ALLERGIC ASTHMA INDUCES THE ACCUMULATION OF SYNOVIAL RESIDENT EOSINOPHILS, TRIGGERING THE RESOLUTION OF INFLAMMATORY ARTHRITIS

M. Liu1, D. Andreev2, K. Kachler1, J. Koelle1, S. Rauber1, A. Ramming1, S. Finotto2, G. Schett1, A. Bozec1. 1University Hospital Erlangen and Friedrich Alexander University of Erlangen-Nürnberg (FAU), Department of Medicine 3, Rheumatology and Immunology, Erlangen, Germany; 2University Hospital Erlangen and FAU, Department of Molecular Pneumology, Erlangen, Germany

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder, involving synovial joints, which affects approximately 1% of the world population[1]. Our former work demonstrated that the Th2-eosinophil pathway is a strong anti-inflammatory mediator of inflammatory arthritis[2]. Allergic asthma is an inflammatory disease of the airway, triggered by type 2 immune response. Hitherto, clinical observations on the impact of asthma on RA showed controversial results. Herein, we investigated the action of allergic asthma on inflammatory arthritis.

Objectives: We aimed to delineate the molecular and cellular responses induced by allergic asthma on inflammatory arthritis, particularly depicting the role of eosinophil subsets in arthritis synovium.

Methods: Allergic asthma was induced in wild type and genetically modified mice by ovalbumin (OVA) treatment. After the initiation of allergic asthma, K/BxN serum was transferred into the asthmatic mice or control mice to trigger serum induced arthritis (SIA). Then, arthritis severity, circulating cytokines and the cytology of lung and synovium were analyzed. Eosinophil subsets were studied by flow cytometry, single cell RNA sequencing analysis, and were isolated and transferred into the synovial cavity of eosinophil deficient arthritis mice. Clinical data of patients with both RA and asthma were collected and checked for the relapse of RA after asthma treatment with anti-interleukin (IL)-5 antibody.

Results: Mice induced with allergic asthma exhibited a rapid resolution of SIA. The OVA-triggered resolution disappeared in eosinophil deficient mice (Ab2iGATA), and was partially blocked by IL-5 neutralization. We could detect that IL-5 was mainly produced by type 2 innate lymphoid cell (ILC2) in the lung. Allergic asthma exclusively induced the proliferation (Ki67+) and accumulation of synovial resident eosinophils (rEos, Siglec-Fint), which switched classical macrophages into alternatively activated macrophages. Synovial induced eosinophils (iEos, Siglec-Fph) appeared only in the acute phase of SIA. Single cell RNA sequencing analysis showed that rEos played an anti-inflammatory role, while iEos had pro-inflammatory properties in arthritis. The roles of rEos and iEos in arthritis were confirmed by transferring rEos/iEos into the synovial cavity of arthritic mice. Patients with both RA and asthma showed a remission relapse of RA after using humanized monoclonal IL-5 antibody for treating severe eosinophilic arthritis.

Conclusion: Allergic asthma induced an IL-5 mediated proliferation and accumulation of synovial rEos. The latter triggered the resolution of inflammatory arthritis. In human, eosinophils induced by asthma were essential for the sustaining of RA remission.

References:

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