Rheumatoid arthritis - aetiology, pathogenesis and animal models

L-ARGININE SUPPLEMENTATION AMELIORATES BONE EROSION IN RHEUMATOID ARTHRITIS THROUGH INHIBITION OF RANKL/RANK/Traf6 PATHWAY AND REPROGRAMMING OSTEOCLAST METABOLISM

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Background: L-arginine is of great importance in numerous biological procedures in human body, e.g. it participates in the urea cycle for detoxification of ammonia, and functions as a modulator in immune responses (1). Our previous investigation demonstrated that treatment with L-arginine reduced clinical symptoms, bone erosion and osteoclast numbers in serum-induced arthritis (K/BxN) (2). In addition, a decreased concentration of L-arginine has been observed in the serum of rheumatoid arthritis (RA) patients. Altogether, it is suggesting that L-arginine supplementation might be a potential treatment against RA.

Objectives: This study aims to investigate the treatment role of L-arginine supplementation in murine arthritis models. The project also plans to delineate the metabolic action of L-arginine supplementation during osteoclast differentiation in the presence of an inflammatory milieu.

Methods: Three murine arthritis models (serum-induced arthritis (K/BxN) model, collagen-induced arthritis model and hTNFtg mice model) were applied in the presence or not of oral L-arginine supplementation. MicroCT and histomorphometry analyses were performed to quantify bone erosion and numbers of osteoclasts. In addition, in vitro osteoclastogenesis were performed in the presence of various amounts of L-arginine with or without treatment with 40ng/ml TNFα. OC differentiation was characterized by TRAP staining. Resorption activity was assessed by pit formation assay. Osteoclast markers and metabolic genes were determined with quantitative real-time PCR analysis and western blot. Dihydrorhodamine 123 staining was used to determine the level of intracellular ROS. Seahorse analyses and mass spectrometry metabolites analyses were conducted to address the metabolic condition.

Results: Arthritis severities were reduced after L-arginine supplementation in arthritis models. Moreover, an amelioration of bone erosion and reduced osteoclast numbers were observed in arthritic mice treated with L-arginine. In vitro treatment of L-arginine inhibited osteoclastogenesis, especially in the late phase of the differentiation, even with exposure to TNFα stimulation. The L-arginine induced osteoclast differentiation inhibition is likely due to an alteration in the RANKL/RANK/Traf6 pathway. L-arginine also boosted the intracellular production of ATP and ROS, promoting mitochondria-driven oxidative phosphorylations (OXPHOS), leading to the failure of activation and even death of the osteoclasts.

Conclusion: These data strongly suggested that L-Arginine ameliorates bone erosion in RA through the inhibition of RANKL/RANK/Traf6 pathway as well as reprogramming of the cellular metabolism during osteoclastogenesis. The immunometabolism action of L-Arginine might therefore help to reduce joint inflammation and destruction in RA.

References:

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