Metabolite Regulation of Subcellular Organelle Function to Chondrocyte Activity and Osteoarthritis Development

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Chondrocyte dysfunction, like senescence, apoptosis, extracellular matrix underproduction, and proteinase overproduction, deteriorates cartilage microenvironment integrity to accelerate the development of osteoarthritis (OA). A plethora of extracellular adverse stresses dysregulate intracellular homeostasis, disrupt survival and metabolism of chondrocytes. Of subcellular organelle, mitochondria are indispensable in ATP production to maintain cellular activity. Autophagy is important to get rid of unwanted organelle or macromolecules, sustaining intracellular homeostasis in physiological and pathological contexts. A plethora of metabolites derived from gut microbiota, skeletal muscle, and central nerve systems, etc., directly or indirectly affect cell fate and metabolism. We uncovered that chronic high fat diet induced gut dysbiosis and dysregulated microorganism-derived metabolite production together with bone mass loss and knee OA histopathology. The metabolite repressed endoplasmic reticulum and mitochondrial function, upregulating apoptotic reaction in chondrocytes. In addition, muscle-derived Irisin, a soluble 112-amino acid, promoted mitochondrial biogenesis, which upregulated glycosaminoglycan production. This molecule also reversed mitochondrial membrane potential and dynamics (fusion and fission), as well as improved autophagic clearance of dysfunctional mitochondria in inflamed chondrocytes. Intra-articular injection of Irisin delayed the development destabilized medial meniscus-mediated OA development and alleviated joint pain, irregular gait pattern and mobility of the injured legs. Taken together, this speech sheds new light onto metabolite actions to organelle function in chondrocytes and highlights a new remedial potential with metabolites for protecting articular cartilage from OA development.