Functional genomics and epigenetics in osteoarthritis: evidence for metabolic deregulation

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of chronic pain and physical disability. It is characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, including the synovium, meniscus (in the knee), periarticular ligaments and subchondral bone. Despite its high prevalence there is no effective method for preventing or retarding the progression of the disease. The main reason for the failures in disease modifying drugs development is the lack of incorporation of the different phenotypes that exist in OA.

It is now established that OA is a heterogeneous disease with a variety of pathophysiologic drivers leading to multiple phenotypes. Among the different OA phenotypes are the inflammatory, cartilage-driven, bone-driven, traumatic/injury driven, aging and oxidative stress-related and the most recently identified the metabolic phenotype. The goal of our research was to identify novel biomarkers for prediction of disease progression and drug development and therapeutic targets targeting the metabolic phenotype.

We demonstrated that OA chondrocytes have impaired expression of *LXR-α, LXR-β, ABCA1 and ApoA*1, genes that are involved in the reverse cholesterol transport (RCT) system and that chondrocytes are capable of internalizing lipids demonstrating that regulation of cellular cholesterol levels is critical for OA pathogenesis. We also showed that Sterol Response Element Binding Protien-2 (*SREBP*-2), a lipid metabolism gene, is involved in OA pathogenesis and provided novel evidence for its TGF-β induced activation through the ITGAV/PI3K/Akt pathway. Furthermore, we demonstrated that miR-33a, which is produced by *SREBP-2*, is a dual regulator of cholesterol synthesis through the TGF-β 1/Akt/SREBP-2 pathway and also of cholesterol efflux-related genes (*ABCA1* and *ApoA1)* in OA chondrocytes. In addition, using a high resolution (8 X 60K) miRNA array platform interrogating 2,549 miRNAs we identified three circulating miRNAs in serum, namely hsa-miR-140, hsa-miR-671, hsa-miR-33 which were significantly down-regulated in OA patient's serum compared to healthy controls. Hsa-miR-33 expression was also tested in articular cartilage samples of the same OA patients and controls. *In silico* analysis predicted that all 3 miRNAs are involved in regulating metabolic processes. Finally, using an animal (rabbit) model of OA, established by Anterior Cruciate Ligament Transection (ACLT), we injected intra-articularly, miRNA-33a-mimic and found significant histological and molecular improvement in the joints with the miRNA-33a-mimic injection compared to the non-injected ones.

In conclusion, we provide evidence, through functional genomics and epigenetics, on the involvement of lipid metabolism in osteoarthritis. We suggest that hsa-miR-33a regulates cholesterol synthesis (*SREBP2*) and cholesterol efflux-related (*ABCA1, ApoA*1) genes and that is could serve as a potential biomarker for the evaluation of osteoarthritis risk and progression and also as a potential novel target for the amelioration of the OA phenotype.

Aspasia Tsezou
Professor Medical Genetics
University of Thessaly, Faculty of Medicine
Larissa, Greece
email: atsezou@gmail.com
cel: +30 6932 913193