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Review

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Features of mitochondrial dynamics in monocytes in inflammatory and metabolic disorders

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Abstract

Mitochondria do not exist as separate formations in the cell; they form a homogeneous network in which the processes of division and fusion continuously occur. A shift in this balance, as well as mitochondrial dysfunction, leads to the development of chronic and metabolic disorders. Metabolic changes in mitochondria control the formation and differentiation of monocytes. Pro-inflammatory activation of monocytes/macrophages leads to a decrease in oxidative phosphorylation and an increase in mitochondrial fusion. To date, the molecular mechanisms that regulate mitochondrial dynamics to control life and death in monocytes are not well understood. In addition, there is ample evidence that abnormal mitochondrial metabolism is involved in the pathogenesis of many diseases. Mitochondrial stress and damage contribute to cell death, metabolic disorders, and inflammation. In this review, we consider in detail the involvement of mitochondrial processes in the development of pathologies and discuss how mitochondria can be therapeutically affected. Attention is also drawn to possible diagnostic studies that target mitochondrial dynamics of disorders in monocytes.

Keywords: Inflammation, macrophages, dyslipidemia, mtDNA, obesity, mitochondria

INTRODUCTION

Chronic inflammatory diseases include metabolic disorders such as obesity and diabetes, as well as vascular diseases, including atherosclerosis[1]. The pathogenesis of these disorders is characterized by the initiation of recruited circulating monocytes into metabolic organs and tissues, as well as into the walls of blood vessels. The metabolic status of monocytes switches in response to environmental stimuli, so cellular metabolism plays a critical role in monocyte activation[2]. It is impossible to overestimate the role of mitochondria in the regulation of metabolism since they are involved in processes such as glucose oxidation and fatty acid biosynthesis[3]. The functions of mitochondria can also include the regulation of signaling pathways and differentiation of immune cells by controlling metabolic processes and the production of mitochondrial reactive oxygen species (mtROS)[4]. Mitochondrial dysfunction or disruption of mitochondrial machinery coupled with decreased mitochondrial mass limits the ability of oxidative phosphorylation to resynthesize ATP[5]. The violation of lipid metabolism leads to the accumulation of lipids in tissues. In addition, mitochondrial dysfunction affects the regulation of the production of intermediate metabolic products, reducing energy production[6]. In 2008, Kim discovered in patients with obesity and insulin resistance that changes in the content of mitochondria occur in liver tissues, adipose tissue, and skeletal muscles, and their oxidative capacity decreases[7]. Mitochondrial dysfunction is closely associated with the pathogenesis of insulin resistance and inflammation[8].

Normally, the balance of mitochondrial dynamics is maintained by their fusion and division processes, as well as mitophagy[9]. The mitochondrial fusion process involves two stages. First, the outer shells are joined, followed by the fusion of the inner shells of the mitochondria. Normally, these processes are coordinated, but mutations may appear in the genes that control them, and fusion and division become independent of each other[10].

Maintenance of repair is carried out in the process of mitochondrial division by separating the damaged organelle and degradation by mitophagy of non-functioning companions. It should be noted that the metabolic processes in the cell can be disrupted by excessive mitochondrial division[11]. Fusion and fission provide an exchange between membrane lipids and intramitochondrial contents in mitochondria, which is very important for maintaining a normal mitochondrial population[12]. Any disturbance in mitochondrial dynamics that alters the normal balance between fission and fusion can lead to an accumulation of damaged and dysfunctional organelles. Thus, mitochondrial dynamics play an important role in the morphology, function, and distribution of mitochondria.

Mitophagy is considered to be one of the main processes of quality control of mitochondrial mechanisms. This is a form of autophagy that selectively removes damaged mitochondria by means of the autophagosomal–lysosomal apparatus[13]. Mitophagy is very important to prevent oxidative damage in the cell, which can affect the enzymes of the respiratory chain.

The purpose of this review is to describe and summarize data on the mechanisms that occur in monocyte mitochondria during inflammatory and metabolic disorders.

FORMATION OF CLASSIC MONOCYTES IN NORMAL AND PATHOLOGICAL CONDITIONS

Classical monocytes (M1) are a population of cells with diverse differentiation potential. They make up about 80%-95% of circulating monocytes. A distinctive feature of non-classical monocytes is that they have a gene expression program that allows them to migrate into tissues under normal conditions[14]. Normally, classical monocytes enter the bloodstream from the bone marrow and circulate for about a day, after which they replace some of the tissue macrophages in the intestines, heart, pancreas, and dermis[15] or form into

non-classical monocytes. Under normal physiological conditions, classical monocytes make up a large proportion of the pool of tissue macrophages and are found in almost all tissues[16,17]. Adult monocytes, in some cases, can repeat the structure of resident macrophages while maintaining their identity[18] and may respond differently during inflammation[19]. There is a subpopulation of classic CD14^{bright}/CD56^{+} monocytes that is less well characterized[15]. CD56^{+} monocytes proliferate in autoimmune diseases such as rheumatoid arthritis and Crohn's disease. Being effective antigen-presenting cells, they can produce more reactive oxygen species and pro-inflammatory cytokines[19].

FORMATION OF NON-CLASSICAL MONOCYTES IN NORMAL AND PATHOLOGICAL CONDITIONS

Non-classical monocytes make up about 2%-11% of circulating monocytes. They have an excellent transcriptomic and metabolic profile (features of the respiratory chain enzyme complex) compared to classical monocytes, which use carbohydrate metabolism as an energy source[20]. Non-classical monocytes may have pro-inflammatory properties and secrete inflammatory cytokines in response to an infection[21]. They are involved in antigen presentation and T cell stimulation[22]. There is an increased content of non-classical monocytes in arthritis. Puchner *et al.* (2018), in an experiment on hTNFtg mice predisposed to arthritis, showed that the number of non-classical monocytes has increased at the preclinical stage[23]. Gazzito Del Padre *et al.* (2021) found that in patients with chronic inflammation of the blood vessels (Behcet's disease), the number of circulating classic monocytes was lower and the number of intermediate monocytes was higher compared to apparently healthy donors[24].

INTERMEDIATE PHENOTYPE IN NORMAL AND PATHOLOGICAL CONDITIONS

Intermediate monocytes (M0) make up about 2%-8% of circulating monocytes[25]. Studies on human and other monocyte subpopulations have shown conflicting results; in one study, a closer association of intermediate monocytes with classical monocytes[26]: and in another with non-classical monocytes[27]. Their functions consist in the production of reactive oxygen species (ROS); they also present antigens, participate in proliferation and stimulate T cells. In addition, they are necessary for inflammatory reactions and angiogenesis[28]. It is unknown whether intermediate monocytes exist as a separate subgroup or are simply transitional stages between classical and non-classical monocytes[29]. Intermediate monocytes are common in bacterial sepsis, Crohn's disease, cardiovascular disease[30], and rheumatoid arthritis[31]. Cormican *et al.* observed that intermediate blood monocytes can be sequentially classified into subpopulations with high and medium expression levels of the MHC II HLA-DR protein. They also showed that the number and proportions of subpopulations are regulated differently in different pathological conditions[32].

THE ROLE OF MITOCHONDRIA IN VARIOUS SUBPOPULATIONS OF MONOCYTES

Recent studies have shown that mitochondria not only produce adenosine triphosphate (ATP) but also participate in the regulation of calcium homeostasis, the formation of reactive oxygen species (ROS), and redox reactions and support the competence of immune cells. Furthermore, the focus will be on the role of mitochondria in monocytes in pathological conditions. Stimulation of monocytes by microbial ligands, such as lipopolysaccharide, peptidoglycan, or β-glucan, reprograms their metabolism to support the increased physiological demands that are necessary to generate an anti-inflammatory response[33]. The reprogrammed phenotype induces increased glycolysis and flux of the mitochondrial tricarboxylic acid cycle and oxidative phosphorylation[34].

For example, a group of scientists proved that LPS stimulation in monocytes causes changes in the morphology of mitochondria. They observed that the mitochondrial length was much shorter after 2 h of LPS treatment, indicating LPS-induced mitochondrial fragmentation in monocytes[35]. A change in the

shape of mitochondria leads to an increase in membrane potential, the accumulation of succinate, and a shift in glycolysis. As a result, the production of ROS in mitochondria is increased, and monocytes produce pro-inflammatory cytokines.

In another study on monocytes from donors of atherosclerotic patients, researchers showed that the polarization of mitochondria, and, consequently, their functional state, can affect the pro-inflammatory activity of immune cells. They examined MMP (mitochondrial membrane potential) in various human monocyte subpopulations using MitoTracker on a flow cytometer. The proportion of monocytes with low levels of mitochondrial dye may be associated with the presence of atherosclerotic lesions in donors and a reduced ability of monocytes to secrete TNF in response to LPS[36]. The authors showed that non-classical monocytes demonstrate a reduced content of MMPs, increased production of reactive oxygen species (ROS), and shortened telomeres compared to classical monocytes. Another group studied dendritic cells of monocyte origin with impaired immunostimulatory ability. In such cells, the MMP content was reduced and signs of a pre-apoptotic state were found[37]. The results obtained allow us to conclude that the body level of mitochondrial depolarization can be associated with various pathologies that are characterized by inflammatory and metabolic disorders due to changes in the structure and functions of mitochondria. It is also interesting to note that the balance of energy metabolism in monocytes changes with age from oxidative phosphorylation to aerobic glycolysis. A decrease in mitochondrial potential leads to a decrease in the reserve respiratory capacity. Thus, the metabolic fitness of elderly monocytes appears to be impaired due to reduced mitochondrial respiratory reserve and a limited ability to utilize additional glucose[38]. All these data indicate the key role of mitochondria in the functioning of monocytes and the formation of a response to the impact of foreign agents.

MITOCHONDRIAL DYNAMICS IN MONOCYTES ARE NORMAL

At the same time, differences were found in glucose metabolism in monocytes/macrophages of various phenotypes depending on their activation. This is essential for macrophages to perform their functions. For example, macrophage activation by LPS induces a classically activated (M1) pro-inflammatory macrophage phenotype in which there is an increase in glycolysis and disruption of the Krebs cycle to support cellular metabolism and produce cytokines. Stimulation of macrophages by IL-4 leads to the activation of an alternative (M2) phenotype of anti-inflammatory macrophages. In this case, cells use fatty acid oxidation (FAO) and oxidative phosphorylation for cellular metabolism and the formation of ATP[39]. FAO is the main mechanism in cell metabolism for the production of ATP.

Lipid metabolism is very important for macrophage function, and it is possible that its deficiency may affect macrophage activation. Geric *et al.* found that the classical activation of macrophages disrupts mitochondrial production, and alternative activation weakly induces it[40]. Moreover, Zhu *et al.* reported that FAO inhibition can reduce the differentiation of monocytes into macrophages *in vitro* and *in vivo*[41].

In response to stress, mitochondria in monocytes try to maintain their normal composition and structure through the action of antioxidants, DNA repair, protein folding, and degradation[42]. Mitochondria often change their shape under different conditions. In particular, mitochondrial dynamics regulate the interconnection of the mitochondrial network, which depends on the metabolic needs of the cell[43]. The processes that control the dynamics of mitochondria have been well studied. It is known that the state of the dynamic network depends on the balance between fusion and fission, which are regulated by specific proteins[44]. The cell's developmental status, metabolism, and microenvironment can upset the balance between these processes. An important feature of mitochondrial dynamics is that it regulates the functions of macrophages[45]. For example, M1 macrophages are known to contain fragmented mitochondria due to

an increase in mitochondrial division caused by DRP1 activation, which leads to increased glycolysis[46]. This process is also associated with mitophagy, an event that follows the division of mitochondria in macrophages[47]. Furthermore, M2 macrophages have elongated mitochondria with a high level of FAO and oxidative phosphorylation due to mitochondrial fusion[48]. Thus, M1 macrophages show more signs of active mitophagy than M2 macrophages.

MITOCHONDRIAL FUSION PROTEINS

The process of mitochondrial fusion is regulated by the Misato protein, which is encoded by the MSTO1 gene that is expressed in all cells. It is localized both to the outer mitochondrial membrane and in the cytoplasm[49]. Mitochondrial fusion includes the fusion of MOM and MIM[50]. Both of these processes are regulated by members of the GTPase family. MOM fusion is regulated by mitofusin 1 (MFN1) and mitofusin 2 (MFN2), which undergo homotypic and heterotypic interactions in adjacent mitochondria[51]. Misato (MSTO1) interacts with MOM and promotes mitochondrial fusion[52]. MOM fusion is, in turn, regulated by MFN1 and MFN2[53]. MIM fusion is mediated by the optic atrophy protein 1 (OPA1), which is expressed in different isoforms through alternative splicing and protease cleavage. The fusion of MOM and MIM occurs almost simultaneously, which allows mitochondria to exchange their contents[54], and this process also protects dysfunctional mitochondria from mitophagy. GTPases, which are located in the outer membrane of mitochondria, control mitochondrial fusion by forming homodimeric or heterodimeric, antiparallel, helical bonds between neighboring mitochondria and C-terminal domains[54]. The deficiency of MFN1 and MFN2 leads to reduced mitochondrial fusion[55]. In addition, MFN2 controls cellular apoptosis and mitochondrial autophagy[56]. OPA1, a mitochondrial fusion protein, may also play a role as mitophagic factors. BNIP3 induces mitochondrial fragmentation through interaction with OPA1.

MITOCHONDRIAL DIVISION PROTEINS

Mitochondrial division is regulated by a dynamin-related protein (DRP1), GTPase; since this protein is localized in the cytosol, specific adapter proteins are required for its anchorage in the MOM[57]. These adapter proteins include fission protein (FIS1), mitochondrial fission factor (MFF), mitochondrial elongation factor (MIEF1/MID51), and mitochondrial elongation factor (MIEF2/MID49)[58]. DRP1 forms a ring-like structure around mitochondria by self-assembly[59]. DRP1 acetylation contributes to cardiomyocyte death and dysfunction, which are associated with metabolic stress[60]. Drp1-mediated mitochondrial division is also required for phagocytes to remove apoptotic cells, thus reducing necrosis and inflammation[61]. The process of division of mitochondria is completed by dividing them into small and fragmented ones. This plays a key role in cell division, as the resulting daughter cells have the same number of mitochondria as the mother cells. Moreover, the division promotes mitochondrial transport and the separation of damaged mitochondria[62]. Thus, mitochondrial fusion contributes to the expansion of mitochondrial networks, which gives an advantage to cells at high energy costs, and a violation of mitochondrial fusion leads to mitochondrial dysfunction[14].

REGULATORS OF MITOCHONDRIAL DYNAMICS

As mentioned above, mitochondrial fusion in mammals is controlled by MFN1 and MFN2, proteins that are localized on the outer mitochondrial membrane[63]. In addition, MFN2 is involved in the modulation of energy metabolism, the interaction of the endoplasmic reticulum and mitochondria, and the regulation of mitophagy[64]. Another component that regulates mitochondrial fusion is OPA1, a transmembrane protein associated with the inner mitochondrial membrane[65]. OPA1 undergoes proteolytic processing, resulting in the short (s) and long (l) isoforms, both required for mitochondrial fusion[66]. Mitochondrial division in mammalian cells is controlled by GTPases DRP1, FIS, mitochondrial fission factor (MFF), and 49 and 51 kDa mitochondrial dynamic proteins[67]. DRP1 acts as a mechano-enzyme that is needed to physically

constrict mitochondria during early division. It is noteworthy that DRP1 lacks a mitochondrial destination sequence; therefore, for the formation of the fission complex, FIS1 must be located on the outer mitochondrial membrane. A slight decrease in the level of MFF leads to elongation of mitochondria and reduces the translocation of DRP1 into mitochondria[68].
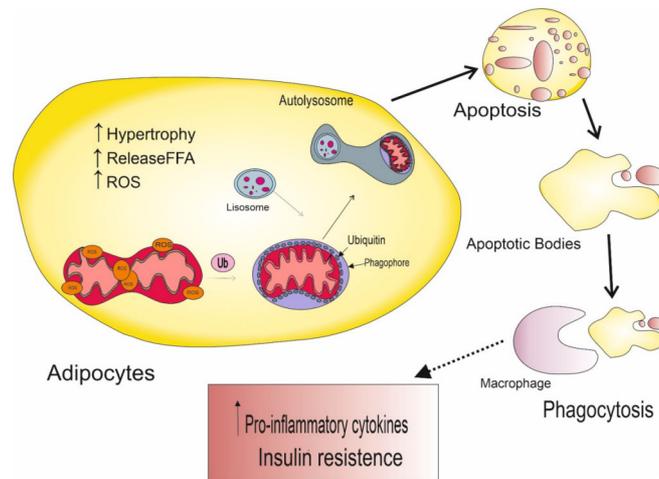
MITOCHONDRIAL TRANSPORT

Mitochondrial transport is carried out through microtubules and actin filaments in the cytoplasm of cells[69]. The movement of mitochondria requires the motor proteins myosin, kinesin, and dynein, which bind MOM proteins to cytoskeletal structures, forming a complex[70]. The division of mitochondria facilitates their movement since, in the cytoplasm, small and fragmented mitochondria are transported better than large and fused ones[71]. Mitochondrial transport promotes the subcellular localization of mitochondria, which is important to ensure the distribution of mitochondria during cell division and to maintain the energy needs of all cell types.

MITOCHONDRIAL DYNAMICS IN METABOLIC AND SOME INFLAMMATORY DISORDERS

We herein emphasize that mitochondrial fusion and fission are closely related to mitochondrial function. ROS are a byproduct of mitochondrial respiration since, when the level of mitochondrial ROS (mROS) is disturbed, processes occur that are involved in the development of inflammatory and metabolic disorders, such as atherosclerosis[72], diabetes, and obesity[73]. Interestingly, disturbances in mitochondrial metabolism, which is regulated by mitochondrial proteins Opa1 and Drp1 in various tissues, lead to the development of metabolic diseases[74].

High-fat and/or -sucrose diets can lead to insulin resistance (IR) and are often associated with mitochondrial dysfunction. Excess fatty acids or sucrose (glucose plus fructose) significantly overload the cell[75]. In the context of obesity, adipocytes play an important role in balancing metabolic homeostasis in response to excess energy. On a high-fat diet, mitochondria prefer a fragmented architecture associated with reduced adenosine 5'-triphosphate (ATP) production efficiency and increased release of reactive oxygen species (ROS)[76]. In obesity, adipocytes undergo hypertrophy, promoting the release of free fatty acids (FFA) during lipolysis and the development of hypoxia in adipose tissue. Necrotic adipocytes are phagocytosed by macrophages that produce chemokines and pro-inflammatory mediators[77]. Immune cells and macrophages are recruited into adipose tissue by inflammatory mediators [Figure 1].

Oxidative stress is characterized by an imbalance between ROS production and the antioxidant capacity of defense systems. Mitochondrial function is required for ATP synthesis to support adipocyte energy requirements for processes such as lipid metabolism (tricarboxylic acid cycle and β-oxidation) and adipocyte differentiation and maturation[78]. Prolonged exposure to oxidative stress leads to oxidative DNA damage, causing mitochondrial dysfunction and disruption of fusion and fission processes, which ultimately lead to a vicious cycle causing lipid accumulation and insulin resistance[79]. Violation of β-oxidation contributes to the accumulation of lipids in the cell, resulting in an increase in the number of active lipid intermediates such as diacylglycerols (DAG) and ceramides (CER), which can inhibit the action of insulin. Decreased substrate oxidation and oxidative phosphorylation lead to decreased electron flow through the electron transport chain (ETC), which causes electron leakage and superoxide production, followed by oxidative stress and mitochondrial damage[80]. Mitophagy removes damaged mitochondria while maintaining normal mitochondrial homeostasis. Homeostasis shifts when mitophagy is disturbed, as non-functioning mitochondria cannot be removed. Because of this, oxidative stress increases and normal mitochondria are damaged. There are numerous studies confirming the critical role of mitochondrial dysfunction in the formation of various pathologies[81].

Figure 1. Pathological effects of a high-fat diet on mitochondrial function in adipocytes.

For example, Drp1 mutations lead to the development of vascular diseases through mechanisms such as myocardial ischemia-reperfusion (I/R), heart failure, and endothelial dysfunction in atherosclerosis[82,83]. Deletion of mitofusin 2 (MFN2), which regulates MOM fusion in conjunction with mitofusin 1 (MFN1) in the liver and skeletal muscle of mice, leads to fragmentation of mitochondrial networks, resulting in glucose intolerance and increased hepatic gluconeogenesis[84]. In brown adipose tissue (BAT), deletion of Mfn2 remodels mitochondrial dysfunction and increases insulin sensitivity and a predisposition to obesity[85]. Moreover, Mfn2 expression has been found to be significantly downregulated in the presence of atherosclerosis in ApoE^{-/-} mice and is also involved in the pathogenesis of atherosclerosis[86,87]. All of these data support a critical regulatory role of Mfn2 in obesity and T2DM-associated glucose metabolism disorders[80] as well as in the development of inflammation in atherosclerosis[88].

In obesity, mitochondrial dynamics are disrupted. Mitochondrial dynamics depend on the availability of nutrients and energy consumption of cells[89]. It is known that, with nutrient deficiency and increased energy consumption, the mitochondrial network becomes elongated, while an abundant supply of nutrients and a decrease in energy requirements are associated with mitochondrial fragmentation[90]. Oma1 deficiency disrupts the mitochondrial fusion-fission balance and affects the reduction of oxidative phosphorylation, thereby enhancing fatty acid oxidation and reducing energy expenditure. The combination of these factors causes obesity in mice[91]. Tezze *et al.* showed that with age in people who lead a sedentary lifestyle, there is a decrease in Opa1, which is associated with loss of muscle mass[92]. Experiments on a mouse model of obesity caused by a high-fat diet have shown that the expression of MFN1 and MFN2 in skeletal muscles significantly decreases, and the expression of mitochondrial division mediators DRP1 and FIS1 increases, which leads to an increase in mitochondrial fission[93].

Mitochondrial dysfunction and its influence on the regulation of monocyte functioning

A common manifestation of inflammation is a change in mitochondrial structure and bioenergetics, which regulate MROs, enhance mitochondrial dysfunction, and promote inflammation and inflammatory cell death[94]. Disruption of the formation of mitochondrial ROS can cause cell damage and inflammatory death of macrophages, which is induced by oxidative stress[95]. Mitochondrial biogenesis and energy metabolism are necessary to regulate the inflammatory state of monocytes[96]. This condition is partially controlled by the peroxisome proliferator-activated gamma-receptor 1-alpha (PGC-1a) coactivator, which plays an important role in mitochondrial biogenesis by regulating genes involved in fatty acid oxidation and

oxidative phosphorylation [Figure 2]. PGC-1a is expressed in endothelial cells, causing an increase in the expression of mitochondrial antioxidant enzymes[94].

PGC-1α is also found in macrophages of atherosclerotic plaque. It has been proven that its overexpression, when treated with conjugated linoleic acid (CLA), prevents the development of foam cells, preventing the capture of oxidized lipids by macrophages. Accordingly, a decrease in the expression of PGC-1a can lead to mitochondrial dysfunction and the formation of foam cells due to an increase in ROS production and a decrease in the action of antioxidants[96]. In addition, the function of mitochondria can be negatively affected by oxidized low-density lipoprotein (oxLDL) and ROS [Figure 2]. Damaged mitochondria release components, for example, mtROS, cardiolipin, and mtDNA, the action of which leads to inflammation due to increased production of interleukins 1ß and 18[95]. With impaired mitochondrial functions in monocytes/macrophages, chronic inflammatory diseases may develop, for example, pulmonary fibrosis, atherosclerosis[97], and rheumatoid arthritis[98]. For the regulation of inflammation, it is very important that mitochondrial processes are not disrupted in monocytes/macrophages[99].

There is now ample evidence pointing to mitochondrial dysfunction as a key mediator of cell death, such as neuronal death in Parkinson's disease (PD)[100]. Smith *et al.* investigated mitochondrial pathology in peripheral monocytes of the control group and PD patients, as well as in lymphocytes and the total number of peripheral blood mononuclear cells (PBMC), by measuring the content of mitochondria (MitoTracker) and the production of mROS (MitoSox). They found that monocytes from PD patients had a significantly lower mitochondrial content and a higher level of mitochondrial ROS. In addition, during the analysis of the level of mROS by mitochondrial content (MitoSox/MitoTracker), higher levels of mitochondrial ROS were found in monocytes of patients with PD[101].
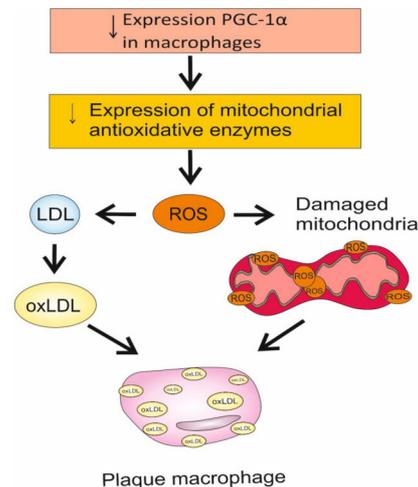
Williams *et al.* drew attention to the fact that patients with urolithiasis have reduced mitochondrial function in circulating monocytes compared to healthy people[102]. Scientists have suggested that this is due to the accumulation of oxalate in the renal epithelium. Perhaps macrophages are involved in the removal of salt crystals. Insufficient clearance may result in increased inflammation, oxidative stress, and tissue damage[103].

Shen *et al.* showed that, compared with wild-type mice, deficiency of receptor-associated tumor necrosis factor 3 (TRAF3), a member of the TRAF family with E3 ligase activity that functions as an important mediator of innate immunity receptor signaling, resulted in a significant decrease in production IL-1β and neutrophil infiltration. These data suggest that TRAF3 regulates mitochondrial ROS production, inflammation activation, and cell death[98].

Geisberger *et al.*, in ex vivo and *in vivo* experiments, showed that macrophage CD36 receptor promotes reprogramming of mitochondrial metabolism from oxidative phosphorylation to ROS production to trigger chronic inflammation in atherosclerosis. Scientists have hypothesized that changing the sodium microenvironment could lead to a loss of mitochondrial function with reduced ATP production in all M1 and M2 macrophages, which could accelerate the development of cardiometabolic diseases[104].

Monocytes in obesity and inflammation: common features and differences

Recruited monocytes are involved in widespread tissue damage in both chronic and acute inflammation. During inflammatory reactions, secretion of inflammatory and anti-inflammatory cytokines occurs, which become key players in the development of a pathological condition[105]. Scientists have not yet been able to identify any single inflammatory cytokine as a specific biomarker. However, what is certain is that, in almost

Figure 2. Pathogenesis of mitochondrial dysfunction and formation of foam cells in response to changes in PGC-1a expression.

all inflammatory conditions, both in resolution and persistent inflammatory situations, there is a change in the profile of circulating cytokines[106]. This means that the acute and chronic phases largely overlap in terms of inflammatory cytokine levels, with differences occurring over time in the change in cytokine production. For example, in atherosclerosis, inflammation is observed with the accumulation of oxidized LDL in the outer and middle layer of the artery, and monocytes penetrate into the tissues, where they differentiate into macrophages[107]. Macrophages can change their inflammatory phenotype when exposed to the microenvironment[108]. Macrophages are divided into macrophages of the first type (M1) that have a pro-inflammatory activation pathway and macrophages of the second type (M2) that have an anti-inflammatory activation pathway[109]. M1 macrophages produce pro-inflammatory cytokines such as TNFa, IL-6, IL-8, and IL-1β[110]. M2 macrophages are responsible for the production of anti-inflammatory cytokines, for example, IL-1 (IL-1ra), IL-10, and CCL118[111]. For the production of inflammatory cytokines, the toll-like receptor (TLR) pathway can be activated to activate the NF-kB transcription factor system. In this case, pathogen-associated molecular patterns (PAMP) are used, such as lipopolysaccharide (LPS), flagellin obtained from bacteria, and a double-stranded viral RNA molecule [112]. Macrophages switch their phenotype to M1 during inflammation, depending on glycolysis for ATP synthesis, and to M2 during oxidative phosphorylation[113]. It is important to note that macrophages M1 and M2 are very plastic, moving from one form to the other. Glycolysis and oxidative phosphorylation occur in both phenotypes and activate the macrophage polarization pathway depending on the environment[114]. The phenotype of macrophages can switch depending on the oxygen level in the cells, and the oxygen level can also affect their metabolic processes[115]. When there is an increase in oxygen in tissues, peroxisome proliferation receptor-γ (PPAR-γ) begins to act in cells, while in mitochondria, there is a transition from aerobic glycolysis to oxidative phosphorylation[116]. As noted above, metabolites play an important role in the differentiation of monocytes and affect their functionality. For example, during prolonged fasting, short-chain fatty acid β-hydroxybutyrate is released from the liver and downregulates the inflammasome-induced NLRP3 IL receptor[117]. The number and composition of monocyte populations can also be influenced by eating behavior[118]. There are studies showing that with obesity, there is an increase in the number of intermediate and non-classical subsets of monocytes in circulating blood[93]. In obese patients, increased expression of TLR4 and TLR8 was observed in monocytes, and they also excessively secreted pro-inflammatory cytokines (IL-1ß and TNF) under the action of LPS[119,120]. In obesity, the function of monocytes changes due to various metabolites; similar processes are observed during inflammation in atherosclerosis. For example, the action of oxidized low-density lipoprotein (LDL) switches the phenotype of monocytes; they begin to increase the expression of

pro-inflammatory chemokines[121,122]. Single nucleotide polymorphisms in the regions of the inflammatory adapter gene and IL-1 receptor antagonist have been shown to influence the response of human monocytes, suggesting that inflammation is involved in this process[123,124]. Restriction of calories and fatty foods has a beneficial effect on many chronic metabolic disorders such as T2DM2, non-alcoholic liver disease, and cardiovascular disease[125], and short-term fasting is sufficient to reduce the number of entire monocyte populations in healthy individuals[126]. To date, the mechanism of change in monocytes due to various dietary habits is not fully known, but modern technologies such as multicolor flow cytometry, mass cytometry, and single-cell RNA sequencing contribute to the understanding of the primary and secondary effects of diet on monocytes[127,128].

DISTURBANCES IN MITOCHONDRIAL DYNAMICS IN MONOCYTES AS A POTENTIAL DIAGNOSTIC TARGET IN DIAGNOSING AND PREDICTING THE COURSE OF METABOLIC AND INFLAMMATORY PATHOLOGICAL CONDITIONS

Due to the high prevalence of metabolic and inflammatory diseases, it is very important to develop a special approach to their diagnosis. This review describes the mechanisms of occurrence of these pathologies at the cellular level and proves that the disruption of mitochondrial dynamics plays a key role. There is a new diagnostic and treatment approach based on the use of photosensitivity, phototheranostics. This approach targets pathologically altered cells and tissues and only targets cellular organelles if the photosensitizing agent accumulates selectively. For example, such selectivity may result from damage to the mitochondrial genome. Scientists believe that such approaches can be applied in atherosclerotic diseases, when mitochondrial DNA mutations associated with atherosclerosis lead to mitochondrial dysfunction[129]. Phototheranostics is part of the medicine of the future; it is not only a new approach in diagnostics, but it can also be effective in subcellular therapy, including at the mitochondrial level.

Malik *et al.* proposed the hypothesis that the content of mtDNA in the tissues of the body may indicate alterations in mitochondrial functions. An increase in the amount of ROS as a result of external influences, for example, as a result of hyperglycemia or an increase in fat content under conditions of oxidative stress, can lead to an increase in mitochondrial biogenesis. The level of mtDNA plays an important role in the proper functioning of mitochondria; its changes can increase oxidative stress and cause inflammation. Changes in mtDNA levels are observed in peripheral blood mononuclear cells and can be used as a marker of pathological processes in tissues[130].

POTENTIAL OF MITOCHONDRIAL THERAPY IN OBESITY AND INFLAMMATION

Maintenance of mitochondrial function is an effective method in the treatment of damaged tissues and can alleviate the clinical manifestations of diseases[131]. Mitochondria may be an important target for the development of new drugs for cardiovascular diseases[132], and they are part of a promising strategy for the treatment of atherosclerosis and metabolic diseases, including obesity, by modulating mitochondria[133]. A series of experiments showed that cardiovascular diseases can be avoided by eliminating the consumption of fatty foods, correcting excess body weight, and controlling blood sugar levels. These recommendations can help avoid mitochondrial damage[134]. In addition, Schneeberger *et al.* reported that proopiomelanocortin (POMC) induces a specific deletion of Ms2, which may lead to resistance of the endoplasmic reticulum (ER) to leptin and reduce the risk of obesity[135].

Mitochondrial antioxidants are currently in the preclinical and clinical stages of testing[136]. Ingredients of natural origin with antioxidant action are also being developed now[137]. Studies on ilexgenin A have shown that it has the ability to inhibit the expression of Drp1 and excessive mitochondrial division; it also reduces the production of ROS and inflammatory factors, thereby reducing inflammation in atherosclerosis[138,139].

Kumar *et al.* suggested that deletion of the CD36 gene in macrophages could provide a potential strategy to combat chronic inflammation in atherogenic conditions by blocking mitochondrial fatty acid import with Etogooxira, which attenuates mitochondrial ROS as well as inflammation activation[140].

The role of fatty acid oxidation in monocyte activation and differentiation is discussed above. It is possible that the regulation of β-oxidation may be useful in the fight against inflammation in atherosclerosis[141]. Scientists have suggested that inhibition of CAO by trimetazidine in macrophages reduces the secretion of the pro-inflammatory cytokine IL-1β[142]. This approach could help slow the progression of atherosclerosis.

CONCLUSION

Mitochondria form a dynamic network that interacts with all cellular components and is involved in the organization of various physiological processes and cellular responses to damaging factors. This review shows that changes in mitochondrial function are the main contributor to the development of inflammatory and metabolic disorders. Proper mitochondrial dynamics are necessary to maintain normal mitochondrial functions and homeostasis in the cell. It is necessary to understand the causal relationships that underlie the mechanisms of inflammation and obesity for further progress in the diagnosis and treatment of these pathologies. In addition, the control over the mechanisms that regulate the dynamics of mitochondria will prevent damage to them. Thus, disturbances in mitochondrial dynamics can serve as a good diagnostic target for identifying the initial stages of chronic and metabolic diseases, the mechanisms of which are based on impaired mitochondrial functions. Moreover, special attention should be paid to the study and development of therapy for these pathologies based on mitochondrial preparations. Targeting mitochondria can be an effective way to combat diseases associated with inflammation and metabolic disorders.

DECLARATIONS

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