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Title: Immune memory in rheumatoid arthritis

Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease with a complex gene and environmental influence. Autoimmune features are present in a majority of RA patients and is characterized by two sets of autoantibodies; Rheumatoid factor targeting the Fc portion of IgG and so called ACPA targeting citrullinated proteins. We have dissected different B cell subsets and tissue compartments to delineate how robust anti-citrulline immunity is in the B cell population. One question has been whether citrulline autoimmunity is found in differentiated plasma cells and whether such Ig secreting cells would primarily reside at the site of inflammation or in the survival niches in bone marrow. We could identify ACPA-specific plasma cells both in RA synovial fluid (from disease flare) and in bone marrow (from patients undergoing hip replacement surgery). This data is well in line with the fact that RA patients mostly do not seroconvert upon successful therapy. Furthermore, both set of plasma cell-derived monoclonal ACPAs carry a high frequency of somatic hypermutation implicating many rounds of germinal center reactions and suggesting that citrulline autoimmunity is not a temporary breach of immune tolerance but a long lasting immune process generating robust memory. On the CD4 T cells side there is a parallel world of citrulline autoimmunity that is being actively pursued in our lab. In addition to this, there are also many observations of more general T cell abnormalities in RA patients, primarily in the affected joints. A recent observation is the presence of T cells with a partial TFH signatures, implicating B cell help, but without CXCR5 which would direct such cells to secondary lymphoid tissue. Especially PD-1 was found to be highly expressed on these cells. We have a long-standing interest in CD4+ T cells with a cytotoxic profile in the RA joint and we have observed an overrepresentation of cells expressing the transcription factors eomes. Altogether, these observations implicate also on the T cell side the result of highly differentiated effector memory lymphocytes, although these are probably both driven by the local inflammatory milieu and may not all represent the autoimmunity found in RA, but this remains to be determined.

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