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 may be 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 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/synovia-specific homing receptors (e.g. vWf3 integrin), derived from blood of diseased arthritic mice (Collagen antibody-induced arthritis model), can migrate toward the inflamed synovia, using in vivo imaging system (IVIS). Moreover, we show that these EVs strongly express 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 vWf3 integrin and taken up by LPS/TNFα-induced activated human synovial cell line in vitro.

Conclusion: Overall, we show the potential of autologous circulating EVs of RA patients to serve as natural nano-carrier for current FDA-approved drugs. We believe that this strategy will increase the specificity and efficiency of current treatment, therefore it will reduce side effects and will improve the quality of life of RA patients and potentially other autoimmune disease patients.

REFERENCES: NIL.

Disclosure of Interests: None Declared.

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AB0077 SEMAPHORIN4B IS UPRREGULATED IN RHEUMATOID ARTHRITIS PATIENTS AND INDUCES EXPRESSION OF INFLAMMATORY MEDIATORS BY MACROPHAGES AND FIBROBLAST-LIKE SYNOVIOCYTES

Keywords: Rheumatoid arthritis, Cytokines and chemokines, Synovium

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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, our group has demonstrated that (Semaphorin 4B and 4D) are increased in RA patients and are associated with inflammatory processes (Garica, 2019; Igea, 2022).

Objectives: The aim of this study is to determine the role of Semaphorin 4B in the pathogenesis of RA.

Methods: Gene expression of Semaphorin 4B 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 monocytes from RA patients (n=12) were differentiated into M1 macrophages by culturing in the presence of IFNγ (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 calcein assays and wound closure assays, respectively.

Results: Semaphorin 4B 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 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 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:

Disclosure of Interests: All patients involved in this study.

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AB0078 EARLY ARTHRITIS: IS JAK-STAT SIGNALING KEY TO DISEASE PROGRESSION?

Keywords: Innate immunity, Targeted synthetic drugs, Inflammatory arthritides

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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.

Figure 1. Semaphorin 4B enhances pro-inflammatory activity in FLS (n=6) and macrophages (n=10) of RA patients. (A) Significative increment of the genetic expression of pro-inflammatory mediators in RA-FLS stimulated with Sema4B (200ng/mL), TNF (10ng/mL) and their combination for 24 hours. (B) Significant increase of the genetic expression of pro-inflammatory mediators in M1 macrophages. Macrophages differentiated from monocytes of RA patients during 6 days (IFNγ 10ng/mL) and stimulated with Sema4B (200ng/mL), LPS (10ng/mL) and their combination for 24 hours. Symbols represent individual patients; bars show the mean ± SEM. *P < 0.05.

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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