Göteborg, 2023

Rho-GTPases in Rheumatoid Arthritis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Föreläsningssalen plan 3, Medicinaregatan 10 A, 405 30 Göteborg, den 14 juni 2023, kl 13.00.

Av Eric Malmhäll-Bah

Fakultetsopponent:
Professor Andrew Cope
King's College, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Malmhäll-Bah E, Andersson KME, Erlandsson MC, Akula MK, Brisslert M, Wiel C, El Zowalaty AE, Sayin VI, Bergö MO, Bokarewa MB. 2022. Rho-GTPase dependent leukocyte interaction generates pro-inflammatory thymic Tregs and causes arthritis. *Journal of Autoimmunity. 2022 Jun 02. 130; 102843*

II. Malmhäll-Bah E, Andersson KME, Erlandsson MC, Silfverswärd S, Pullertis R, Bokarewa MB. Metabolic signature and proteasome activity controls synovial migration of *CDC42^{hi}*CD14^{+} cells in rheumatoid arthritis. *Frontiers in Immunology. 2023, under revision.*

III. Andersson KME, Malmhäll-Bah E, Oparina N, Tao W, Pandit A, Erlandsson MC, Chandrasekaran V, Silfverswärd S, Pullertis R, Bokarewa MB. Pluripotency factor PBX1 predicts treatment efficacy in rheumatoid arthritis. *Journal of Clinical and Cellular Immunology. 2022 Jul 12. 13(5)*.

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Rho-GTPases in Rheumatoid Arthritis

Eric Malmhäll-Bah

Reumatologi och inflammationsforskning, institutionen för medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2023.

Abstract

Heterogeneity of rheumatoid arthritis (RA) and lack of predictive markers implying response to anti-rheumatic drugs affects success in RA alleviation. The aims of this thesis were to identify intercellular interactions and molecular pathways in RA linked to signal transducers of the Rho-GTPase family as well as the effect of anti-rheumatic treatments on these molecular pathways. **Paper I:** Mice with conditional knockout of GGTase-I in macrophages (GLC mice) develop RA due to hyper activation of Rho-GTPases. Reciprocal expression of the Rho-GTPases Cdc42 and Rac1 in T cells as well as suppression of caudal HoxA cause migration of thymic Tregs into joint-draining lymph node. **Paper II:** We examined Rho-GTPase dependent biological processes by utilizing transcriptome of blood $CD14^+$ monocytes from two independent RA cohorts and of synovial tissue macrophages at single cell resolution. This resulted in a metabolic gene signature identifying circulating progenitors of RA synovial antigen presenters. Inhibition of JAK suppressed this progenitor population, explaining part of its anti-rheumatic effect. **Paper III:** With transcriptomic data of blood $CD4^+$ T helper cells from two independent RA cohorts, we demonstrated that the transcription factor PBX1 marks recent thymic emigrants. RA patients with high *PBX1* expression in $CD4^+$ T cells had favorable outcomes to anti-rheumatic treatment, predicting good response to inhibition of TNF-α and stable remission. **Conclusion:** This doctoral thesis work demonstrates that Rho-GTPases mediate interplay between T-helper cells and macrophages supporting antigen presentation and IFN-γ signaling, driving RA pathology. Also, I propose two approaches for endotyping RA, a metabolic signature in $CD14^+$ monocytes and expression of *PBX1* in $CD4^+$ T cells marking the recent thymic emigrants. The former identifies patients which may benefit from inhibition of JAK and the latter TNF-α.

Keywords: Rho-GTPases, rheumatoid arthritis, innate immunity, adaptive immunity, antigen presentation, RA treatment

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