

Toll-like receptor 3 increases antigen-presenting cell responses to a pro-apoptotic stimulus but does not contribute to systemic lupus erythematosus genetic susceptibility.

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Abstract

OBJECTIVES: TLR3 mediates skin solar injury by binding nuclear material released from apoptotic keratinocytes, resulting in the production of pro-inflammatory cytokines. Because the TLR3 gene is located in 4q35, a known systemic lupus erythematosus (SLE) susceptibility locus, we wondered whether TLR3 single nucleotide polymorphisms (SNPs) were associated with inflammatory mechanisms relevant to the development of SLE, and disease susceptibility.

METHODS: Functional assays were carried out in TLR3-transfected HEK293 cells and in monocyte-derived dendritic cells (moDCs). TLR3 and IFN β immunofluorescence studies were performed in skin samples from 7 SLE patients and 3 controls. We performed a SNP association study in a discovery cohort of 153 patients and 105 controls, followed by a confirmation study in an independent cohort of 1,380 patients and 2,104 controls.

RESULTS: TLR3 and IFN β are overexpressed in SLE skin lesions. TLR3 overexpression in HEK293 cells amplifies their sensitivity to a pro-apoptotic stimulus. Taking advantage of a naturally occurring polymorphic TLR3 variant (rs3775291) that weakly versus strongly responds to poly I:C stimulation, we found that TLR3 is associated with amplified apoptotic responses, production of the Ro/SSA autoantigen and increased maturation of myeloid-derived dendritic cells (moDC) after exposure to UV irradiation. However, TLR3 SNPs are not associated with susceptibility to SLE in a large population of patients and controls.

CONCLUSIONS: TLR3 is overexpressed in SLE skin lesions and amplifies apoptotic and inflammatory responses to UV-irradiation in antigen-presenting cells in vitro. However, TLR3 SNPs do not impact susceptibility to the development of the disease.

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