Background: The investigation of anti-inflammatory and immunosuppressive functions of kynurenic acid (KYNA) is now in focus. Previously, we demonstrated the opposite effects of KYNA and different KYNA analogs on the TNF-α, alarms and α-defensin production, correlation with the effects on the TSG-6 expression in rheumatoid arthritis (RA).

Methods: 93 RA patients were involved and divided subgroups based on DAS28 activity score. Peripheral blood mononuclear cells (PBMC) was isolated from RA patients and healthy controls. As cytokine inducers heat inactivated Staphylococcus aureus (SA1) were used. In parallel in vitro experiments, the SA1 induced PBMCs were pretreated with a newly synthesized KYNA analog (compound SZR-72) was synthesized by direct amidation of KYNA). The concentrations of the above mentioned inflammatory mediators in the supernatants were quantified by using ELISA kits and the TSG-6 expression was also determined by RT-qPCR method.

Results: The SA1 induced TNF-α, EN-RAGE, calprotectin and α-defensin production was significantly higher in RA patients’ group than in healthy controls. KYNA analog attenuated the SA1 induced TNF-α, EN-RAGE, calprotectin and α-defensin production, and increased TSG-6 production and TSG-6 mRNA expression in PBMC cells from RA patients. The SA1 induced TNF-α and TSG-6 production correlated with the DAS28 activity score. The TNF-α inhibitory effect of the KYNA analog correlated inversely with the TSG-6 stimulatory effect in all subgroups of RA patients based on DAS28 activity score.

Conclusion: TSG-6 expression could participate in the suppression of inflammatory cytokines, such as TNF-α, EN-RAGE, calprotectin and α-defensin. We suppose that the elevation of the TSG-6 expression by KYNA and especially by new KYNA analogs might be one of the mechanisms that are responsible for their suppressive effect on TNF-α production as a feedback mechanism in RA. KYNA and KYNA analogs have an important role in influencing TSG-6 expression, and there is a possible benefit with potential therapeutic consequence of targeting TSG-6 expression by kynurenes in inflammatory conditions in RA.

References:

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AB0109 THE ROLE OF CD70 IN THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a progressive, chronic inflammatory autoimmune disease. Pro-inflammatory molecules, activated lymphocytes, and the migration of inflammatory cells are important in the development of RA. There are many unknown causes of RA. And there are many patients who are refractory to treatment with known disease-modifying anti-rheumatic drugs. So, unknown cause of RA needs to be elucidated.

CD70 is a member of the tumor necrosis factor (TNF) superfamly and a ligand for CD27. The interaction of CD70 with its receptor CD27 promotes expansion and differentiation of memory and effector T cells as well as B-cell expansion and plasma cell differentiation. Hypoxia is an important micro-environmental factor in RA synovium. Hypoxia induces activation of hypoxia inducible factor (HIF). The expression of HIF-2α is up-regulated in human RA synovium. Reactive oxygen species (ROS) has been implicated in the pathophysiology of RA.

Objectives: In this study, we tried to examine the presence of CD70 in RA synovium and investigate the role of CD70 in the development of RA associated with HIF-2α and ROS.

Methods: Fibroblast-like synovioyte (FLS), peripheral blood (PB) and synovial fluid (SF) were used for experiments. FLS was stimulated with recombinant human (rh)-IL-17 and rh-TNF-α. N-acetyl-L-cysteine (NAC) was used as a ROS scavenger. HIF-2α inhibitor (PT-2385) was used for examine the effect of HIF-2α in RA-FLS. RT-PCR, qPCR, western blotting, flow-cytometry, ELISA, cell migration assay, and scratch wound assay were performed.

Results: CD70 mRNA is present and elevated by stimulation with IL-17 and TNF-α in both RA-FLS and osteoarthritis (OA)-FLS (Fig 1). CD70 also expresses on the surface of RA-FLS and OA FLS (Fig 2). CD70 expression on the surface of FLS is elevated by stimulation with IL-17 and TNF-α in both...