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

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder, involving synovial joints, which affects approximately 1 percent 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 synovium and synovial 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 (AbdGATA), 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 (eEos, Siglec-F-IL-5), which switched classical macrophages into alternatively activated macrophages. Synovial induced eosinophils (iEos, Siglec-F-Phq) appeared only in the acute phase of SIA. Single cell RNA sequencing analysis showed that eEos played an anti-inflammatory role, while iEos had pro-inflammatory properties in arthritis. The roles of eEos and iEos in arthritis were confirmed by transferring eEos/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 iEos. The latter triggered the resolution of inflammatory arthritis. In human, eosinophils induced by asthma were essential for the sustaining of RA remission.

References:

Acknowledgments: Mengdan Liu and Darja Andreev contributed equally to this study.


Disclosure of Interests: none.

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PRECLINICAL EFFICACY OF R835, A NOVEL IRAK1/4 DUAL INHIBITOR, IN RODENT MODELS OF JOINT INFLAMMATION

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Background: Interleukin receptor associated kinases (IRAK) 1 and 4 are kinases involved in Toll-Like Receptor (TLR) and Interleukin-1 Receptor (IL-1R) signaling pathways, which regulate innate immunity and inflammation. Dysregulation of IRAK1/4 signaling can lead to a variety of inflammatory conditions including rheumatoid and gouty arthritis. As a result, IRAK1/4 are promising therapeutic targets for rheumatic diseases (1). We have identified a potent and selective IRAK1/4 inhibitor, R835, that substantially suppressed the elevation of LPS (TLR4 agonist)-induced serum cytokines in healthy human volunteers in a recently completed phase 1 study.

Objectives: The aim of our study was to investigate the effect of IRAK1/4 selective inhibition as a potential therapeutic approach for rheumatological diseases. We evaluated the inhibition by our clinical candidate, R835, on TLR-, IL-1R- and NLRP3 inflammasome-induced cytokine production, as well as in preclinical models of arthritis.

Methods: The effect of R835 on TLR- or IL-1R-induced cytokine production was evaluated in vitro using THP-1, human primary endothelial cells and human primary dendritic cells. The activity of R835 on the NLRP3 inflammasome was also tested in vitro using THP-1 cells. The pharmacokinetic-pharmacodynamic relationship of R835 was evaluated in a rat model of IL-1β-induced serum release. Mice were pre-treated orally with vehicle or R835 prior to challenge, serum cytokine and plasma compound levels were determined. The efficacy of IRAK1/4 inhibition by R835 in rodent models of joint inflammation was evaluated in a mouse model monosodium (MSU)-induced peritonitis, in rat model of MSU-induced gouty arthritis and in a rat model of collagen-induced arthritis (CIA).

Results: In human cells, R835 blocked proinflammatory cytokine production in response to TLR, IL-1R and NLRP3 inflammasome activation. In mice, R835 dose-dependently decreased serum cytokines in response to administration of IL-1β. Mice pre-treated with R835 demonstrated dose-dependent reductions in MSU crystal-induced serum and peritoneal cytokine levels, as well as neutrophil influx in the peritoneal cavity. Prophylactic and therapeutic treatment with R835 also resulted in significant inhibition of MSU crystal-induced knee edema in paclitaxel pre-treated rats. In a rat model of CIA, R835 blocked both onset and progression of disease, by reducing inflammation, cartilage degeneration and synovial inflammation.

Conclusion: R835 is a promising clinical candidate for the treatment of a range of cytokine-driven rheumatological diseases. R835 has proven to have desirable pharmacokinetic properties, was well tolerated and suppressed LPS-induced serum cytokines in healthy volunteers in a recent phase 1 study.

References: