Adaptive immunity (T cells and B cells) in rheumatic diseases

IMMUNOGENICITY OF TNF ALPHA ANTAGONISTS IN RHEUMATIC INFLAMMATORY DISEASES: IMPACT ON CLINICAL RESPONSE

Selma Bouden 1, Liila Laadhar 2, Imen Ayadi 2, Mariam Salemi 1, Rabha hospital, tunis, Tunisia; 2Rabha hospital, tunis, Tunisia

Background: One of the mechanisms implicated in the loss of response to TNF alpha antagonists in rheumatic inflammatory diseases is the formation of antibodies against these drugs (anti-drug antibodies: ADA).

Objectives: The objective of our study was to determine the incidence of ADAb and low trough levels and to evaluate the therapeutic impact of the presence of ADA, the rate of ADA and trough serum concentration of the drug at the time of sampling and six months later.

Methods: A longitudinal, prospective and multicenter study was conducted including patients with rheumatoid arthritis (RA) or spondyloarthritides (SpA) treated with IFX or ADA as a first biotherapy for at least six months. ADAb and trough levels were measured. The evaluation of the therapeutic response was made at the time of sampling and six months later.

Results: Fifty patients were included (17 RA and 33 SpA). ADAb were positive in 39% of SpA and 35% of RA. They were positive in 40% of cases for IFX and 25% for ADA. The presence of ADAb was negatively related to the trough levels of IFX and ADA during RA (p=0.01 and p<0.0001) and SpA (p=0.01 and p<0.0001). For the two pathologies, no impact of the presence of ADAb, the rate of ADAb or the trough levels was noted on the therapeutic response at the time of sampling. However, the presence of ADAb was related to a higher activity of SpA six months after the sampling (p=0.05). Factors that were related to ADAb formation were a high BMI in RA (p=0.05) and a longer duration of evolution of RA (p=0.03).

Conclusion: The presence of ADAb and low trough levels seem to not affect the therapeutic response in patients on TNF alpha antagonists. However, they are associated with a higher activity of SpA six months after the sampling and a longer evolution of RA.

Disclosure of Interests: None declared


STUDY OF FUNCTIONAL ORIENTATION OF B CELLS IN PHYSIOLOGY AND SJÖGRENS SYNDROME

Marina Bouidriga 1, Alexis Grasseau 1, Nedra Chtri 1, Divi Corne 2, Jacques-Olivier Pers 2, Sophie Hillon 1, Laetitia Le Potier 1, Univ Brest, Inserm, UMR1227, Lymphocytes B et Autoimmuneité, Brest, France, Brest, France; 1CHU de Brest, Brest, France, Brest, France

Background: Sjögren’s syndrome (SS) is a chronic systemic autoimmune disease, characterized by mouth and eye dryness, due to irreversible destruction of glandular tissue by infiltrated lymphocytes. It is now well established that B cells play a key role in the pathophysiology of SS. Indeed, B cells exhibit various signs of hyperactivity and produce excessive amounts of pro-inflammatory cytokines and immunoglobulins (Ig), especially IgG type-antibodies (Abs) (Kroese et al., 2014). Currently, it is suggested that the interleukin (IL)-21 (Wang et al., 2018) and IFNα (Yao et al., 2013), promote the generation of active IgG-producing plasma cells (PC). On the other side, some studies highlight the protective role of IgM producing cells in autoimmunity through enhanced effectorcytokis and immune-regulatory properties (Ehrenstein and Notley, 2010).

Objectives: This study aims to understand the influence of IL21 and IFNα on the B cell differentiation and the subsequent functional responses of the cells according to their maturation stage. Moreover, this will also enable a further understanding of the contribution of these cytokines to the pathogenesis of SS.

Methods: We established in vitro models to study the differentiation of different B cell subsets in a T-independent (TI) and T-dependent (TD) manner, under different cytokine stimulations. Naïve, switched memory and CD27-negative memory B cells were isolated from peripheral blood of healthy controls (HC) and SS patients and thereby cultured in those different conditions. After three days of culture, the expression of surface markers and transcription factors was analysed by flow cytometry and molecular identity was further determined by transcriptional analysis. Additional functional assay was also performed to measure Abs and cytokine secretion.

Results: First results on HC suggest that switched memory B cells differentiate into IgG and IgA-secreting plasmablasts (PB), when stimulated in a TI manner. This process is highly increased in presence of IFNα. Unswitched memory B cells mostly become PB able to secrete IgM and IL10. IL21 and IFNα oppose distinct effector functions. IL21 promote activation of B cells with an upregulation of the surface marker CD11c and T-bet transcription factor. Transcriptomic studies are still in progress to further define the molecular profile of those distinct effector B cells.

REFERENCES


Disclosure of Interests: None declared


IMPACT OF METABOLIC CHANGES DURING AGING ON HUMAN EX VIVO NAÏVE AND MEMORY CD4+ T CELL FUNCTION

Yuling Chen 1,2, Pelle Löwe 2, Hao Wu 3, Frank Buttgeriet 1, Timo Gabor 2,3
1Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany; 2German Rheumatism Research Centre (DRFZ) Berlin, a Leibniz Institute, Berlin, Germany; 3Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Gastroenterology, Infectiology and Rheumatology, Berlin, Germany

Background: Age-related dysfunction in immune cells (immunosenescence), such as T cell dysfunction, may contribute to the development of rheumatoid arthritis (RA). In aged people, senescent T cells tend to produce low amounts of pro-inflammatory cytokines leading to low-grade inflammation. However, cellular metabolism modulates effector functions such as cytokine production and proliferation in T cells by providing energy and building blocks. Metabolically, naïve and memory CD4+ cells are relatively quiescent immune cells. Currently, the metabolic phenotype of naïve and memory CD4+ T cells and how metabolism affects functions of naïve and memory CD4+ T cells in aged people are not well understood.

Objectives: Therefore, we analysed the differences in the metabolic phenotype of peripheral naïve and memory CD4+ T cells in young and aged healthy donors to explore fundamental processes of immune-aging in the pathogenesis of RA.

Methods: Naïve and memory CD4+ T cells were isolated from PBMCs of young donors (18-35 years) and old donors (>50 years) by using MACS™ technology. Purity of isolated cell fractions was assessed by flow cytometry. Ex vivo naïve and memory CD4+ T cells were analysed by Seahorse™ Technology to determine proton efflux rate (PER) as a measure of glycolysis (glycPER) and oxygen consumption rate (OCR) as a measure of mitochondrial respiration (mitoOCR). Cytokine expression and secretion was measured by flow cytometry and multiplex assay. Finally, TCR-stimulated memory CD4+ T cell proliferation was determined using CSFE and Ki-67 after 3 days and 4 days by flow cytometry.

Results: We included 9 young (20-32 years, 25.0±3.4 years) and 9 aged gender-matched donors (52-67 years, 57.8±5.7 years) for PER and OCR measurement. Memory CD4+ T cells demonstrated higher basal glycolysis, compensatory glycolysis as well as basal OCR and spare respiratory capacity than naïve CD4+ T cells. Memory CD4+ T cells from young donors had higher basal glycolysis, and compensatory glycolysis than aged donors, but lower ratio of basal mitoOCR/ glycPER. Although we did not observe differences in intercellular cytokine expression measured by flow cytometry after 5h stimulation of memory CD4+ T cells, we determined a significant higher amount of secreted IL-6, IL-7, IP-10, monocyte chemoattractant protein-1 and activin in the supernatant of memory CD4+ T cells from aged donors as compared to those from young donors. Cell division index, proliferation, percent of divided cell, and Ki-67 expression after 3 and 4 days of stimulation showed no statistical differences between both groups.

Conclusion: Here, we demonstrate a higher basal glycolysis, basal OCR, mitochondrial and glycolytic capacity of human ex vivo memory CD4+ T cells as compared to naïve T cells. A decrease of basal glycolysis, compensatory glycolysis in memory CD4+ T cells of aged people which results in an enhanced cytokine expression can be assumed to culminate in T cell dysfunction leading to the development of RA during aging.

Acknowledgement: The work of Yuling Chen was funded by the Chinese Scholarship Council (2014063050248). The work of Timo Gabor was funded by the Deutsche Forschungsgemeinschaft (353142848).

Disclosure of Interests: Yuling Chen: None declared, Pelle Löwe: None declared, Hao Wu: None declared, Frank Buttgeriet: None declared, Timo Gabor: Research Grant from: Pfizer