L-ARGININE REPROGRAMS OSTEOCLAST PURINE METABOLISM AMELIORATING BONE LOSS IN RHEUMATOID ARTHRITIS

S. Cao1,2, R. Song1,2, X. Meng1, K. Kacher1, M. Fuchs3, X. Meng1, Y. Lu1, V. Taudte1, M. Kunz1, U. Schloetzer-Schrehardt1, U. Schleicher1, X. Chen1, G. Schett1, A. Bozec1.

1Universitätsklinikum Erlangen, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Department of Internal Medicine 3–Rheumatology and Immunology Erlangen, Germany; 2Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Department of Rheumatology, Shanghai, China; 3Friedrich-Alexander University of Erlangen-Nürnberg, Chair of Medical Informatics, Erlangen, Germany; 4Friedrich-Alexander University of Erlangen-Nürnberg, Institute of Experimental and Clinical Pharmacology and Toxicology, Erlangen, Germany; 5Universitätsklinikum Erlangen, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Department of Ophthalmology, Erlangen, Germany; 6Universitätsklinikum Erlangen, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Erlangen, Germany

Background: Bone erosion is a clinical feature of rheumatoid arthritis related to disease severity and poor functional prognosis. Excessive osteoclast differentiation and insufficient osteoblast function are the main reasons for the erosive process in RA. Our previous investigation indicated that L-arginine supplementation not only diminished arthritic inflammation in the serum-induced arthritis (K/BxN) model but also decreased inflammatory joints osteoclast numbers (1).

Objectives: In the present study, we aim to investigate the metabolic action of L-arginine supplementation in RA, especially on periarticular bone erosion and systemic bone loss. We plan to depict the metabolic features of TNFα induced inflammatory osteoclasts after in vitro L-arginine supplementation.

Methods: Three murine arthritis models (serum-induced arthritis (K/BxN) model, collagen-induced arthritis model, and TNFα mice model) were analysed in this study. L-arginine was supplemented within the drinking water after the induction of arthritis. Parameters included bone mass (spine) and periarticular skeleton (tibia) from the respective groups were quantified by μCT. HE and TRAP staining were performed to address further the erosion area and osteoclast numbers in periarticular sites. In vitro osteoclast differentiation was conducted with or without L-arginine treatment, in the presence or not of TNFα activation. Seahorse and SCENITH analyses were adopted to delineate the metabolic features.

Results: L-arginine supplementation was associated with downregulation of TNFα and IL-1β expression. Seahorse and SCENITH analyses indicated TNFα promoted glycolysis while blocking mitochondria-driven oxidative phosphorylations (OXPHOS) in pre-osteoclasts. Meanwhile, JC-1 staining and TEM images also showed that TNFα decreased mitochondria membrane potential and prompted damage of mitochondria. Surprisingly, L-arginine rescued the TNFα inhibition of OXPHOS while promoting ATP production. RNA-seq and MS data confirmed the boost of OXPHOS after L-arginine treatment under TNFα activation. To interfere with OXPHOS, L-arginine inhibited cJun thus altered arginase-1 and arginase-2 expression. Moreover, the increased ATP in L-arginine treated cells facilitated mitophagy, which promoted mitochondria trafficking and heterotypic fusion, contributing to the inhibition of osteoclastogenesis. Increasing Adenosine deaminase (ADA) is essential for the production of inosine and hypoxanthine due to the decreased inhibitory regulation of the transcription factor c-Jun.

Conclusion: These data strongly demonstrated that L-arginine ameliorates bone erosion in RA through metabolic reprogramming and perturbation of purine metabolism in osteoclasts. L-arginine might therefore benefit RA therapy by reducing joint inflammation and also ameliorating bone destruction.

REFERENCE: