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ANTIGEN-SPECIFIC B CELLS CAN ACQUIRE AND PRESENT THE RHEUMATOID ARTHRITIS CANDIDATE AUTOANTIGEN AGGREGAN FROM A NON-INTERNALISABLE SURFACE

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Background and objectives Recent experiments propose an essential role for B cells in the development of several autoimmune diseases either as autoantibody-producing cells or an antigen presenting cells (APC). However, the exact contribution of B cells in the early stages of rheumatoid arthritis (RA) remains unknown. One candidate autoantigen in RA is aggrecan, which, together with the disaccharide polymer hyaluron (HA), forms a major structural component of cartilage as part of an extracellular matrix (ECM). As B cells have been shown to be capable of acquiring antigens tethered to the surface of other cells, it is also possible that ECM tethered components may also be potential targets for joint-specific B cells. Therefore, we aimed to test the hypothesis that autoreactive B cells are important in the initiation of RA due to their unique ability to acquire integral joint autoantigens such as aggrecan leading to the activation of autoreactive T cells and subsequently disease progression.

Materials and methods To monitor the acquisition of aggrecan we generated aggrecan-specific B cells. We have then addressed whether antigen-specific B cells are able to extract aggrecan tethered via HA to a non-internalisable surface measured by flow cytometry and T cell activation assays.

Results We show, as expected, that aggrecan-specific B cells are able to present soluble aggrecan to CD4 T cells approximately 10^3 – 10^4 times more efficiently than non-specific B cells. Based on kinetic analysis, we also demonstrate that aggrecan-specific B cells are able to acquire HA-tethered aggrecan from an immobilised surface within periods as short as 1 h. Furthermore, we show that aggrecan acquisition by specific B cells leads to efficient autoreactive T cell activation. Finally we have also extended this novel assay to mimic the synovial

ECM, where aggrecan-specific B cells can extract aggrecan directly from nasal cartilage explants.

Conclusion We demonstrate that antigen-specific B cells can acquire immobilised aggrecan leading to the stimulation of autoreactive CD4 T cells. These findings support the hypothesis that B cells may play an essential APC role in the early stage of joint pathogenesis. Therefore, a better understanding of these early processes could lead to define novel targets for therapy suitable in the early phase of RA.