patients during attacks and inhibited by colchicine treatment

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Background

FMF is a systemic auto-inflammatory disorder, characterized by recurrent episodes of fever and serosal inflammation. The *MEF* gene, which is associated with FMF, encodes for the protein pyrin. FMF associated mutations, interrupt with pyrin normal function, leading to activation of the innate immune system and overexpression of IL-1β, and consequently to a systemic inflammatory response. Toll-like receptors (TLRs) play an essential role in the innate immune responses, by recognition of pathogen-associated molecular patterns and endogenous peptides. TLRs trigger a cascade of signaling events, leading to cytokine production. TLR2 is implicated in several inflammatory conditions, but its role in the pathogenesis of FMF is not completely clear.

Objectives

To study the role of TLR2 in the inflammatory process of FMF.

Materials and methods

We tested TLR2 naïve expression on monocytes of FMF attack-free patients (n=20) by FACS. We further tested the effect of sera from FMF patients in acute attack (n=6) on TLR2 expression by monocytes of healthy controls. The role of TLR2 was studied in respect to *MEFV* mutation, performed in THP-1 cells. TLR2 downstream signaling was studied by ELISA to measure IL-1β secretion, or by Western-blot to measure NF-κB.

Results

FMF attack-free patients have increased $CD14^{+}TLR2^{+}$ cell-count, as compared to healthy donors. High dose of colchicine treatment (≥2mg/d) inhibited this increased expression of TLR2 in FMF patients. Colchicine *in vitro* also inhibited the levels of TLR2 expression on THP-1 cells. Sera from FMF patients in acute attack induced TLR2 expression by both monocytes of healthy donors and THP-1 cells, and IL-1β secretion in healthy monocytes, and colchicine inhibited this induction. Furthermore, TLR2 agonist (Pam2CSK4) increased the secretion of IL-1β by PBMCs of healthy donors, and this activation was inhibited by colchicine. In *MEFV* -mutated THP-1 cells, TLR2 expression was spontaneously up-regulated by 3.8 folds, while TLR4 expression was elevated by 2 folds as compared to wild-type. Wild-type THP-1 cells presented elevated NF-κB expression when cultured with Pam2CSK4, whereas colchicine treatment abolished this expression. *MEFV*-mutated THP-1 cells expressed elevated levels of NF-κB, as compared to their wild-type counterparts.

Conclusion

TLR2 activation is up-regulated in monocytes of FMF patients, and colchicine inhibits this up-regulation *in-vitro* and *in-vivo*. Elevated expression of TLR2 promotes IL-1β production, and thus contribute to the uncontrolled inflammation manifested in FMF.

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