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, Guldheds gatan 10A, Göteborg, fredagen den 26 april 2019 kl. 9.00

av

Katrin Thorarinsdottir

Fakultetsopponent:
Docent Lisa Westerberg

Avdelningen för mikrobiologi, tumör- och cellbiologi,
Karolinska institutet

Avhandlingen baseras på följande delarbeten


*These authors contributed equally to the study


INSTITUTIONEN FÖR MEDICIN

ISBN: 978-91-7833-351-6 (PDF)

http://hdl.handle.net/2077/58499
B cell subpopulations in the pathogenesis of rheumatoid arthritis

Katrin Thorarinsdottir, Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden, 2019

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

ISBN: 978-91-7833-351-6 (PDF)