B cell subpopulations in the pathogenesis of rheumatoid arthritis

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, fredagen den 26 april 2019 kl. 9.00

av

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Fakultetsopponent:

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Avdelningen för mikrobiologi, tumör- och cellbiologi,
Karolinska institutet

Avhandlingen baseras på följande delarbeten

I. Thorarinsdottir K*, Camponeschi A*, Cavallini N*, Grimsholm O, Jacobsson L, Gjertsson I, Mårtensson I-L. CD21$^{-/low}$ B cells in human blood are memory cells. *Clin Exp Immunol*. 2016; 185: 252-262.
*These authors contributed equally to the study

II. Thorarinsdottir K, Camponeschi A, Jonsson C, Nilsson J, Forslind K, Visentini M, Jacobsson L, Mårtensson I-L, Gjertsson I. CD21$^{-/low}$ B cells associate with joint damage in rheumatoid arthritis patients.
Submitted

III. Thorarinsdottir K, Forslind K, Agelii ML, Rudin A, Jacobsson L, Mårtensson I-L, Gjertsson I. Memory B cell subsets correlate with autoantibody titers, disease activity and joint damage in untreated early rheumatoid arthritis.
In Manuscript

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B cell subpopulations in the pathogenesis of rheumatoid arthritis

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ABSTRACT

B cell depleting therapy has proven to be an effective treatment in rheumatoid arthritis (RA), a disease characterized by the presence of autoantibodies against citrullinated proteins (ACPA) and the Fc portion of IgG (rheumatoid factor, RF). This demonstrates the vital role B cells play in the disease. The aim of this thesis was to explore the role of B cell subpopulations in the pathogenesis of RA. Our interest in a specific B cell population arose with the discovery of murine autoreactive B cells, $CD21^{-/low}$ cells, which expressed low surface levels or lacked the complement receptor 2 (CD21). CD21 helps activate B cells, as it is a part of the B cell co-receptor complex.

In Studies I-III we analyzed B cell populations in human peripheral blood with the help of flow cytometry utilizing multiple cell markers. In Studies II-III, clinical as well as radiographic data was collected from RA patients.

In **Study I** we established that $CD21^{-/low}$ B cells are found in human peripheral blood and discovered that in healthy donors (HDs) this B cell population is mainly composed of memory B cells (MBCs) based on their phenotype and response to combined stimuli. In **Study II** we compared the B cell populations in peripheral blood of patients with established RA and HDs. We saw a higher proportion of a $CD21^{-/low}$ subpopulation, i.e. $CD21^{-/low}$ $CD27^{-}IgD^{-}$ (double negative, DN) in patients with autoantibodies (ACPA/RF) compared to HDs. Additionally, the frequency of $CD21^{-/low}$ DN cells was higher in ACPA/RF positive patients with more joint destruction compared to those with less, and the $CD21^{-/low}$ DN population correlated positively with the level of destruction. The $CD21^{-/low}$ DN population was highly enriched in the inflamed joints of RA patients and a third of the cells expressed RANKL, which stimulates osteoclastogenesis. In **Study III**, we compared the B cell populations in peripheral blood in newly diagnosed untreated RA patients and HDs. We observed that the proportion of $CD21^{+}CD27^{+}$ MBCs correlated positively with RF and ACPA titers. In addition, the frequency of $CD21^{+}$ DN cells and $CD21^{-/low}$ DN MBCs correlated positively with tender joint count and joint narrowing score respectively.

In conclusion, it seems that different MBCs have different roles in RA where $CD21^{+}$ $CD27^{+}$ MBCs appear to drive the autoantibody response, the $CD21^{+}$DN MBCs the joint inflammation and the $CD21^{-/low}$ DN MBCs the joint damage.

Keywords: Rheumatoid arthritis, B cells, $CD21^{-/low}$ B cells, DAS28, joint destruction

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