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EFFECT OF MACROPHAGE MIGRATION INHIBITORY FACTOR ON HUMAN MACROPHAGES FROM ARTHRITIS PATIENTS

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Career situation of first and presenting author Post-doctoral fellow.

Introduction Macrophage migration inhibitory factor (MIF) is a key regulator of pro-inflammatory cytokines and has been implicated in angiogenesis and pathogenesis of several diseases such as rheumatoid arthritis (RA). Macrophages are considered to be one of the key players in the hyperplastic synovial tissue that invades and degrades adjacent cartilage and bone in patients with inflammatory arthritis.

Objectives In this study a comparative analysis was performed to examine the expression of MIF, and the effect it has on the macrophage polarisation and on the angiogenic and inflammatory mechanisms of macrophages in patients with RA, Psoriatic Arthritis (PsA), Osteoarthritis (OA) and in Arthralgia patients.

Methods PBMCs (Peripheral Blood Mononuclear Cells) were isolated from healthy donors, and patients with OA, RA, PsA and Arthralgia. Primary macrophages (Mfs) were subsequently differentiated and polarised from circulating CD14+ monocytes into M1 and M2 phenotypes. The levels of MIF expression in PBMC, Mf and Synovial tissue was evaluated by real-time-PCR (RT-PCR) and Immunohistochemistry (IHC). The effect of MIF on polarisation of Mfs was investigated by examining M1 and M2 Mf specific markers by RT-PCR and Flow Cytometry. Polarised Mf supernatants were harvested and assayed for soluble MIF by ELISA. The effect of MIF on angiogenic and inflammatory markers (MCP-1, IL-6, IL-8, Ang-2, VEGF, Hif1a, PDGF-B, bFGF, RANTES and ICAM-1) of polarised Mfs was investigated by Real-PCR, Western blot and ELISA.

Results MIF expression was significantly increased in RA tissue compared to OA and PsA. In contrast MIF expression in RA PBMCs was significantly decreased when compared to HC, Arthralgia, and PsA. RA tissue biopsies demonstrated significantly higher MIF expression when compared to PsA, OA, and Arthralgia. In polarised macrophages MIF expression was found to be increased in RA and PsA compared to healthy controls. Addition of rhMIF activated pro-inflammatory and angiogenic responses in unpolarised and polarised HC Mfs with increases in gene expression levels of IL-1 β , IL-6, MCP-1, ICAM-1, Hey-1, VEGF and Hif1a. Soluble IL-6 expression was also elevated in M0 macrophages.

Conclusions MIF may have a key role in promoting pathogenesis of RA and has a good potential as a therapeutic for RA.

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POTENTIAL ROLE FOR THE CHEMOKINE CCL22 IN THE DEVELOPMENT AND EARLY PROGRESSION OF RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Young investigator.

Introduction CCL17 and CCL22 are chemokines that bind to the receptor CCR4, which is expressed on various immune cells as well as on neurons. CCL17 has been shown to mediate the pro-inflammatory and algogenic actions of GM-CSF in murine arthritis models¹ and CCL22 could activate nociceptive neurons in cell culture² or induce hyperthermia by acting on the hypothalamus.³ Our previous studies have indicated that chemokine production by osteoclasts (OCs) might contribute to bone damage and arthralgia in the presence of anti-citrullinated protein antibodies.^{4, 5}

Objectives We analyzed the expression and potential roles of CCL17 and CCL22 during rheumatoid arthritis (RA).

Methods We compared CCL17 and CCL22 levels in the sera of individuals at risk of developing RA, in patients at early stages of RA and in healthy controls. We also studied the production of these molecules in OC cultures. We analyzed whether CCL22 can induce arthralgia or affect OC development.

Results Serum levels of CCL22 were elevated in individuals at risk of developing RA and in early untreated RA, when compared to healthy controls. On the contrary, CCL17 levels showed no significant difference between the studied cohorts. In the group of RA patients, higher CCL22 concentrations were associated with smoking. In OC cultures CCL22 production was triggered by M-CSF or GM-CSF and CCL22 levels correlated with both of these cytokines in the synovial fluid of RA patients. CCL22 induced arthralgia when injected into the ankle joints of mice and it stimulated OC differentiation in cell culture.

Conclusions The early increase of CCL22 might contribute to the development of RA, potentially by inducing pain and osteoclastogenesis. Inflammatory cytokines, like GM-CSF and M-CSF, and also by environmental triggers such as smoking can contribute to the increase of CCL22.

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