

The role of B cells in rheumatoid arthritis

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This thesis is based on the following studies:

- I. Rehnberg. M, Amu. S, Tarkowski. A, Bokarewa. M, Brisslert. M.
Short- and long-term effects of anti-CD20 treatment on B cell ontogeny in bone marrow of patients with rheumatoid arthritis
Arthritis Research and Therapy 2009; 11: R123.
- II. Rehnberg. M, Brisslert. M, Amu. S, Zendjanchi. K, Håwi. G, Bokarewa. M.
Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment
Arthritis Research and Therapy, 2010; 12: R111
- III. Rehnberg. M, Brisslert. M, Bokarewa. M.
Epstein-Barr virus persistence in patients with rheumatoid arthritis drives antibody production by the CD25⁺ B cell population.
Submitted for publication.



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THE ROLE OF B CELLS IN RHEUMATOID ARTHRITIS

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ABSTRACT

It has been known for a long time that B cells play a role in rheumatoid arthritis (RA). By production of autoantibodies, presentation of auto-antigens and by producing cytokines B cells may contribute to the pathogenesis of RA. In recent years it has been shown that anti-B cell therapy is a powerful tool in the treatment of RA. The aim of this thesis was to a) investigate the effect on B cell ontogeny following B cell depletion therapy, b) during B cell depletion therapy evaluate serological and humoral immune responses and finally, c) try to establish a connection between Epstein-Barr virus (EBV) infection, CD25+ B cells and outcome of B cell depletion therapy.

In paper I we could show that in bone marrow of RA patients following anti-CD20 treatment with rituximab (RTX) IgD expressing naïve cells are depleted whereas immature and memory B cells were still detectable. However, the long-term effects clearly showed a reduction of memory B cells in bone marrow. The examination of rheumatoid factor (RF) production revealed that RFs decline short after treatment but returned to baseline levels concurrently with the IgD expressing B cells when patients were subjected to an additional course.

In paper II the cellular and humoral immune responses were evaluated by immunisation of RA patients before or during RTX treatment with a protein vaccine against influenza and a pneumococcal polysaccharide vaccine. The results suggest that both cellular and humoral immune responses are affected in patients receiving RTX treatment and we therefore suggest that immunisation should be performed before RTX treatment.

In paper III we investigate the effects of EBV on selected B cell subsets and how infection may affect the clinical response to RTX treatment. The phenotypical study showed that B cells are more mature in EBV infected patients and the CD25+ B cell subset was more mature as compared to the CD25- B cell population. The evaluation of clinical response to RTX treatment with regard to B cell subsets showed that non-responding EBV+ patients had a significantly larger CD25+ plasma cell population. When investigating the effects of EBV stimulation in vitro we found that the CD25+ B cell population developed into antibody-producing cells to a higher extent than did the corresponding CD25- B cell population.

The results of our studies indicate that B cells play an essential role in the pathogenesis of RA. During RTX treatment we suggest that the IgD expressing population may harbour the autoantibody producing B cells. We also claim that there are subsets of B cells (i.e. CD25+ B cells) that may have significant impact on the pathogenesis of RA, and the clinical outcome following RTX treatment.

Keywords: B cells, rheumatoid arthritis, B cell depletion therapy

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