Background: Reactive oxygen species accumulation and iron overload are involved in the pathogenesis of rheumatoid arthritis (RA). Ferroptosis, as a non-apoptotic form of programmed cell death, characteristically depends on iron and lipid peroxidation. However, the role of ferroptosis in RA has not been explored.

Objectives: To explore the role of ferroptosis in immune imbalance of rheumatoid arthritis.

Methods: Iron content in synovial fluid was determined by colorimetry. Lipid peroxidation was assessed by flow cytometry and immunofluorescence. MDA and GSH were used as markers to assess ferroptosis. K/BxN spontaneous arthritis mice and serum-induced arthritis mice were used as in vivo animal models of ferroptosis.

Results: Iron overload and hyperlipid peroxidation of mononuclear-macrophages were found in the synovial fluid of RA patients. Lipoxygenase-1, the specific inhibitor of ferroptosis, alleviated the progression of arthritis mice model by increasing M2-like macrophage numbers. Mechanistically, iron overload in arthritis lesion induced anti-inflammatory macrophage ferroptosis by promoting glutathione peroxidase 4 (GPX4, a classical anti-ferroptosis molecule) to undergo P62-dependent autophagy degradation.

Conclusion: Our results provide compelling evidence that macrophages ferroptosis plays a major role in RA. M2-like macrophages are more sensitive to ferroptosis than M1-like macrophages under iron overload circulation. This finding heavily contributes to the immune imbalance of rheumatoid arthritis.

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SITE SPECIFICITY OF RHEUMATOID ARTHRITIS INFLAMMATION: A SECONDARY ANALYSIS OF BIOPSYs FROM RADIAL AND Ulnar ASPECTS OF MCP JOINTs

Background: Ulnar drift is a common complication of Rheumatoid Arthritis (RA). There is no clear consensus regarding the etiology of the hand deformity. Observations from corrective hand surgery and other studies have noted more pronounced inflammation in the radial site of the MCP-joints (3,4). This could partly explain the pathophysiology behind the ulnar deviation.

Objectives: To determine if there is more pronounced inflammation, measured by increased CD-68 expression (5) and Krenn-synovitis score (6), at the radial side of the MCP joints compared to the ulnar side, in patients with verified RA.

Methods: We included RA patients from a previous study who had biopsies taken from the most affected joints based on clinical examination and ultrasound (7). Twenty-nine PIP-, MCP- and wrist-joints were biopsied. Biopsies from the MCP-joints were taken from the dorso-ulnar and dorso-radial concavity. Inflammation was graded by the Krenn-synovitis score (0-9) and the density of CD-68-positive cells (%). The difference between radial and ulnar joint inflammation was calculated by paired t-test. P-value <0.05 was considered statistically significant.

Results: In 8 patients biopsies were taken from both the ulnar and the radial site of the same MCP-joint. The mean difference in inflammation on the radial and ulnar site of MCP-joints was based on differences in CD-68 density: 0.67% (95%-CI -4.77 to 6.10; P = 0.77) (Figure 1) and Krenn-score: 0.83 (95%-CI -1.31 to 2.98; P = 0.36), respectively.

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Figure 1. Paired data on CD-68 percentage in radial and ulnar sites.

Conclusion: There was no difference in concentration of inflammatory cells or overall synovial pathology between the radial and ulnar site of MCP-joints in RA patients. The impression of a more pronounced inflamed synovium on the radial site of MCP joints, as observed during surgery, does not seem to arise from an immunological preference, but rather to be linked to a larger synovial volume.

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