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Immunoglobulins and Serotonin modulate human macrophage polarization

A.L. Corbí, M. De las Casas-Engel & A. Domínguez-Soto
Myeloid Cell Laboratory, Centro de Investigaciones Biológicas (CIB), Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain

Background: Macrophages exhibit a huge functional plasticity and can acquire a continuum of polarization states in response to endogenous and nonself stimuli. Microbe-derived factors, or cytokines like GM-CSF, promote the acquisition of pro-inflammatory, bactericidal, tumor-suppressive, and immunogenic activities, a process commonly referred to as M1 polarization and whose hallmark is the ability to release large amounts of IL-12/IL-23. Conversely, cytokines like M-CSF promote anti-inflammatory, scavenging, tumor-promoting, tissue repair, and proangiogenic functions (M2 polarization), and the ability to produce high levels of IL-10. The modulation of macrophage polarization represents a potential strategy for therapy of chronic inflammatory pathologies and diseases with an altered inflammatory status (cáncer).
Materials and methods: Gene expression profiling was used to identify genes exclusively expressed in pro-inflammatory or anti-inflammatory human macrophages, and whose validity was beeen demonstrated through the analysis of macrophages from the sinovial fluid of rheumatoid arthritis patients and tumor-associated macrophages. These biomarkers has been used to search for factors with ability to promote a shift between the macrophage polarization state.
Results: Serotonin inhibits LPS-induced release of proinflammatory cytokines, upregulates M2 polarization–associated genes and reduces M1-associated genes through through the 5HT7 and 5HT2B serotonin receptors. Intravenous immunoglobulins induces a M2-to-M1 polarization switch on human and murine M2 macrophages, and limits tumor progression with a concomitant change in the polarization of tumor-associated myeloid cells via Fc □ receptors.
Conclusions: Serotonin skews macrophage polarization towards M2 at the functional and transcriptomic levels, and contributes to the maintenance of an anti-inflammatory state via 5HT2B and 5HT7. By contrast, Intravenous immunoglobulins promotes a M2-to-M1 macrophage polarization switch that might be therapeutically useful in cancer, in which proinflammatory or immunogenic functions should be promoted.

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CARD9 mediates autoantibody-induced autoimmune diseases by linking the syk tyrosine kinase to chemokine production

T. Németh*, K. Futosi*, K. Csorba†, C. Sitaru†, J. Ruland‡ & A. Mócsai*
**Department of Physiology, Semmelweis University School of Medicine, Budapest, Hungary and MTA-SE 'Lendület' Inflammation Physiology Research Group of the Hungarian Academy of Sciences and the Semmelweis University; †Department of Dermatology, University Medical Center, Freiburg, Germany; ‡Institut für Klinische Chemie und Pathobiochemie, Klinikum rechts der Isar, Technische Universität München, München, Germany*

Background: In contrast to the well-defined role of CARD9 in fungal recognition pathways, its function in non-infectious autoimmune inflammation has not been described yet, despite the fact that a genome-wide association screen raised a possible association between CARD9 gene polymorphisms and a human autoimmune arthritis. Here, we investigated the role of CARD9 in autoantibody-mediated diseases by a transgenic method.
Materials and methods: We used the neutrophil-, macrophage-, Fc receptor- and Syk-mediated K/BxN serum transfer arthritis and the anti-collagen type VII antibody-mediated epidermolysis bullosa acquisita (EBA) models. Neutrophils (or macrophages) were stimulated through their Fcγ receptors, followed by the analysis of the superoxide release (as a *short-term response)* and the chemokine release (as a *long-term response*).
Results: The absence of CARD9 resulted in a partial, but significant decrease in arthritis severity and CARD9$^{-/-}$ mice showed a moderate skin inflammation in the EBA model compared to the wild type animals. Neutrophil (and monocyte) accumulation at the site of inflammation was strongly reduced in the absence of CARD9, while CARD9$^{-/-}$ neutrophils (and monocytes) had normal migratory capacities to the joints in wild type/CARD9$^{-/-}$ mixed bone marrow chimeras. Surprisingly, the synovial levels of the chemokines CXCL1 and CXCL2 were dramatically reduced in the absence of CARD9 upon arthritis induction. While Fcγ receptor-activated Syk$^{-/-}$ neutrophils (and macrophages) failed to produce superoxide or release chemokines compared to wild type cells among *in vitro* conditions, CARD9$^{-/-}$ neutrophils (and macrophages) showed normal short-term, but strongly reduced long-term responses.
Conclusions: CARD9 plays an important role in the development and progression of autoimmune arthritis and autoimmune blistering skin disease in mice, likely by linking the Syk tyrosine kinase to chemokine production in innate immune cells.

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The role of neutrophil extracellular traps in the pathogenesis of obesity

Q. Braster*, H. Hartwig*, C. Silvestre-Roig*, E. Lutgens* & O. Soehnlein*†
**Department of Pathology, Academic Medical Center (AMC), Amsterdam, the Netherlands; †Institute for Cardiovascular Prevention (IPEK), LMU Munich, Germany*

Background: Obesity is a chronic inflammatory disease associated with a prominent mortality and morbidity in western countries. Low-grade chronic inflammation of the adipose tissue results in insulin resistance and increased cardiovascular risk. During obesity, neutrophils infiltrate the adipose tissue and mediate insulin resistance via the granule-proteins Neutrophil Elastase (NE) and myeloperoxidase (MPO). Neutrophils can make these granule-proteins available extracellularly via degranulation or via display on Neutrophil Extracellular Traps (NETs). During NET release neutrophils release DNA-protein structures as a mechanism of extracellular pathogen killing. However, NET release has also been implied in various pathological scenarios including acute lung injury and atherosclerosis. One critical step for NET formation is the chromatin decondensation which is associated with histone citrullination, a process catalyzed by the enzyme PeptidylArginine Deiminase 4 (PAD4). Hence, by using the PAD4 inhibitor Cl-amidine, we analyzed the role of NET release on obesity-mediated pathogenesis.
Material and methods: C57BL/6 mice received a 60% high fat diet (HFD) for 10 weeks and were injected subcutaneously with a daily dose of 10 mg mL^{-1} kg^{-1} Cl-amidine or vehicle. To determine the effect of the HFD a glucose and insulin tolerance