Missed opportunity for targeted therapeutic intervention?

Novel, pathogenic B cell population accumulates in the inflamed joint of rheumatoid arthritis patients

Written by Dr Achilleas Floudas, IRC Postdoctoral Research Fellow at Trinity College Dublin and Professor Ursula Fearon, Professor of Molecular Rheumatology, Clinical Medicine, Trinity College Dublin

There is a long known-association of rheumatoid arthritis (RA) and autoantibodies. While autoantibodies have been extensively used for diagnostic purposes in RA, the characterisation of a specific mechanism of action describing their potential involvement in disease pathogenesis remains elusive[1]. B cell depletion therapy however, has demonstrated significant efficacy in ameliorating disease progression in autoantibody positive as well as autoantibody negative RA patients with significant but limited reduction in the levels of circulating rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)[2]. With synovial accumulation of B cells correlating with increased radiographic scores in RA patients and rituximab (anti-CD20) therapy leading to disease amelioration in patients naïve to methotrexate and those with poor responses to other biologics, it becomes evident that B cells contribute to disease pathogenesis beyond their capacity to produce autoantibodies[3]. Recent studies, have identified IgA expressing FcRL4+ memory B cells in the joints of RA patients[4]. While, FcRL4+ B cell derived antibodies are primarily targeting commensal bacteria, these B cells show reduced antibody production and reduced capacity to differentiate towards plasma cells[4,5]. One potential pathogenic avenue for FcRL4+ B cells is the expression of RANKL and the promotion of bone resorbing osteoclast activation[4,6].

However, several key questions remain poorly understood: What is the phenotype of B cells accumulating in the RA joint? What parameters dictate B cell migration to the site of inflammation? What is the degree of non-antibody mediated contribution of B cells in disease pathogenesis?

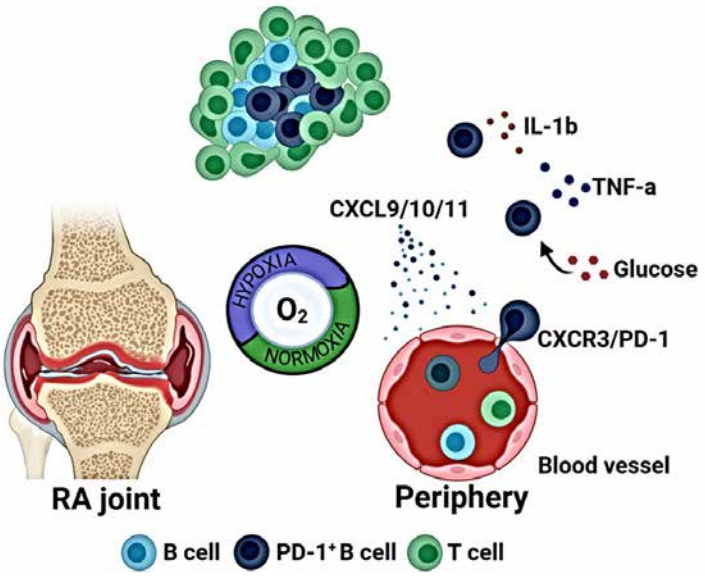
Using flow cytometric analysis of RA patient synovial biopsies we have identified a dramatic accumulation of switched memory ($CD27^+IgD^-$) and double negative ($CD27^-IgD^-$) memory B cells[7]. Extensive characterisation of synovial and paired RA patient peripheral blood B cell chemokine receptor expression showed a preference of synovial B cells for the expression of CXCR3. CXCR3 expressing B cells can be found in the peripheral blood of RA patients and primarily consist of switched memory and double negative memory B cells at frequencies that closely resemble the B cell population distribution of the inflamed RA joint[7]. Blockade of CXCR3 resulted in reduced invasion capacity of RA patient B cells in response to synovial biopsy conditioned media and there is a negative correlation between the peripheral blood frequency of CXCR3 expressing B cells and disease severity in RA. Although, other chemokine receptors are contributing to the synovial accumulation of memory B cells in RA, the aforementioned studies, highlight an important role for CXCR3 and raise the possibility for inhibiting synovial migration of B cells as an early therapeutic intervention.

Interestingly, CXCR3 expressing RA B cells, stimulated in-vitro through the B cell Receptor (BCR) and under physiologically relevant conditions resulted in the expression of programmed death 1 (PD-1)[7]. Recent studies have highlighted an increased synovial expression of PD-1 in subjects prior to the development of RA, indicating that this is a primary immune dysregulation in RA pathogenesis[8]. The PD-1 pathway has been a therapeutic target for T cell responses of cancer patients, leading in some cases to the development of arthritis, however there is a paucity of data on the role of PD-1 expressing B cells[9].

PD-1 B cells form the dominant B cell population in RA synovial tissue and exhibit high T cell co-stimulatory capacity and pro-inflammatory cytokine production with increased expression associated with disease pathogenesis in RA[7]. Interestingly, PD-1 B cells rely on STAT3 signalling with marked activation of the mTOR pathway[7]. Previous studies have revealed that the environment to the inflamed RA joint is highly hypoxic, with hypoxia correlating with synovial inflammation and immune cell infiltration[10,11]. RA patient PD-1 B cells maintained their increased proinflammatory cytokine and costimulatory profile even under hypoxic conditions that closely resemble the inflamed RA joint. Synovial tissue hypoxia promotes glycolysis, based on RNAseq analysis and the novel non-invasive fluorescent lifetime imaging microscopy that allows for direct visualisation of bound and unbound cellular NADH, RA patient PD-1 B cells are highly glycolytic and are located in ectopic lymphoid-like structures of the inflamed joint[7].

While B cell depletion has shown efficacy in the treatment of RA patients, the elimination of all CD20 expressing cells is arguably a major alteration of the immune system and could have unwanted effects if patients undergo chronic treatment. The identification of CXCR3 as a dominant mediator of memory B cell migration to the inflamed joint and the characterisation of pathogenic PD-1 B cells in RA, highlight two previously unappreciated avenues for a more targeted therapeutic intervention.

References available on request



Schematic: Peripheral blood memory B cells expressing PD-1 invade the synovial tissue in part, due to increased expression of the chemokine receptor CXCR3. Under the hypoxic conditions of the inflamed RA joint, PD-1 B cells express proinflammatory mediators including IL-1β and TNF-α. PD-1 B cells are highly glycolytic, are located within secondary lymphoid structures in the inflamed joint and have increased T cell costimulatory capacity.