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Review Article

ROLE OF MITOCHONDRIA ON REGULATION OF SYNOVIOCYTES

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ABSTRACT

Synoviocytes are the intimal cells of synovium responsible for the production of synovial fluid components that posses antigen-presenting capacity and generate inflammatory mediators like cytokines for inflammation and cartilage destruction in various inflammatory joint diseases. Mitochondria are considered the powerhouse of the cell as it generates most of the energy in the form of ATP through oxidative phosphorylation to carry out different cellular functions. Besides this, mitochondria play a crucial role in cellular biogenesis, homeostasis, and autophagy to extrude born out organelles in order to maintain normal cellular activities and regulation of different metabolic pathways. Because of its important role in the maintenance of normal cellular physiology, its impairment leads the cells to pathologic states like the generation of oxidative state, altered programmed cell death phenomenon, upregulation of inflammatory mediators for the development of inflammatory joint diseases. Due to this relation, many inflammatory joint diseases and cellular aging can be overcome by maintaining normal mitochondrial function. This review article reflects on the structure and functions of synoviocytes and mitochondria, interlink between mitochondria and synoviocytes, and the role of mitochondria on activation of synovial joint inflammations due to its dysfunctions. The aim of this review article is to highlight the relationship between mitochondrial impairment and synovial damage so as to help to explore various treatment options on a molecular level.

Keywords: Synoviocytes, homeostasis, autophagy, oxidative state, inflammatory joint disease

INTRODUCTION

Synovium is the specialized thin connective tissue layer that lines the joint capsules and joint cavities. These connective tissue layers maintain the synovial joint homeostasis through secretion of lubricin and hyaluronic acid[1]. Synovium is relatively acellular with 1-2 cell thickness, functionally divided into two layers; intima (surface layer) and subintima (sub-lining layer), which are 20-40mm and 5mm thick, respectively. However, in case of inflammatory arthritis the intimal layer is relatively thickened due to abundant CD55 positive fibroblast-like cells with small amount of CD68 positive macrophages, heavy infiltration of subintimal layer with T and B lymphocytes, plasma cells, macrophages, with stromal edema, angiogenesis and increased number of cytokines production[2, 3]. The synovial subintimal layer consists of scattered blood vessels, fat cells, and fibroblasts, with very few numbers of macrophages or lymphocytes. The synoviocytes are the intimal cells of synovium believed to be responsible for the production of synovial fluid components for the lubrication of intra-articular joints and blood-synovial fluid exchanges[4]. Synoviocytes are grouped into three different regions; surface, stromal, and perivascular regions. Histological studies of synovial linings show a lack of desmosomes or tight junctions[5]. This porous structural organization facilitates the relative diffusions of nutrients into the joints, making the joint vulnerable to microbial migration, adhesion, proliferation, and accumulation of immune complexes[6]. According to Barland, in 1962, human synovial intimal cells are of two types; type A (macrophage-like synoviocytes, MLS) and type B (fibroblast-like synoviocytes, FLS)[7, 8]. The type A synoviocytes posses antigen-presenting and phagocytic activity, whereas type B synoviocytes are believed to be the proper synoviocytes that produce specialized matrix constituents like collagens, fibronectin, and hyaluronan. MLS possess a large number of Golgi apparatus and lysosomes and express surface receptors like CD14, CD16, and CD68 and participate in the removal of dead cells and microbes from the joint space[9, 10]. Similarly, FLS contains a huge proportion of rough endoplasmic reticulum, developed Golgi apparatus, a small number of vacuoles, and express common markers like collagen, vimentin, and CD90. Unlike other fibroblasts, FLS express CD55 (decay-accelerating factor, DAF), CD106 (vascular cell adhesion molecule 1, VCAM-1), uridine diphosphoglucose dehydrogenase (UDPDG) and lubricin[11-15].

Normal synoviocytes in healthy synovium are inactivated, non-proliferative, and non-invasive, whereas activated, proliferative, migratory, and reactive oxygen species (ROS) damaged synoviocytes are found in RA synovium[16].FLS in the synovial intimal membrane generate cytokines and matrix-degrading molecules that induce inflammation and proteases for cartilage destruction in an inflammatory joint disease like RA [6]. During the disease progression of inflammatory arthritis, MLS generate large amount of tumor necrosis factor-α(TNF), chemokines, interleukin(IL) 1β ,that further activates FLS to produce matrix metalloproteinases (MMP) like collagenases, gelatinases, stromelysins and inflammatory mediators like IL-6, prostaglandin(PG) E2, cyclooxygenase(COX)-2 for joint inflammation and cartilage damage[17]. FLS in an arthritic synovial joint is resistance to apoptosis, and form the hyperplastic growth and destruction of articular cartilage in RA [18, 19].

Mitochondria are the powerhouse of the cell as these generate most of the energy to carry out cellular mechanisms in the aerobic condition through oxidative phosphorylation, tricarboxylic acid(TCA) cycle, and fatty acid oxidation(FAO). Mitochondria play a leading role in cellular biogenesis, growth regulation, maintenance of calcium homeostasis, and synthesis of different biomolecules like hormones, pyrimidine, and heme[20]. Mitochondria produce adenosine triphosphate(ATP) via mitochondrial respiratory chain(MRC); thus, it is considered as a core site for reactive oxygen species(ROS) generation[21]. Excessive production of ROS target mitochondria itself in the pathological state. As mitochondrion is vital for cellular regulation, any dysfunction or damage leads to the activation of pathological mechanisms, which give rise to inflammatory arthritis.

This review not only focuses on the various functions of mitochondria on joint cells but also discusses the effect of its impairment on inducing pathological signals on synoviocytes in inflammatory joint diseases.

Physiological function of mitochondria:

Mitochondria, also known as a powerhouse of the cell, is an important organ of eukaryotes. It is phospholipid bilayer, consists of four distinct compartments; outer membrane, intermembrane space, inner membrane, and the matrix. Each compartment has different functions [22].Most of the ATP generation takes place in the mitochondrial matrix by the respiratory chain pathway. During ATP generation, the electron from NADH transferred to oxygen, causing the flush of protons in the matrix. The mitochondrial complexes I, III, and IV favors the generation of a proton gradient across the matrix [23]. The transmembrane proton gradient maintains a continuous flow of Ca2+ ion into the matrix in normal condition. In physiological stress, increased uptake of Ca2+ ion into matrix takes place to carry out oxidative phosphorylation. Excessive Ca2+ into matrix leads to disruption of the OXPHOS pathway to cause abnormal cellular signaling, mitochondrial membrane degeneration, cell-damaging, aging, neurodegenerative, and inflammatory disorders like OA and RA [24-26].

Mitochondrial reactive oxygen species (ROS) are vital for aging and cellular homeostasis. Leakage of the electron from the mitochondrial membrane combines with oxygen molecules to form superoxide, and these superoxides are dismutated by manganese superoxide dismutase enzyme (Mn-SOD) to form hydrogen peroxide, a reactive oxygen species[27]. Recent studies show that ROS generated from complex I cause oxidative stress to mitochondria and ROS derived from complex III has cell signaling function[9]. Reactive nitrogen species (RNS), powerful oxidant molecules, are produced by mitochondria through the aerobic metabolic pathway.RNS causes modulation of mitochondrial O2 consumption through regulating Ca2+ into the mitochondrial matrix. Therefore, RNS and ROS help in programmed cell death, regulation of biogenesis, and managing oxidative stress[10].

Mitochondrial DNA (mtDNA) is double-stranded and circular in nature that encodes 37 genes and 13 essential protein responsible for carrying out electron transport chain and transcription[13, 28]. mtDNA is not histone binding and contains unmethylated cytosine, so it is very prone to oxidative damage and undergo further mtDNA mutations [14]**.** Mutated mtDNA polypeptide drives an inflammatory response with the recruitment of immunological factors like cytotoxic T cells in synovial joints. Mitochondria also play a role in

cellular scavenger besides biogenesis, where it removes the defective mitochondria by mitophagy under stress conditions. Mitochondrial fusion and fission are the morphological changes of mitochondria in oxidative stress and increased metabolic energy demand [29]. Under the enzymes MFN (mitofusin) 1, 2, and OPA (optic atrophy) 1, mitochondrial fusion is carried out to fulfill high energy demand, counter the accumulation of mtDNA mutation on aging, increase cell division to carry out apoptosis and enhance biogenesis [16, 30]. Mitochondrial fission is formed by the dynamin-related protein1 (DRP1) and mitochondrial fission 1(FIS1) in decreased OXPHOS and increased aerobic glycolysis condition [30]. It carries out mitophagy, increases mtDNA mutation, and increase mitochondrial mass [16]. Mitochondrial fusion and fission are vital processes for genetic stability and to carry out mitochondrial metabolism. Mitochondria play not only an important role in metabolism reprogramming but also essential for cell apoptosis and the regulation of innate immunity against injury by causing inflammatory responses [20]. Injury releases mitochondrial damaged associated molecular patterns(DAMP) to activate and promote neutrophils, Ca2+ flux, and phosphorylation of mitogen-activated protein (MAP) kinase, thus leads to PMN migration and degranulation [31].

Relation between mitochondria and synoviocytes:

Mitochondria act as a major component of the maintenance of physiologic homeostasis due to its vital play on the regulation of cellular aging and death through apoptosis, autophagy, or cellular necrosis [32, 33]. Because of this significant function, dysfunction of mitochondria is responsible for carrying out several degenerative and inflammatory diseases

To depict interrelation between dysfunction of mitochondria on synoviocytes activation, Marta et al. used 31 healthy synovial tissues [21]. The collected healthy synovial cells were treated with oligomycin(OLI) to inhibit mitochondrial ATP synthase, interleukin-1β to induce an inflammatory response, and N-acetylcysteine to prevent activation of nuclear factor-kB (NF-kB) [34, 35]. The results showed that OLI caused mitochondrial dysfunction promotes COX-2 expression and PGE2 production on synovial cells. The synovial cells pretreated with OLI show overexpression of COX-2 and PGE2 on a low concentration of IL-1β. Furthermore, as OLI pre-incubated synoviocytes were treated with N-acetylcysteine, the level of COX-2 and PGE2 were decreased. Thus, the mitochondrial dysfunction promotes COX-2 expression causing increased production of PGE2, IL-1β, TNF-α in synoviocytes to induce inflammatory responses in inflammatory arthritis [36, 37]

Role of mitochondria on rheumatic diseases:

Mitochondrial dysfunction promotes the formation of various inflammatory mediators to cause several rheumatoid conditions like osteoarthritis or inflammatory arthritis like RA and JIA.

Osteoarthritis:

Osteoarthritis is the most common age-related degenerative disease occurring in about 15% of the old population. The increased articular cartilage degradation and mortality of chondrocytes seen in OA are associated with mechanical stress imbalance and impaired catabolic process in the joint [38]. Mitochondrial damage is responsible for calcification of joint cartilage, increase oxidative stress, activation of inflammatory

mediators, and cell death, which ultimately induce cartilage destruction [39]. The stress response in normal chondrocytes is maintained with the aid of ATP generated from the mitochondrial respiratory chain (MRC) complex. Dysfunction of mitochondria causes decreased MRC activities in complex II and III and reduced mitochondrial membrane potential (Δψm) in OA chondrocytes, which alters the rate of ATP generation and consumption and impairs the balance between chondrocyte matrix synthesis and mineralization. Inhibition of MRC complex III and V also induces the secretion of inflammatory mediators and ROS generation in chondrocytes in OA [21, 40, 41]. The inhibition of MRC complex V results in inhibition of mitochondria regulated chondrocytes autophagy and increases degradation of chondrocytes through apoptosis [42-44]. Likewise, many researchers have argued that pro-inflammatory and pro-oxidative mediators impair the mitochondrial activities and alter the mtDNA capacity to repair in OA chondrocytes [42, 45, 46]**.** Mitochondria also regulate chondrocytes survival through apoptosis and autophagy [42]**.**

Inflammatory arthritis:

Rheumatic arthritis and juvenile idiopathic arthritis are some of the cytokines mediated autoimmune inflammatory joint diseases [39]. Arthritic synoviocytes are characterized by hypoxia and NO or TNF associated inflammation in RA and JIA and are associated with decreased activity of MRC complex IV. Inhibited MRC complex IV further alters Δψm switching from electron transport chain to glycolysis. In inflammatory arthritis, ROS production due to Δψm exceeds the defense mechanism of antioxidants and causes proteins, lipids, and DNA damage [47, 48]. Excessive ROS production induces DNA damage, which results in the formation of DNA adducts like 8-oxo-7,8-dihydro-2'-deoxyguanine(8-oxo-dG) that acts as a mediator of oxidative stress driving disease progression in arthritis [49]. Oxidative damage facilitates inflammatory arthritis by expression of angiogenesis,cyclooxygenase-2, MMP9/13, and disruption of nuclear factor B(NF-kB) signals [50-52]. Angiogenesis occurs early in joint inflammation that increases the expression of chemokines and pannus formation of endothelial cells and follows the joint inflammation, synovial cartilage, and bone destruction in RA[48, 53, 54]. The dysfunction of mitochondria in inflammatory joint disease is seen due to its altered metabolism and hypoxic conditions. Normal oxygen tension in a healthy synovial joint is less than 8%, but oxygen tension in RA synovium is found to be less than 1% [16, 55]. Hypoxia is a condition of reduced supply of oxygen, and mitochondria are highly sensitive to oxygen concentration [56]. Hypoxia activates hypoxia-inducible factor(HIF) expression to mediate inflammation, angiogenesis, cell migration, proliferation, suppress apoptosis of synovial cells, and various inflammatory cells in RA synovium [57]. In hypoxic conditions, Local enhancement in steady blood supply in the pannus unable to restore tissue oxygen levels, thus give rise to the cell infiltrations and invasion. A significant number of authors postulate the decreased oxygen tension in inflammatory joint diseases such as RA favors a substantial surge in the focal expression of neural cell adhesion molecule(NCAM), and 8-oxodG, which shows loss of endocytic cell-pericyte adhesion and DNA impairment [54]. It is widely believed that glycolytic intermediates function as anabolic supports for the cell proliferation and biosynthesis of inflammatory proteins [58, 59]. Increased production of lactate from the glycolysis cycle

induces the secretion of IL-6, IL-23, inhibits T cell motility, and enhances IL-17 production, thereby promoting RAFLS invasiveness [60, 61].

CONCLUSION

Mitochondria are one of the significant components of cell which play a crucial role in the regulation of cellular biogenesis, growth, and maintenance of homeostasis. As mitochondrion is vital for cellular control, any dysfunction or damage leads to the activation of pathological mechanisms, which give rise to inflammatory arthritis. Mitochondrial impairment causes oxidative stress, protein and DNA damage, and over-activation of immune cell that occurs in rheumatic joint diseases. This review article highlighted the connection between mitochondrial dysfunction on the activation of synoviocytes in inflammatory joint diseases, which is presented as a potential new therapeutic target for prevention and treatment on a molecular level.

Conflict of interest: We have no conflicts of interest to disclose.

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