Mitochondria and Mitophagy: Biosensors for cartilage degradation and Osteoarthritis.

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Osteoarthritis (OA) is the most prevalent musculoskeletal disease and a leading cause of disability worldwide. OA mostly affects the population aged over 50 years and it is estimated that the population with OA will double in the next 30 years. The pathogenesis of OA is a complex process that involves the entire joint. The pathological cascade of events in OA occur at the molecular, cellular and tissue level and not only involve cartilage degradation but also sub-chondral sclerosis, synovial inflammation as well as damage to other joint structures such as ligaments and menisci, causing pain and loss of articular function (1). Although the cartilage degradation is not the only event responsible for joint degradation its role in OA pathogenesis continuous to be relevant. One factor that contributes to the pathological cascades is the imbalance between apoptosis and autophagy in the articular cartilage (1).

Mitochondria are currently in the focus of biomedical research due to their role in aging and in the development of human pathologies (2). Mitochondria are the organelles that convert the nutritional molecules into adenosine triphosphate (ATP), generating most of the energy necessary for the cell. Mitochondrial dysfunction causes a series of metabolic alterations that lead to an increase in the production of reactive oxygen species (ROS) and decreasing ATP and oxygen consumption. Mitochondrial dysfunction causes also an inflammatory response inducing synthesis of cytokines and MMPs. Mitochondria contain their own genetic material, mtDNA; mtDNA has a high mutation rate, due to the absence of an effective system of repair and its proximity to the main source of ROS production in the cell, the electron transport chain.

Increasing evidence suggests that mitochondria are involved in the pathogenesis of OA (3). Analyses of mitochondrial function in OA chondrocytes reveal decreased activity of the mitochondrial respiratory complexes II and III as well as increased mitochondrial mass, compared to healthy chondrocytes. Mitochondrial dysfunction can contribute to cartilage degeneration in OA. Increased ROS production, impaired anabolic and growth responses of chondrocytes, excessive and reduced chondrocyte apoptosis and autophagy respectively, and enhanced inflammatory responses are particularly important. Compared to normal cartilage, OA chondrocytes fail to generate energy and mitochondrial biogenesis is altered. All the data suggest that mitochondria and mitochondrial function needs to be regulated in order to prevent the generation of high levels of ROS and oxidative stress.

Autophagy, which is activated under hypoxic and energy stress to provide energy for the cell, is a key regulator of cellular homeostasis through the removal of damaged macromolecules and organelles, including mitochondria (4). Mitophagy is the elimination of depolarized/damaged mitochondria. Pharmacological activation of autophagy in chondrocytes significantly protected against mitochondrial dysfunction suggesting that mitophagy may function to eliminate damage/dysfunctional mitochondria in chondrocytes and prevent oxidative stress (4). Studies in human chondrocytes showed that activation of autophagy is critical in protecting against mitochondrial dysfunction (5). Moreover, the mammalian target of rapamycin inhibitor DNA damage-inducible transcript 4 protein (DDIT4, also known as REDD1) is a key mediator of cartilage homeostasis through the regulation of autophagy and mitochondrial biogenesis; expression of DDIT4 is decreased in OA cartilage, and deficiency of this protein exacerbates the severity of injury-induced OA (6).

In this issue of Osteoarthritis and Cartilage, Ansari MY et al. suggest that Parkin-mediated mitophagy is an important mechanism to limit ROS production and improve OA chondrocyte survival under pathological conditions (7). Parkin is an E3 ubiquitin ligase; it is selectively recruited to dysfunctional mitochondria with low membrane potential. After recruitment, Parkin mediates the engulfment of mitochondria by autophagosomes and the selective elimination of impaired mitochondria. Authors propose that increased expression of Parkin might be involved in the clearance of damaged mitochondria and indeed OA chondrocytes with depleted Parkin expression showed increased production of ROS, accumulation of dysfunctional mitochondria, and apoptosis. These authors speculate that loss of Parkin function could contribute directly to the pathogenesis of OA.

The interaction between Parkin and mitochondrial NAD-dependent protein deacetylase sirtuin 3 (SIRT-3) is a very interesting aspect to understand the relevance of the results reported by Ansary MY et al. SIRT-3, the chief deacetylase mitochondrial protein, has been shown to mediate age-related changes in cartilage redox regulation; this action protected against early-stage OA in rats and SIRT-3 has been described as a metabolic sensor that responds to changes in the energetic state of the cell through oxidized nicotinamide adenine dinucleotide, to regulate mitochondrial acetylation and protect against mitochondrial damage. SIRT-3 activates mitophagy and its deficiency impairs mitophagy by increasing acetylation of Pink/Parkin and decreasing Parkin expression (8) (Figure 1).

Mitochondrial dysfunction has also been associated with a disbalance between ROS production and expression of superoxide dismutase 2 (SOD2), the major mitochondrial antioxidant protein. Downregulation of SOD2 has been reported in OA chondrocytes (9). Levels of this enzyme are decreased in the superficial layer of OA cartilage and markedly down-regulated in end-stage OA cartilage. Both SOD2 and SIRT-3 activity decreased with age in cartilage and treatment with SIRT-3 increased SOD2 activity suggesting that SIRT-3 could mediate age-related changes in cartilage redox regulation and protect against OA by rescuing acetylation-dependent inhibition of SOD2 activity (10).

The proposed theory for the participation of mitochondria in OA suggests that dysfunction of the mitochondrial respiratory complex leads to increased production of ROS, resulting in mtDNA damage followed by mutations that compromise mitochondrial protein function and further increase production of ROS and reactive nitrogen species (RNS). mtDNA shows very high mutation and sequence evolution rates. The accumulated mtDNA mutations throughout evolution persist today as high frequency continent-specific mtDNA polymorphisms and are called haplogroups (11, 12). Specific mtDNA haplogroups have been consistently linked with a wide spectrum of diseases, including OA. Evidence has accumulated from a series of studies for an association between mtDNA haplogroups and prevalence, incidence and progression of OA in different cohorts of patients (13, 14). In terms of a direct relationship between mtDNA damage and haplogroups, greater damage could be expected in those haplogroups associated with increased ROS production. mtDNA haplogroups H and J have been found to differ in the gene expression and activity of SIRT-3 under simulated mild oxidative stress conditions using transmitochondrial cybrids, where H cybrids showed higher SIRT-3 activity and expression than J cybrids (15). These data suggest that mtDNA mutations and variants could modulate mitophagy through their capacity to regulate different nuclear target genes such as SIRT-3 and NAD-dependent protein deacetylase sirtuin-1 (SIRT1). SIRT1 is involved in mitochondria biogenesis inducing the expression of –peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α; the so-called master regulator of mitochondrial biogenesis) (16).

A decreased capacity for mitochondrial biogenesis in chondrocytes is linked to reduced AMP-activated protein kinase (AMPK) activity and decreased expression of SIRT1, PGC1α; TFAM (transcription factor A, mitochondrial), nuclear respiratory factor 1 (NRF1) and NRF2 (16). AMPK is a key molecule associated with metabolism in chondrocytes that regulates energy metabolism through the downstream mediators such as SIRT1 and mechanistic target of rapamycin (mTOR) (17). Activation of the AMPK–SIRT1–PGC1α pathway increases mitochondrial biogenesis in chondrocytes, limiting OA progression. Furthermore, deficiency in AMPK and SIRT1 modulates PGC1α activity, leading to reduced oxidative stress and procatabolic responses in chondrocytes from patients with OA (16).

All these results open a wide new spectrum of therapeutic approaches with the common goal of restoring mitochondrial function in chondrocytes and reducing the mitochondrial stress. Some new potential therapies could be: 1) To activate the AMPK-SIRT-3 pathway in order to induce Parkin expression and mitophagy 2) To activate the AMPK-SIRT-3 pathway in order to induce SOD2 activity a reducing Mitochondrial stress. 3) Activation of the AMPK–SIRT1–PGC1α pathway to promote mitochondrial biogenesis, 4) The development of cellular therapy using cells with harboring “good mitochondria”, or even the administration of isolated “good mitochondria” into the osteoarthritic joint.

In summary, the study of Ansary MY et al. is in line with other published results that confirm the relevant role of mitochondrial activity and function in the process of articular cartilage degradation and in the pathogenesis of OA. In particular, some molecules such as AMPK, Parkin, SIRT-1, SIRT-3 and PGC1-alpha may represent therapeutic targets for modulating mitophagy and mitochondrial biogenesis, which may represent new therapeutic alternatives in OA. It is necessary to confirm these promising results using in vivo models.

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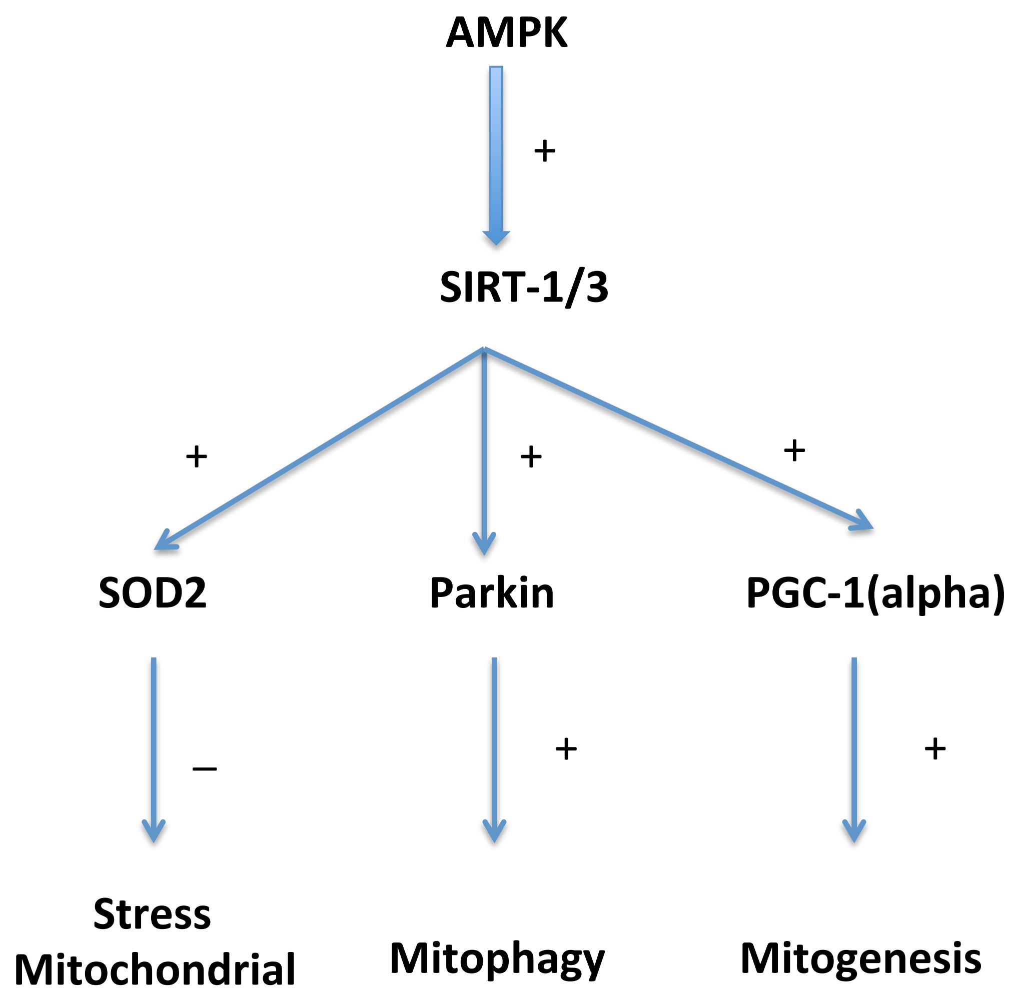
LEGEND OF FIGURE

Figure 1: AMPK-SIRT-PARKIN pathway in OA chondrocytes. Hypothetical view on the key role of AMPK-SIRT-Parkin in regulating mitochondrial function and defense against excessive ROS.

Figure 1


AMPK
+
SIRT-1/3
+
+
+
SOD2
Parkin
PGC-1(alpha)
–
+
+
Stress
Mitochondrial
Mitophagy
Mitogenesis