Rheumatoid arthritis—new therapeutic approach suppresses joint inflammation

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Rheumatoid arthritis (RA) is a chronic condition characterised by uncontrolled inflammation in the joints. It involves several types of immune cells, macrophages playing a particularly crucial role. Working as part of an international collaboration, researchers from MedUni Vienna's Center for Pathophysiology, Infectiology and Immunology have now discovered and characterised a new subgroup of macrophages, which can greatly suppress this inflammation. In combination with the conventional anti-inflammatory drug methotrexate, this could offer a completely new treatment option in the future. The study has now been published in leading journal *Frontiers in Immunology*.

The study by Anna Ohradanova-Repic and colleagues from MedUni Vienna's Institute of Hygiene and Applied Immunology, Center for Pathophysiology, Infectiology and Immunology, which was conducted in collaboration with the Cochin Institute in Paris (France), Kagoshima University (Japan) and Minho University (Portugal), shows that not only pro-inflammatory macrophages (known as M1) are present in the joints of those with rheumatoid arthritis, but also a new population of anti-inflammatory macrophages, which inhibit joint inflammation, when stimulated to do so. These new macrophages have both M1 and M2 characteristics. M2 macrophages are responsible for damping down and controlling inflammation and are often hijacked and bred by tumours to protect them from being destroyed by the immune system.

Ohradanova-Repic explains: "Activated macrophages, which carry a specific marker called folate receptor beta (FR) on their surface, have long been detected in RA joints and were thought to be pro-inflammatory. However, since these macrophages have also been discovered in tumours, we suspect that their role in rheumatoid arthritis could be different, namely positive, since tumour macrophages have an anti-inflammatory effect."

Adenosine molecule as driver of switchover from M1 to M2

The researchers demonstrated that FR-positive macrophages react in an unexpected way to danger signals such as pathogens: they were not pro-inflammatory M1, but switched into the anti-inflammatory M2 state and greatly suppressed the immune system, especially the T-cells. The underlying mechanism: danger signals trigger a chain of molecular events in FR-positive macrophages, which results in the production of the immunosuppressant molecule adenosine, which suppresses inflammation.

The scientists led by lead investigator Hannes Stockinger from MedUni Vienna also discovered that the conventional anti-inflammatory drug methotrexate promotes adenosine production in these macrophages. In order to transport methotrexate directly to these macrophages and minimise its side-effects, the researchers developed a new methotrexate formulation, which increases adenosine production by these macrophages and prevents inflammation in an arthritis mouse model.

Says Stockinger: "Thus this study highlights the control of adenosine production by specific macrophage subgroups as an attractive target for therapeutic measures in immune-mediated disorders." The study was financed at the Medical University of Vienna by the EU FP7 and Horizon 2020 projects NANOFOL and FOLSMART.

More information: Anna Ohradanova-Repic et al. Extracellular Purine Metabolism Is the Switchboard of Immunosuppressive Macrophages and a Novel Target to Treat Diseases With Macrophage Imbalances, *Frontiers in Immunology* (2018). DOI: 10.3389/fimmu.2018.00852

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