

Rheumatoid arthritis (RA) is characterised by the presence of autoantibodies to 'citrullinated' proteins, the citrullination of which is mediated by peptidylarginine deiminase (PAD). Among these enzymes, two PAD isotypes – PAD 2 and 4 – play a major role in RA pathogenesis. In RA, joints are infiltrated with inflammatory cells, mainly monocyte/macrophages and lymphocytes, and T cell contact-mediated activation of monocytes is known to result in secretion of pro-inflammatory cytokines, such as IL-1 and TNF, Cox-2, PGE2 or metalloproteinases, all involved in the pathophysiology of RA. Our objective was therefore to determine if cell–cell interaction could also play a role in PAD expression by monocytes. To this end, the authors analysed the expression of PADs by peripheral blood monocytes at basal level or after stimulation through contact with T cells.

Methods Human monocytes were derived from the blood of healthy donors. Cells from the HUT-78 T cells were cultured in the absence of stimulation or stimulated with PHA and PMA. The expression of PAD isotypes in human monocytes was determined by real-time PCR and immunoblotting using isotype-specific probes.

Results Upon contact with stimulated HUT-78 cells, PADI2 and four mRNAs were found to be upregulated in human monocytes, as were the PAD2 and PAD4 proteins. The expression of PADs was time-dependent as substantiated by the kinetics of PADI mRNA expression which revealed that after 4 h of contact PADI mRNAs were increased but declined rapidly to levels below baseline after 12 h of co-culture, whereas the production of PAD2 and PAD4 enzymes increased at 24 and 48 h of culture.

Of note, the PAD6 enzyme was not detected contrary to its mRNA. The authors also tested synovial fibroblasts for PAD expression, but no isotype (PAD1, 2, 3, 4 and 6) was detected in any of the conditions tested whereas MMP-1, IL-6 and PGE2 were induced.

Conclusion After contact-mediated activation, PAD2 and PAD4, the principal PAD isotypes produced by human monocytes, are upregulated. This observation provides one explanation as to how activated inflammatory cells could constitute a source of PAD enzymes in inflamed synovial tissues.

A4 UPON CONTACT WITH STIMULATED T CELLS, EXPRESSION OF PEPTIDYLARGININE DEIMINASE 2 AND 4 IS UPREGULATED IN HUMAN MONOCYTES

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