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T cells and chemokines in rheumatoid arthritis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen
Arvid Carlsson, Medicinaregatan 3, Göteborg
Fredagen den 10 september, klockan 9:00
av Jonathan Aldridge

Fakultetsopponent:
Professor Vivianne Malmström
Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten:

I. Aldridge J, Pandya JM, Meurs L, Andersson K, Nordström I, Theander E, Lundell AC, and Rudin A. Sex-based differences in association between circulating T cell subsets and disease activity in untreated early rheumatoid arthritis patients. *Arthritis Research & Therapy 2018; 1:150*

II. Aldridge J, Andersson K, Gjertsson I, Hultgård-Ekwall AK, Hallström M, van Vollenhoven R, Lundell AC, and Rudin A. Blood PD-1^{+}TFh and CTLA-4^{+}CD4^{+} T cells predict remission after CTLA-4Ig treatment in early rheumatoid arthritis. *Rheumatology (Oxford) e-published before print 210519*

III. Aldridge J, Lundell AC, Andersson K, Mark L, Lund Hetland M, Østergaard M, Uhlig T, Schrumpf Heiberg M, A. Haavardsholm E, Nurmohamed M, Lampa J, Nordström D, Hørslev-Petersen K, Gudbjornsson B, Gröndal G, van Vollenhoven R, and Rudin A. Blood chemokine levels are markers of disease activity but not predictors of remission in early rheumatoid arthritis. *Submitted Manuscript*

IV. Aldridge J, Hultgård-Ekwall AK, Mark L, Bergström B, Andersson K, Gjertsson I, Lundell AC, and Rudin A. T helper cells in synovial fluid of patients with rheumatoid arthritis primarily have a Th1 and a CXCR3^{+}Th2 phenotype. *Arthritis Research & Therapy 2020; 1:245*

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T cells and chemokines in rheumatoid arthritis

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ABSTRACT

In this thesis, we investigated if circulating proportions of specific $CD4^+$ T cell subsets and blood chemokine levels were associated with disease activity and/or could predict remission in patients with early rheumatoid arthritis (eRA). We also compared the effect of different biological treatments on both T cell subset proportions and chemokine levels. Finally, we examined which T helper cell subsets are most abundant in the synovial fluid of inflamed joints, and which T cell associated cytokines induced the secretion of proinflammatory cytokines and chemokines by fibroblast-like synoviocytes (FLS).

To enable these studies, we analysed blood samples and assessed disease activity in patients with untreated eRA who participated in the NORD-STAR randomised treatment trial. Synovial biopsies and paired blood and synovial fluid were sampled from patients with established RA. FLS were propagated from synovial biopsies. The proportions of T cell subsets were analysed by flow cytometry and cytokine and chemokine levels were measured by bead-based immunoassays and ELISA.

In untreated eRA, circulating proportions of Th2, Th17 and CTLA-4^+ conventional $CD4^+$ T cells associated positively with disease activity in male, but not female patients. In patients treated with CTLA-4Ig, but not anti-TNF or anti-IL6R, baseline proportions of PD-1^+TFh and CTLA-4^+ conventional CD4+ T cells predicted remission at week 24. Only treatment with CTLA-4Ig reduced the proportions of PD-1+TFh. Plasma chemokine levels decreased in all treatment groups except in patients given anti-IL6R. Baseline chemokine levels did not predict remission in eRA. TPh, Th1 and CXCR3^+Th2 were the most abundant $CD4^+$ T cell subsets in RA synovial fluid, and the majority of B cell supporting TPh and PD 1highTFh cells expressed a Th1 or CXCR3^+Th2 phenotype. IL-4, IL-13 and IL-17 induced FLS to secrete CXCL8, CCL2 and CXCL1, while IFNγ induced CXCL10.

In conclusion, we show that baseline proportions of circulating T cell subsets may be used as biomarkers of remission for CTLA-4Ig treatment in eRA. Our findings also indicate that both classical and non-classical CXCR3^+ T cell subsets mediate joint inflammation in RA and their associated cytokines induce secretion of proinflammatory chemokines by FLS.

Keywords: Rheumatoid arthritis, $CD4^+$ T cell, chemokines, disease activity, biomarker, remission, CTLA-4Ig, anti-IL6R, anti-TNF

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