7 TOLL-LIKE RECEPTOR TRIGGERING CAN SYNERGISE WITH IGE-MEDIATED ACTIVATION IN ACPA+RA

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Background and objectives Antibodies against citrullinated proteins (ACPA) are highly specific for rheumatoid arthritis (RA). Recently, the authors described a cellular immune response against citrullinated antigens that was only present in ACPA+RA-patients. This response was mediated via crosslinking IgE-ACPA bound to basophils, and suggests a major role for FcεRI-positive cells in the pathogenesis of RA. However, it is unknown whether mast cells, the main FcεRI expressing cell in synovium, can also be activated via this mechanism. As only limited information is present on TLR-expression and function in human mast cells, it is not known whether endogenous TLR ligands thought to contribute to chronicity of RA can also activate mast cells. The objective of the current study was to delineate the ability of IgE ACPA to activate human mast cells and to reveal potential synergistic effects with TLR-triggering.

Materials and methods Mast cells were differentiated from peripheral blood CD34+ stem cells. Real-time quantitative PCR and flow cytometry were used to evaluate RNA and protein expression of TLRs, respectively. For TLR-mediated stimulation, mast cells were stimulated with pathogen-associated TLR ligands as well as HMGB1 and HSP70, endogenous TLR ligands implicated in RA. IgE-mediated activation was achieved by sensitising mast cells with serum of RA patients, after which the cells were activated using citrullinated fibrinogen. Activation of mast cells was measured using flow cytometry and cytokine assays (multiplex assays and ELISA).

Results The authors show the presence of mRNA for TLR1-9 and protein expression of TLR-2 and -4 in human mast cells, with transcripts of TLR-4 being most abundant. Mast cells responded to TLR triggering with cytokine production, but not with degranulation. In contrast, mast cells sensitised with sera from ACPA+RA-patients readily degranulated upon exposure to citrullinated proteins, but not to their non-citrullinated

counterparts. Remarkably, simultaneous triggering of mast cells via citrullinated proteins and endogenous RA-associated TLR-ligands greatly enhanced cytokine production. This was IgE-dependent as neutralisation of IgE completely abrogated the effects evoked by citrullinated antigens.

Conclusions Our data show that human mast cells functionally express TLRs and that the activation via these receptors can synergise with IgE-mediated activation in ACPA+RA. These findings provide a new perspective of the role of mast cells and IgE-ACPA as a contributor to auto-immune processes present in RA patients, and suggest that inhibition of mast cells or blocking IgE might offer new treatment strategies in ACPA+RA.