A5 RHEUMATOID FACTOR AMPLIFIES THE MACROPHAGE SECRETION OF $\text{TNF}\alpha$ INDUCED BY ACPA-CITRULLINATED FIBRINOGEN IMMUNE COMPLEXES

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Based on their tight specificity for the disease, their association to its most severe forms and their production in the inflamed synovial tissue where citrullinated fibrin, their main antigenic target, is also abundant, the autoantibodies to citrullinated proteins (ACPA) probably play a central role in the pathophysiology of rheumatoid arthritis (RA). To substantiate this hypothesis the authors developed an original and totally human in vitro model in which monocyte-derived macrophages from healthy donors are stimulated with ACPA-containing immune complexes (ACPA-IC) generated by capturing ACPA on immobilised citrullinated fibrinogen. Using this model, the authors confirmed the proinflammatory potential of ACPA-IC, as their interaction with macrophages induced $\text{TNF}\alpha$ secretion. As IgM rheumatoid factor (RF) is an autoantibody directed to the Fc fragment of IgG, as it is also

produced and concentrated in the rheumatoid synovial tissue and it is linked to the severity and activity of RA, the authors evaluated in our model its influence on the macrophage stimulation by ACPA-IC.

Using two different human pentameric IgM with RF activity derived from the serum of patients with cryoglobulinaemia and the macrophages from more than 25 healthy individuals, the authors observed a highly significant dose-dependent enhancement of TNF α secretion in response to ACPA-IC when the complexes were formed in the presence of IgM RF. This effect was dramatic as TNF α production was enhanced up to 300 times. It was not observed when using IgM devoid of RF activity, and IgM RF alone did not induce TNF α production.

The capacity of IgM RF to amplify TNF α production by macrophages is probably linked to its multivalency: by linking several IgG involved in ACPA-IC it is probably responsible for gathering Fc γ receptors on the macrophage membrane and for increasing the number of IgG-engaged Fc γ receptors.

These results evidence in vitro the major proinflammatory role of IgM RF. They have a high pathophysiological significance since TNF α production is central in RA, and since ACPA and RF are linked to the aggressiveness of the disease.