THE THERAPEUTIC POTENTIAL OF CIRCULATING AUTOLOGOUS TISSUE HOMING EXTRACELLULAR VESICLES FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS PATIENTS

Keywords: Animal models, Rheumatoid arthritis, bDMARD

Background: Progress has been achieved with the introduction of biologics for the management of inflammatory diseases such as rheumatoid arthritis (RA), however such medications induce immune suppression, which is nonselective to the pathogenesis of the disease, resulting in higher rates of infections. Therefore, there are unmet medical needs in the treatment of such diseases, which should be addressed by novel approaches. Accumulating evidence suggests that extracellular vesicles (EVs) play a role in the establishment, maintenance and modulation of autoimmune processes.

Objectives: In the current study, we hypothesized that isolation of circulating autologous tissue-specific homing EVs from RA patients - may improve the delivery of current FDA-approved anti-inflammatory drugs, which will be encapsulated into these EVs. The drug-loaded EVs will be injected back to the diseased subjects and will naturally find their way to the inflamed tissue.

Results: Indeed, we found that autologous labeled EVs, expressing joint/synovial homing receptors (e.g. αvβ3 integrin), derived from blood of diseased arthritic mice (Collagen antibody-induced arthritis model), can migrate toward the inflamed synovium, using in vivo imaging system (IVIS). Moreover, we show that these EVs strongly expresses glucose transporter 1 (mGLUT1) which in turn, improve their therapeutic potential to be loaded with anti-inflammatory drugs using glucose-coated gold nanoparticles (GNPs). Finally, we show that EVs derived from plasma of RA patients overexpresses αvβ3 integrin and taken up by LPS/TNF-α stimulated macrophages. These results suggest that Sema4B is involved in inflammatory processes observed in the RA synovium and might be a potential therapeutic target in the treatment of RA.

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AB0076

SEMAPHORIN4B IS UPREGULATED IN RHEUMATOID ARTHRITIS PATIENTS AND INDUCES EXPRESSION OF INFLAMMATORY MEDIATORS BY MACROPHAGES AND FIBROBLAST-LIKE SYNOVIOCYTES

Keywords: Rheumatoid arthritis, Cytokines and chemokines, Synovium

Background: Several studies have shown that different semaphorin family members are involved in the pathogenesis of rheumatoid arthritis (RA). On one hand, our group has demonstrated that Semaphorin 3B and 3F are reduced in RA patients and play a protective role. On the other hand, Sema4A and Sema4D are increased in RA patients and are associated with inflammatory processes (Garcia, 2019; Igea, 2022).

Objectives: The aim of this study is to determine the role of Sema4B in the pathogenesis of RA.

Methods: Gene expression of Sema4B was obtained from the gene expression array available in Gene Expression Omnibus-NCBI (GSE77298). Fibroblasts-like synoviocytes from RA patients (RA-FLS) (n=8) were stimulated 4 and 24 h with Sema4B (200ng/mL), TNF (10ng/mL) or the combination of both. Peripheral blood mononocytes from RA patients (n=12) were differentiated into M1 macrophages by culturing in the presence of IFN-γ (10 ng/ml) for 6 days. Afterwards, macrophages were stimulated 24 h with Sema4B (200ng/mL), LPS (10ng/mL) or the combination of both. The expression of inflammatory mediators was determined by quantitative PCR (qPCR) and ELISA. Viability and migration of FLS were determined using calcine assays and wound closure assays, respectively.

Results: Sema4B expression was significantly higher in the synovial tissue and FLS of RA patients compared to healthy controls (HC) and osteoarthritis patients (OA), respectively. A significantly higher expression of SEMA4B in the synovium and FLS of RA patients compared to, respectively, was found. Interestingly, TNF stimulation induced the expression of SEMA4B by RA-FLS. Functional studies showed that Sema4B did not affect the viability of FLS but increased their migratory capacity. Moreover, Sema4B alone did not induce the expression of inflammatory mediators (data non shown), but significantly enhanced the TNF-induced expression of IL6, IL8, TNF, CCL2 and MMP3 (Figure 1A) and the secretion of the TNF. Finally, Sema4B alone did not modulate the expression of inflammatory mediators in macrophages, but significantly enhanced the LPS-mediated expression of TNF, CCL2, and MMP1 (Figure 1B), as well as the TNF protein secretion.

Conclusion: Our data demonstrate that, in an inflammatory context, Sema4B induces FLS migration and the production of inflammatory mediators by FLS and macrophages. These results suggest that Sema4B is involved in inflammatory processes observed in the RA synovium and might be a potential therapeutic target in the treatment of RA.

REFERENCES:

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AB0077

EARLY ARTHRITIS: IS JAK-STAT SIGNALING KEY TO DISEASE PROGRESSION?

Keywords: Innate immunity, Targeted synthetic drugs, Inflammatory arthritis

Background: Janus kinase inhibitors (JAKi) are a new therapeutic class approved for the treatment of chronic arthritis. JAKi suppress the activity of STAT tyrosine kinases, interfering with the signaling pathway which is critical for immune cell proliferation, survival and differentiation. Our group has demonstrated that early treatment with a JAKi, in animal models, abrogates disease and prevent bone damage. We hypothesize that JAK-STAT pathway is key to chronic arthritis onset and its early inhibition might have a major effect on disease control.
THEAFLAVIN ALLEVIATES COLLAGEN-INDUCED ARTHRITIS IN MICE BY DECREASING REACTIVE OXYGEN SPECIES AND PRO-INFLAMMATORY CYTOKINES

**Keywords:** Rheumatoid arthritis

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**Background:** An autoimmune disease that causes inflammation and bone and cartilage deterioration is rheumatoid arthritis (RA). In the pathogenesis of RA, oxidative stress and pro-inflammatory cytokines are important factors. The main polyphenol in black tea, theaflavins (TFs), has been used medically to treat a variety of inflammatory illnesses by reducing inflammation and reactive oxygen species (ROS).

**Objectives:** The medications available to treat RA have a variety of side effects. The current study was designed to assess the anti-arthritis properties of theaflavin in a mouse collagen-induced arthritis model.

**Methods:** In order to induce arthritis in DBA/1 mice, type II collagen was administered intradermally. From days 21 through days 42, different doses of theaflavin (50 mg/kg/day) were orally administered. To determine the effect of theaflavin on collagen-induced arthritis, histological analyses were conducted. In addition, the generation of reactive oxygen species (ROS), nitric oxide, and the activities of enzymatic antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase, and glutathione reductase) in the joint homogenate of mice were examined. The levels of TNFα, IL-6, and IL-1β were also measured by ELISA to detect inflammation.

**Results:** Our results showed anti-oxidant and anti-inflammatory effects of theaflavin in arthritic mice. Histopathological studies corroborated the anti-arthritis properties of theaflavin. The compound was found to be effective in lowering ROS and nitric oxide levels while increasing enzymatic antioxidant activities. Theaflavin therapy also reduced TNFα, IL-6, and IL-1β levels.

**Conclusion:** In mice with arthritis, theaflavin was successful in reducing inflammation and oxidative stress. These results suggest that theaflavin may be used in conjunction with other treatments to manage RA.

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Disclosure of Interests: None Declared.

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**AB0080**

IMBALANCE OF MONOCYTE/MACROPHAGE POLARIZATION IN PERIPHERAL BLOOD AND SYNOVIAL FLUID OF RHEUMATOID ARTHRITIS PATIENTS

**Keywords:** Innate immunity, Rheumatoid arthritis

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**Background:** Macrophages strongly contribute to the pathogenesis of rheumatoid arthritis (RA), initiating the inflammatory response, the join damage, but also may promote the resolution of inflammation and the restoration of tissue immune-homeostasis [1,2]. This seems to be related to an unbalanced immunological response mediated by macrophages through their polarization into “classically” and “alternatively” activated phenotypes (M1 or M2) [3,4]. However, little is known about the M1 and M2 phenotype of their circulating precursors (monocytes) in the peripheral blood (PB) and the synovial fluid (SF) of RA patients.

**Objectives:** To characterise the polarization status (M1 and M2) of PB and SF monocytes of RA patients together with their distribution in the monocyte subsets by flow cytometry (FC).

**Methods:** Nineteen RA patients not yet treated with biological DMARDs (mean age 62±14 years), who fulfilled the 2010 ACR/EULAR classification criteria for RA and treated in accordance with EULAR recommendation, as well as 19 age-matched healthy subjects (HSs) were enrolled after signed informed consent.