Göteborg, 2019

Smoking and T cell co-stimulation in rheumatoid arthritis

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

Fredagen den 10 maj 2019 klockan 9:00

av

Caroline Wasén

Fakultetsopponent:

Professor Bent Winding Deleuran

Aarhus Universitet, Danmark

Avhandlingen baseras på följande delarbeten:

I. Wasén C, M Turkkila, A Bossios, M Erlandsson, KM Andersson, L Ekerljung, C Malmhäll, M Brisslert, S Töyrä Silfverswärd, B Lundbäck, and MI Bokarewa. Smoking activates cytotoxic $CD8^+$ T cells and causes survivin release in rheumatoid arthritis. *Journal of Autoimmunity 2017; 78: 101-10*

II. Wasén C, MC Erlandsson, A Bossios, L Ekerljung, C Malmhäll, S Töyrä Silfverswärd, R Pullerits, B Lundbäck, and MI Bokarewa. Smoking is associated with low levels of soluble PD-L1 in rheumatoid arthritis. *Frontiers in Immunology 2018; 9(1677)*

III. Wasén C, C Ospelt, M Erlandsson, KME Andersson, S Töyrä Silfverswärd, M Brisslert, S Gay, MI Bokarewa. Nicotine changes microRNA profile to control the Foxo1 mediated memory program of $CD8^+$ T cells in rheumatoid arthritis. *Manuscript*

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Smoking and T cell co-stimulation in rheumatoid arthritis

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ABSTRACT

In this thesis I investigated if smoking limits the co-stimulatory system of $CD8^+$ T cells in rheumatoid arthritis (RA). I took special interest in the co-inhibitory receptor PD-1 and its ligand PD-L1.

Blood samples from RA patients with known smoking status and experimental models of RA (RA mice) in which orally administered nicotine simulated smoking were used. Additionally, $CD8^+$ T cells were isolated from human blood and stimulated *in vitro*. Flow cytometry were used to analyze the expression of PD-1. ELISA was used to measure the soluble form of PD-L1 in serum samples from RA patients and healthy controls. Quantitative PCR was used for transcriptional analysis of proteins and microRNAs involved in $CD8^+$ T cell regulation. Microarray analysis of microRNA was performed in samples of human $CD8^+$ T cells.

Smokers had fewer activated $CD8^+$ T cells that expressed PD-1 compared to non-smokers, and human $CD8^+$ T cells stimulated with nicotine *in vitro* had lower expression of PD-1 messengerRNA. RA mice treated with nicotine had fewer PD-1 expressing $CD8^+$ T cells in the bone marrow. This was related to the increased production and release in circulation of the onco-protein survivin, a predictive marker for severe RA. $CD8^+$ T cells of smokers adopted a naïve/memory phenotype and had different expression of several microRNA that are involved in the regulation of memory T cell formation, including the FOXO signaling pathway. Smokers also had lower levels of soluble PD-L1 in serum. The low PD-L1 levels were linked to altered expression of antibody receptors on antigen-presenting cells producing soluble PD-L1. The presence of RA-specific autoantibodies was associated with serum levels of soluble PD-L1.

I conclude that smoking interferes with the PD-1 inhibitory system on $CD8^+$ T cells, which may contribute to higher risk for RA in smokers. This can occur because of the reduced inhibitory control of the $CD8^+$ T cells with low PD-1 expression, but also because of a reduced supply of sPD-L1. Furthermore, I suggest that microRNA interfere with the FOXO signaling pathway and influence the phenotype of $CD8^+$ T cells in smokers.

Keywords: Rheumatoid arthritis, $CD8^+$ T cell, programmed cell death-1, programmed cell death-1 ligand 1, smoking, microRNA

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