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Review Article

Role of Mitochondria in the Chronification of Inflammation: Focus on Dysfunctional Mitophagy and Mitochondrial DNA Mutations

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Abstract

Inflammation is a natural reaction of the innate immune system that evolved primarily to protect the human body from invading pathogens and to heal injuries. There are two different types of inflammation, acute and chronic inflammation, differing in duration, underlying causes, and characteristics. The acute-to-chronic transition can be determined by several pathomechanisms, including dysregulation of immune response and failure to eliminate the underlying cause. Moreover, epigenetic changes that refer to modifications in gene expression that are heritable but do not involve changes to the underlying DNA sequence can also contribute to prolonged inflammation. Emerging evidence suggests that dysfunctional mitochondria can promote the development of chronic inflammation. In this respect, the mechanisms triggering defective mitophagy, a selective form of autophagy that exterminates dysfunctional mitochondria to maintain cellular homeostasis, attracted special attention. The hypothesis on the pivotal role of mutations in mitochondrial DNA causing defective mitophagy stimulated the area of the research that applies editing of the mitochondrial genome. The mitoCAS9 vector and two single guide RNAs to the G15059A mutation were used to eliminate the mutation from the macrophage-like cells. The normal activity of the initially defective mitophagy was restored in intact macrophage-like cells, confirming the causal role of the G15059A mutation in the disruption of the mitophagy process. The unraveling of the underlying mechanisms of chronic inflammation will help to develop targeted therapeutic approaches aimed at restoring mitochondrial health and alleviating chronic inflammation that can be used for the treatment of a wide range of chronic inflammatory diseases.

Keywords: Chronification of inflammation; Defective mitophagy; Dysfunctional mitochondria; Resolution of inflammation; Mitochondrial genome editing; Mutations in mtDNA.

Abbreviations: ATP, adenosine triphosphate; BNIP3, BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3; cGAS, GMP-AMP synthase; COPD, chronic obstructive pulmonary disease; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats; CVD, cardiovascular disease; Drp1, dynamin-1-like protein; FIS1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing 1; IBD, inflammatory bowel disease; IL, interleukin; LC3, an autophagosome marker; LDL, low-density lipoprotein; MMP, mitochondrial membrane potential; Mff, mitochondrial fission factor; Mfn1/2, mitofusin-1/2; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; MTS, mitochondrial targeting sequence; NF-κB, nuclear factor-kappa B; NIX, BH3-only family signaling protein; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; Nrf 1/2, nuclear respiratory factors 1/2; OPA1, dynamin-like 120 kDa protein; PARKIN, 465-amino acid residue E3 ubiquitin ligase; PGC1α, peroxisome proliferator-activated receptor alpha; PINK1, tensin homolog-induced putative kinase 1; ROS, reactive oxygen species; sgRNA, single guide RNA; SLE, systemic lupus erythematosus; STING, stimulator of interferon genes; TC-HSMAM1, Thp1 Cybrid-High Sum Mutation Antiatherogenic Mutation 1; Tfam, mitochondrial transcription factor A; TNF-α, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

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Introduction

Inflammation is a vital immune response that helps the body combat infections and heal injuries. Nevertheless, in certain cases, inflammation can become chronic, leading to persistent tissue damage and the development of various diseases.[1,2] Recent research has shed light on the role of mitochondria, the energy-producing powerhouses of cells, in the chronification of inflammation. In particular, dysfunctional mitophagy and the presence of mutations in mitochondrial DNA (mtDNA) have emerged as key factors in this process.[3,4]

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Mitochondria are known to serve essential functions in cell metabolism, energy production, and signaling. They are also actively involved in regulating inflammation.[5] When mitochondria become damaged or dysfunctional, a process called mitophagy is initiated. Mitophagy is a selective form of autophagy that removes damaged or dysfunctional mitochondria to preserve the homeostasis of cells; however, when mitophagy is impaired, dysfunctional mitochondria accumulate within cells. The accumulation of dysfunctional mitochondria leads to the release of reactive oxygen species (ROS) and pro-inflammatory molecules.[5] These molecules can perpetuate chronic inflammation, contributing to the progression of a significant number of inflammatory conditions. According to current knowledge, mutations in mtDNA can disrupt mitochondrial function and impair cellular energy production. Consequently, mitochondrial dysfunction leads to increased oxidative stress and the development of inflammation.[3] Apart from impairing mitochondrial function, mtDNA mutations can act as danger signals, activating the innate immune system and triggering an inflammatory response.[4] Understanding the role of mitochondria, specifically dysfunctional mitophagy and mutations in mtDNA, in the chronification of inflammation is a burgeoning area of research. Accumulating evidence suggests that defective mitophagy, in consequence of mutations in mtDNA, largely contributes to the chronic nature of inflammation and the pathogenesis of chronic inflammatory diseases, including neurodegenerative, cardiovascular, metabolic, and autoimmune disorders.[6] Herein, we propose that dysfunctional mitophagy caused by mtDNA mutations has a crucial role in the chronification of inflammation, since it fails to eliminate damaged mitochondria and, thus contributes to the persistence of the inflammatory response. The purpose of this review was to summarize the evidence underlining the role of mitochondria in inflammation chronification, with a particular focus on impaired mitophagy and mutations in mitochondrial DNA. The unraveling of the underlying mechanisms implicated in the development of chronic inflammation will help find targeted therapeutic approaches to restore mitochondrial health and alleviate chronic inflammation that can be used for the treatment of a wide range of chronic inflammatory conditions.

Chronic inflammation as a health and socioeconomic burden

Chronic inflammation, if left untreated or uncontrolled, can lead to significant morbidity and mortality in various ways. The specific morbidity and mortality rates associated with chronic inflammation depend on the underlying cause, duration, and severity of the inflammation, as well as the affected organ or system. Chronic inflammatory diseases are currently considered the most significant death cause worldwide, with more than 50% of all mortalities being attributable to the following conditions: ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, nonalcoholic fatty liver disease and autoimmune and neurodegenerative disorders.[7] Several examples of chronic inflammation-associated pathologies that pose significant health problems and, consequently, enormous socioeconomic burdens are presented in Table 1.[8–37] Indeed, chronic inflammatory conditions listed in Table 1 are closely related to aging. In this regard, it is worth mentioning the growing popularity of the term inflammaging, which is a combination of two words, such as inflammation and aging.

Inflammaging

Inflammaging refers to a phenomenon of the persistence in the human body of chronic low-grade inflammation without the overt infection, *i.e.,* sterile inflammation, in the process of aging.[38] Inflammation is the body's natural immune response to harmful stimuli such as infections or injuries. It is typically beneficial as an acute response in the short term. However, with age, the immune system can become dysregulated and unable to fully neutralize the inflammatory processes resulting from a lifelong antigenic load and exposure to damaging agents. In this way, inflammaging results in the activation of immune mechanisms that are often distinct from those involved in an acute immune response, leading to tissue damage and degeneration. Chronic inflammation can contribute to the development of various age-related diseases, such as cardiovascular and neurodegenerative diseases, diabetes, and cancer, as discussed in a review by Cevenini *et al.*[39]

The etiology of inflammaging and its potential causal role in contributing to detrimental health outcomes remains largely unclear. The evidence accumulated to date suggests that a combination of genetic, environmental, and lifestyle-related factors, including genetic predisposition, oxidative stress, changes in gut microbiota, impaired cellular repair mechanisms, and exposure to environmental toxins contributes to the development of inflammaging.[38] Therefore, lifestyle-related factors including regular exercise, a healthy diet, stress management, and adequate sleep pattern have been proposed as potential approaches to mitigate inflammaging and promote healthy aging.[40] Further research is needed to fully comprehend the complex molecular mechanisms underlying inflammaging and develop effective strategies that will be helpful in maintaining healthy aging and preventing age-related diseases.

Acute and chronic inflammation: acute-to-chronic transition

Inflammation is an evolutionarily preserved process determined by the activation of immune and nonimmune cells that safeguard the host from bacteria, viruses, toxins, and infections by eradicating pathogens and supporting tissue repair and recovery.[41] In general, the inflammatory response can be described as a time-limited activation of inflammatory activity that occurs in the presence of a threat and ceases when it is eliminated. The cellular basis and pathophysiology of an acute inflammatory response have been long-established.[42,43] In response to tissue damage or infection, the blood vessels in the affected area dilate, allowing increased blood flow to that area. This is called vasodilation and is mediated by the release of inflammatory mediators such as histamine and prostaglandins that cause the relaxation and dilatation of blood vessels. Besides, the blood vessels in the affected area become more permeable, allowing fluids, proteins, and immune cells to leak out into the underlying tissue. The further discharge of inflammatory mediators such as histamine and bradykinin mediate the increased vascular permeability. Immune cells such as neutrophils and macrophages are recruited to the site of inflammation from the bloodstream. They migrate toward the affected tissue governed by chemokine signaling. These immune cells play a crucial role in the clearance of pathogens and debris. Neutrophils and macrophages engulf and destroy pathogens and debris through a process called phagocytosis. They recognize and bind to pathogens or cellular debris, engulf them, and then destroy them with enzymes and toxic molecules. Both immune cells and damaged tissue release inflammatory mediators, such as cytokines, chemokines, and prostaglandins, which help to amplify and propagate the inflammatory response. These mediators can further recruit immune cells, increase vascular permeability, and activate other cellular responses. Once the inflammatory response has cleared the pathogens and debris, tissue repair mechanisms are initiated. In addition, macrophages,

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Table 1. Chronic inflammation in disease

Disease or condition	Effects of chronic inflammation	Data on global burden
CVD[8,9]	Chronic inflammation has been linked to the development and progression of cardiovascular diseases, such as atherosclerosis, coronary artery disease, and stroke. Inflammation in the arteries can cause damage to the blood vessel walls, leading to the formation of plaques, narrowing of the arteries, and increased risk of the development of blood clots, heart attacks, or strokes.	CVD: data on burden across time, location, cause, and risk factors[10]
Chronic respiratory diseases[11,12]	Chronic inflammation in the respiratory tract can lead to conditions, such as COPD, asthma, and bronchitis. Inflammation in the airways can cause persistent coughing, difficulty breathing, and reduced lung function, resulting in a significant increase in morbidity and mortality rates, especially in severe cases.	Nonobstructive chronic bronchitis: all-cause mortality data[13]; COPD: data on the prevalence, deaths, disability adjusted life years, and attributable risk factors[14]; Asthma: a global cohort analysis of incidence and mortality[15]
IBD[16]	Conditions such as Crohn's disease and ulcerative colitis are chronic inflammatory diseases that affect the digestive tract. Chronic inflammation in the gut can cause symptoms, such as abdominal pain, diarrhea, rectal bleeding, and weight loss. If left untreated, IBD can be complicated with intestinal strictures and abscesses, as well as determine an elevated risk of colon cancer.	IBD: a systematic analysis of the global burden[17]
Joint diseases[18]	Chronic inflammation can affect the joints and lead to conditions such as rheumatoid arthritis and osteoarthritis. In both conditions, the molecular mechanisms of cartilage breakdown show considerable overlap, especially with respect to some inflammatory mediators. Rheumatoid arthritis is an autoimmune disease, in which the development of chronic inflammation in the joints is the main feature, resulting in joint pain, swelling, stiffness, reduced mobility, and, consequently, significant morbidity and impaired quality of life. Osteoarthritis, or degenerative joint disease is a common chronic condition that affects the joints, particularly the cartilage that cushions the ends of bones within joints. It is the most common type of arthritis and can occur in any joint in the body, but it most frequently affects weight-bearing joints, such as the knees, hips, and spine, along with small joints of the hands.	Rheumatoid arthritis: a systematic analysis of the global burden[19]; Osteoarthritis: a systematic analysis of the global burden[20]
Organ damage[21–23]	Chronic inflammation in organs, such as the liver (*e.g.*, chronic hepatitis), kidneys (*e.g.*, chronic glomerulonephritis), and pancreas (*e.g.*, chronic pancreatitis), can result in organ damage, loss of function, and increased mortality rates if not managed properly.	Chronic liver diseases: global burden data[24]
Increased cancer risk[25–27]	Chronic inflammation accompanies the development of certain types of cancer, including colorectal cancer, liver cancer, and lung cancer. The inflammatory milieu stimulates cellular proliferation and survival, degradation, and remodeling of the extracellular matrix, and weakening of vascular barriers to promote immune cell migration, all of which facilitate cancer progression. Besides, collateral damage of cells from inflammation can trigger apoptosis, necrosis, and mutations, driving the tissue further away from homeostasis and accelerating transformation.	Cancers: global burden data[28]
Psoriasis[29]	Psoriasis is a systemic inflammatory condition of the skin (red, scaly patches that may be itchy and painful) caused by dysfunctional interactions between innate and adaptive immune responses.	Psoriasis: global burden data[30]
T2DM[31]	Chronic inflammation is thought to contribute to insulin resistance, a hallmark of type 2 diabetes. Inflammation in adipose tissue and other organs can disrupt insulin signaling, leading to impaired glucose metabolism and elevated blood sugar levels.	T2DM: global burden data[32]
Alzheimer's disease[2,33]	Chronic inflammation has been implicated in the development and progression of Alzheimer's disease, a neurodegenerative disease that affects the brain. Inflammation in the brain can lead to the accumulation of amyloid plaques and tau tangles, which are the major features of Alzheimer's disease.	Alzheimer's disease: global burden data[34]
SLE[35,36]	SLE is an extremely complex autoimmune disease characterized by the interplay between multiple immunopathogenic factors, including host autoantigens and both cellular and humoral immune components that promote the generation of a hyperinflammatory milieu resulting in organ and tissue damage. Among numerous immunopathological SLE-related disorders, the most significant is glomerulonephritis mediated by the immune complex accumulation in micro-vessels of kidneys. Inflammation caused by SLE can also affect other body systems, such as skin, joints, blood cells, brain, lungs, and heart.	SLE: global burden data[37]

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus.

play a role in clearing debris and promoting tissue healing through the release of growth factors and other signaling molecules.

Acute inflammation is typically initiated by a specific cause, such as an infection, injury, or tissue damage. If the underlying cause persists or is not effectively eliminated, acute inflammation may continue and eventually result in chronic inflammation. For example, a persistent infection that is not effectively cleared by the immune system can lead to chronic inflammation.[44] Shifts in the inflammatory response from short-term to long-term can lead to the breakdown of immune tolerance and widespread changes in all tissues and organs, as well as normal cellular physiology, which can increase the risk of developing many noncommunicable diseases both in young and older people.[45] Dysregulated inflammatory response and chronic inflammation have been associated with the development and progression of various chronic pathologies, such as atherosclerosis, types 1 and 2 diabetes mellitus, metabolic syndrome, inflammatory bowel disease (IBD), and neurodegenerative diseases.[46,47] These conditions are characterized by the development of long-standing (sterile) inflammation continuing for an extended period.[48] The immune system mistakenly initiates an inflammatory response, even without a causative factor or after the initial cause of inflammation has been eliminated, resulting in the sustained secretion of cytokines. Chronic inflammation can also impair the function of the immune system, leading to increased susceptibility to infections and tumors and a poor response to vaccines.[49] In addition, chronic inflammation during pregnancy and childhood can have severe developmental implications that include increasing the risk of chronic inflammatory conditions over the life span.[50]

There are certain social, psychological, environmental, and biological factors that hinder the resolution of acute inflammation and, consecutively, promote a state of low-grade, noninfective systemic chronic inflammation.[51] Thus, prolonged exposure to polluted air is related to chronic inflammation.[52] There are lifestyle-related factors, such as poor diet, sedentary lifestyle, continuous emotional stress, and insufficient sleep, that can contribute to the development of chronic inflammation.[53] Some individuals may have a genetic predisposition to the development of chronic inflammation,[9] which can be associated with their immune response, inflammation-regulating genes, or other genetic factors. These genetic factors can negatively influence the duration and intensity of inflammation, potentially preceding the development of chronic inflammation.

In summary, acute inflammation and chronic inflammation are two different types of inflammation that occur in the body, and they differ in duration, underlying causes, and features.[54] Acute inflammation is a short-term, rapid, and self-limited response of the human body to an injury, infection, or other harmful stimuli. It helps to recruit immune cells to the site of injury or infection, remove damaged tissue, and promote tissue repair. Chronic inflammation is a long-term, persistent inflammatory response that can last for weeks, months, or even years. If acute inflammation is characterized by classic signs of inflammation, including redness, swelling, heat, pain, and loss of function at the site of injury or infection, chronic inflammation may not necessarily exhibit the same signs and symptoms as acute inflammation.[55] Chronic inflammation, if left untreated, can have detrimental effects on tissues and organs over time. It can cause tissue damage, scarring, and dysfunction, and contribute to the pathogenesis of chronic diseases. The process of inflammation chronification is complex and involves dysregulation of the immune response and failure of the normal resolution mechanisms (described in the next section). Therefore, it is important to manage chronic inflammation appropriately to prevent its potential adverse health effects. Measures to prevent the development of chronic inflammation typically involve identifying and addressing the underlying causes, *i.e.,* treating infections, managing autoimmune conditions, reducing exposure to environmental toxins, and adopting a healthy lifestyle.

Pathomechanisms of inflammation chronification

The key pathomechanisms contributing to the chronification of inflammation include the dysregulation of the immune response, the failure of inflammation resolution mechanisms, and the presence of altering DNA structure epigenetic changes.

Dysregulation of immune signaling pathways

In chronic inflammation, a continuous immune response is often not properly regulated or controlled.[56,57] In this way, immune cells, such as macrophages, neutrophils, and lymphocytes, can continue to release inflammatory mediators such as cytokines, chemokines, and ROS, facilitating the prolongation of the inflammatory response. Numerous attempts have been made to identify the causes of the dysregulation of immune signaling pathways to prevent the development of chronic inflammation and chronic inflammatory diseases. Dysregulation of immune signaling pathways, particularly the nuclear factor-kappa B (NF-κB) and a predicted nucleoside-triphosphatase, a carboxy-terminal leucine-rich repeat, and an amino-terminal pyrin domain domains-containing protein 3 (NLRP3) inflammasome signaling, can be affected by one or a combination of factors and, thus, contribute to chronic inflammation development. Controlled activation of NF-κB signaling is essential for regular innate and adaptive immune responses, while dysregulation of NF-κB signaling in lymphocytes contributes to the development of conditions extending from chronic inflammation and autoimmunity to lymphoma.[58] The transcription factor NF-κB is a chief regulator of lymphocyte survival and activation and NLRP3 inflammasome is the innate immune system receptor.[58,59] Interestingly, in autoimmune conditions, the immune system erroneously attacks the body's own tissues, leading to chronic inflammation. There is a piece of evidence demonstrating that the chronic inflammation seen in people with abdominal aortic aneurysms is a consequence of an impaired autoimmune response to autologous components of the aortic wall.[60] Other autoimmune conditions, characterized by the aberrant activity of the immune system, including rheumatoid arthritis, systemic lupus erythematosus (SLE), and IBD among others, are also accompanied by chronic inflammation.[61]

Genetic mutations or alterations in the genes that encode proteins involved in immune signaling pathways can lead to dysregulation of the immune response. For example, mutations in genes encoding components of the NF-κB pathway or NLRP3 inflammasome can disrupt their normal function, leading to aberrant immune signaling.[62,63] Besides, aging can unfavorably affect immune signaling pathways, leading to their dysregulation. Alterations in both NF-κB and NLRP3 inflammasome signaling have been implicated in age-related immune dysfunction and the development of low-grade inflammation.[64,65] Moreover, certain RNA viruses (influenza A virus) can activate the NLRP3 inflammasome pathway owing to mitochondrial antiviral signaling protein on the outer mitochondrial membrane and, thus, cause the dysregulation of the immune response.[66] Immune signaling pathways are tightly regulated by feedback mechanisms to prevent excessive inflammation. Dysfunctional feedback loops can be accountable for dysregulated immune signaling. For example, impaired negative feedback of

NF-κB signaling can result in its prolonged activation and chronic inflammation, as reviewed by Singh.[67] The evidence indicating that post translational modifications, such as phosphorylation, ubiquitination, and acetylation, play critical roles in regulating immune signaling pathways was reviewed.[68,69] For example, aberrant phosphorylation of NF-κB or NLRP3 inflammasome components can lead to their dysregulated signaling.[70] The impact of other factors, such as metabolic imbalance, hormonal changes, and gut microbiota dysbiosis, on NF-κB and NLRP3 inflammasome immune signaling has been extensively reviewed.[71–73] Environmental factors can also disrupt immune signaling pathways. Heavy metal pollution can induce neurotoxicity, inflammation, and tau hyperphosphorylation leading to neurodegenerative disease. For example, manganese exposure can induce the GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, a key mediator of inflammation, responsible for the powerful innate immune defense programs.[74] Both cGAS and STING are broadly expressed in mammalian cells, acting as major regulators of type I interferon and cytokine expression.[75]

Dysregulated immune signaling pathways may be associated with the development of an autoimmune reaction. The way how oxidized mtDNA, an autoimmune disease biomarker, induces short- and long-term immune activation leading to prolonged inflammatory and autoimmune responses was discussed in a recent review.[76] Fragmented oxidized mtDNA enters the cytosol where it activates NLRP3 inflammasome and generates the production of interleukin (IL)-1β, IL18, and cGAS-STING, inducing type I interferons and interferon-stimulated genes. Besides, dysfunctional immune responses in an autoimmune disorder, such as type 1 diabetes mellitus, can involve aberrant activation of NF-κB and NLRP3 inflammasome signaling by mtDNA.[77,78]

Failure of inflammation resolution mechanisms

Inflammation resolution is a dynamic and regulated process that follows acute inflammation and involves the removal of inflammatory mediators, tissue repair and functional restoration, facilitating the recovery of homeostasis.[79] In chronic inflammation, the resolution mechanisms may fail, leading to persistent inflammation.[80]

As mentioned above, if the initial trigger of inflammation, such as an infection, persists or is not effectively cleared, it can hinder the resolution of inflammation. Chronic infections or persistent presence of pathogens, repeated, and persistent infection with Chlamydia, for example, can sustain immune response and prevent inflammation from resolving.[44] Dysfunctional immune cells that are unable to properly carry out their functions can impair the resolution process.[81] Immune cells, such as macrophages, neutrophils, and regulatory T cells, play critical roles in inflammation resolution caused by infectious pathogens. For instance, macrophages that are unable to switch from a pro-inflammatory to an anti-inflammatory phenotype may contribute to unresolved inflammation.[82] However, the effect of some lifelong infections caused by cytomegalovirus, Epstein-Barr virus, hepatitis C virus, and other pathogens on chronic inflammation remains controversial.[83]

The resolution of inflammation requires a delicate balance between pro-inflammatory and anti-inflammatory mediators. In the presence of an imbalance with sustained production of pro-inflammatory mediators or insufficient production of anti-inflammatory mediators, inflammation resolution can be impaired. For example, deficiencies in specialized proresolving lipid mediators such as resolvins and lipoxins can prevent inflammation resolution.[84] The clearance of dead cells, debris, and immune cell infiltrates is critical for inflammation resolution.[85] Dysfunctional clearance mechanisms such as impaired phagocytosis or reduced efferocytosis (clearance of apoptotic cells) can lead to the accumulation of inflammatory infiltrates and hinder inflammation resolution.[86] Moreover, hampered removal of cells undergoing apoptosis may lead to the initiation of the development of systemic autoimmunity, the hallmark of SLE.[87] Deficiencies in complement component C1q, a protein complex that plays a prominent recognition role in adaptive and innate immunity, primarily contribute to the insufficient clearance of apoptotic cells. Deficiency of C1q affecting the clearance of dying cells can lead to the development of systemic autoimmunity, as in SLE.[88] Notably, C1q deficiency is a rare defect in the classical pathway of the complement system with autosomal-recessive inheritance pattern that caused by mutations occurring in either of the following C1q genes: *C1qA*, *C1qB*, and *C1qC*.[89] As most SLE patients do not have hereditary C1q deficiency, there is indirect evidence for the significance of C1q in the disease inflammatory processes such as hypocomplementemia developed as a result of activation via the classical pathway, C1q accumulation in tissues affected, and the occurrence of anti-C1q autoantibodies. C1q plays a crucial role in the recognition of various damaging molecules, ranging from pathogen-associated molecular ligands to damage-associated molecular targets.[90] In this way, C1q serves as a molecular bridge between the phagocytic cell and the apoptotic debris that needs to be removed. Utilizing a C1q-deficient mouse model of SLE, it was shown that C1q improves the response to self-antigens by amending the mitochondrial metabolism of effector $CD8^+$ (cytotoxic) T lymphocytes.[91] In addition, opsonization, which facilitates the appropriate clearance of cellular fragments plays a significant role in SLE pathogenesis. Under physiological conditions, the identification of dead cells is maintained by opsonins, C1q including. Both a failure in the efficient and immunologically silent opsonization of fragments of dead cells and the aberrant immunogenic opsonization by autoantibodies of secondary necrotic cell-originated materials support the development of autoimmune response during SLE and promote chronic inflammation.[92] Besides, a joint action of C1q and DNase I augments the clearance of necrotic chromatin.[93]

Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, can impair the resolution of inflammation and, thus, contribute to the development of chronic inflammation.[94] Persistent oxidative stress can cause damage to the biological macromolecules and tissues and impact the resolution process by perpetuating inflammation.[95]

Low-grade inflammation intertwines with metabolic disequilibrium. Patients with schizophrenia have a pronounced metabolic inflammatory imbalance, as evidenced by the presence of increased pro-inflammatory activity and obesity with changes in the metabolism of carbohydrates, lipids, and their metabolites.[96] This study showed that adipose tissue accumulation during the disease progression and treatment with antipsychotics affects a number of key homeostatic factors by disrupting the mechanisms responsible for lipid and carbohydrate metabolism and leading to undesirable changes in cytokine and adipokine profiles. The involvement of cytokines and inflammasomes in the process of development of metabolically associated fatty liver disease, which exhibits a robust immune-inflammatory dimension, was demonstrated.[97] The innate immune system components such as inflammasomes and cytokines are the sources of sterile inflammation in the liver in obesity and metabolic syndrome. The close relationship between innate immune signaling in metabolically associated fatty liver disease was described.[98]

Aging can affect inflammation resolution, with altered function of

immune cells, impaired tissue repair mechanisms, and dysregulated signaling pathways. Age-related changes, including cellular senescence, sarcopenia, and obesity, can contribute to the failure of inflammation resolution, as recently reviewed by Livshits *et al.*[99] Additionally, chronic inflammation can result in tissue damage, which triggers ongoing tissue repair processes.[100] These repair processes involving the recruitment of immune cells, production of growth factors, and formation of new blood vessels, can perpetuate the inflammatory response, and contribute to the chronification of inflammation.

Epigenetic changes contributing to prolonged inflammation

Epigenetic changes are heritable modifications that affect gene expression; however, unlike DNA mutations, they do not involve changes in the underlying DNA sequence. The main epigenetic mechanisms include DNA methylation, chromatin modifications, histone modifications, and loss of imprinting and noncoding RNA. These epigenetic changes can be considered potential molecular causes of chronic inflammation and, hence, implicated in the pathogenesis of many inflammatory disorders. Dysregulated epigenetic modifications can result in altered expression of pro- and anti-inflammatory genes, leading to impaired inflammation resolution and dysregulation of immune responses.[101]

DNA methylation is a common epigenetic modification where methyl groups are added to cytosine residues in DNA, resulting in gene silencing.[102] Hypermethylation of pro-inflammatory genes can lead to their persistent silencing, reducing the production of anti-inflammatory proteins and contributing to prolonged inflammation.[103] DNA methylation can impact the inflammation resolution.[104] These epigenetic changes can also affect immune signaling pathways, leading to dysregulation of immune responses.[105]

Histones are proteins that govern DNA packaging into a compact structure called chromatin. Modifications to histones, such as acetylation, methylation, and phosphorylation, can alter the accessibility of genes for transcription. Persistent inflammation can lead to aberrant histone modifications, resulting in a sustained pro-inflammatory gene expression pattern.[106] Histone modifications can have an impact on the inflammation resolution process[104] and immune signaling pathways, resulting in dysregulation of immune responses.[105]

Noncoding RNAs, such as microRNAs and long noncoding RNAs, are involved in the regulation of gene expression. According to the current understanding, they can act as fine-tuners of inflammatory responses by either promoting or inhibiting the expression of pro-inflammatory or anti-inflammatory genes. Dysregulation of noncoding RNA functions caused by epigenetic changes can disrupt the balance of inflammatory gene expression and contribute to prolonged inflammation.[107]

Chromatin remodeling refers to changes in the structure of chromatin that affect gene accessibility. Adenosine triphosphate (ATP)-dependent chromatin remodeling complexes can be influenced by epigenetic modifications and can lead to prolonged inflammation by controlling the accessibility of pro-inflammatory genes.[108] Overall, epigenetic changes can play a role in the chronification of inflammation by altering the expression of pro-inflammatory and anti-inflammatory genes and disrupting the balance of immune responses. However, the field of epigenetics is still an active area of research, further studies are needed to fully understand the relationship between epigenetic changes and chronic inflammation.

Mitochondria and chronification of inflammation

The role of mitochondria in the chronification of inflammation is a rapidly evolving area of research that aims to elucidate the underlying mechanisms. Our recent review has suggested that mitochondria, which are known as the powerhouses of the cell, owing to their role in producing energy, may also play a crucial role in the chronification of inflammation.[82] Moreover, the evidence indicating the contributing role of mitochondria to the chronification of inflammation was also discussed previously.[4,109]

Dysfunctional mitochondria can contribute to chronic inflammation by several pathways, including oxidative stress, immune dysregulation, and metabolic changes. One key mechanism is the production of ROS during mitochondrial respiration, which can lead to oxidative stress and damage to cellular components, such as proteins, lipids, and DNA.[110] Oxidative stress can elicit inflammation by activating immune cells and promoting the release of pro-inflammatory cytokines.[111] Mitochondrial dysfunction can also impair cellular energy production, leading to metabolic changes that can affect immune cell function and promote chronic inflammation. Reduced energy production by mitochondria can impair the ability of immune cells to clear infections, leading to persistent inflammation.[112] Additionally, mitochondria are involved in the regulation of immune responses through mitophagy, particularly autophagy, the regulated and selective process of removing excess or dysfunctional mitochondria through lysosomal fusion, thereby controlling the quantity and quality of mitochondria in the cell. Mitochondrial quality control system that responds to a wide range of stress stimuli to regulate mitochondrial fission, fusion, biogenesis, and mitophagy, have been discussed in several reviews.[113,114] In particular, the regulatory mechanisms of mitochondrial autophagy during the pathogenesis of chronic inflammation-associated cardiomyopathy have been described.[115,116] The reviews summarized the evidence demonstrating that in hypoxia conditions, mitochondrial autophagy regulated by FUN14 domain-containing 1 (FUNDC1), 465-amino acid residue E3 ubiquitin ligase (PARKIN), BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), and BH3-only family signaling protein (NIX) is increased, leading to peroxisome proliferator-activated receptor alpha (PGC1α)- and nuclear respiratory factors 1/2 (Nrf1/2)-mediated decrease in biogenesis of mitochondria (Fig. 1). In this way, homeostasis of mitochondria necessary for the activity of cardiac cells is achieved.

Dysfunctional mitochondria that are not eliminated by mitophagy can release mtDNA into the cytoplasm and that can activate immune cells and trigger inflammation, as reviewed.[117,118] Indeed, dysfunctional mitochondria can contribute to chronic inflammation to a large extent. Therefore, targeting mitochondrial dysfunction may become a potential therapeutic strategy for the treatment of chronic inflammatory conditions. Further comprehensive studies are required to understand the underlying mechanisms.

Defective mitophagy and inflammatory response

Defective mitophagy can impact the inflammatory response and contribute to the development of inflammatory disease. In fact, defective mitophagy enhances and prolongs the inflammatory response and, thus, may be responsible for the chronification of inflammation.[6,82,119] Improper mitophagy can lead to the accumulation of dysfunctional mitochondria, which release mtDNA and mitochondrial reactive oxygen species (mtROS) into the cytosol.[120] These molecules can activate intracellular signaling pathways that promote the production of inflammatory cytokines, such as IL1β, IL6, and tumor necrosis factor-alpha, and contribute to the development of chronic inflammation. Respective studies have

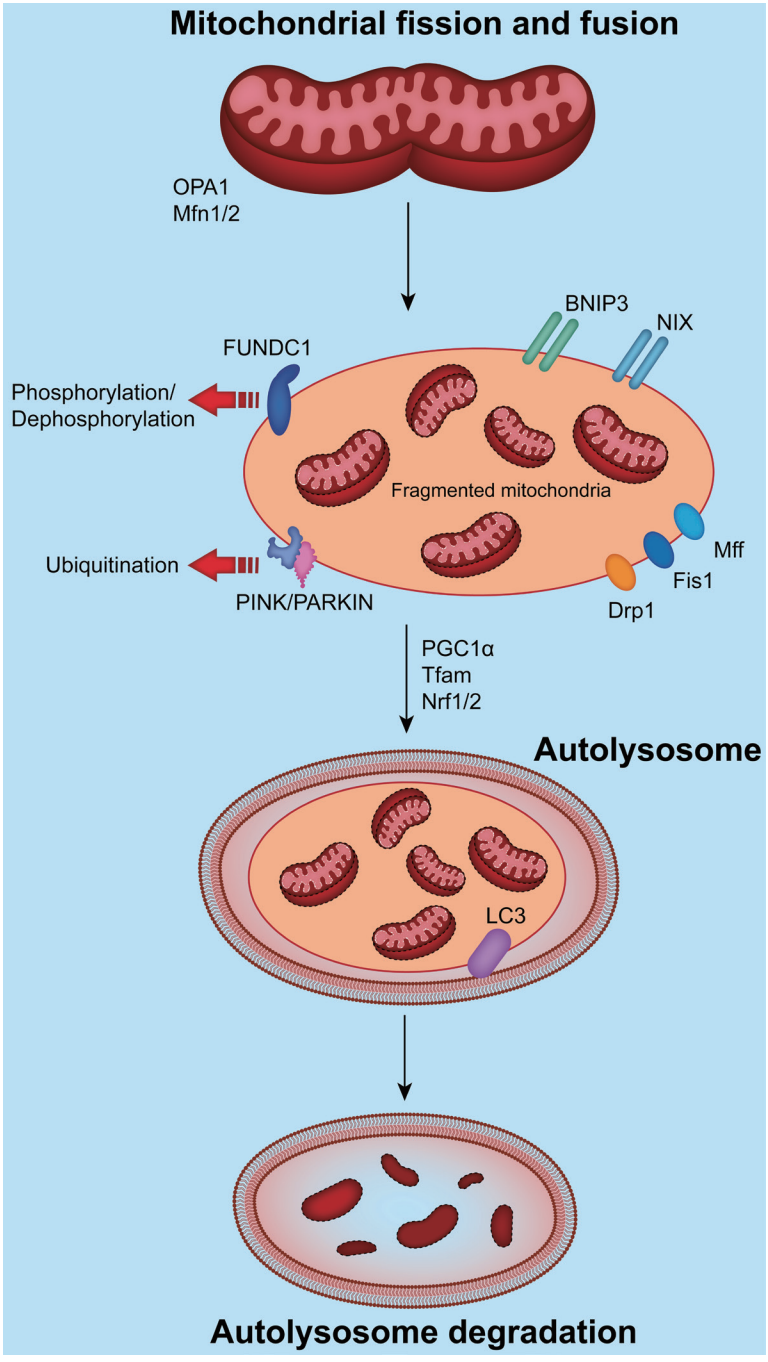


Fig. 1. Schematic representation of the regulation of mitochondrial autophagy during the pathogenesis of chronic inflammation-associated cardiomyopathy. Under hypoxic conditions, the equilibrium between Drp1-, FIS1-, and Mff-facilitated mitochondrial fission and OPA1-, Mfn1-, and Mfn2-facilitated mitochondrial fusion is broken. Such disbalance leads to mitochondrial fragmentation and structurally impaired mitochondria. Damaged (fragmented) and dysfunctional mitochondria are undergoing a loss of mitochondrial membrane potential. Mitochondria with low membrane potentials engage FUNDC1 that can phosphorylate/dephosphorylate different proteins, causing an increased expression of an autophagosome marker LC3 and the formation of mitochondrial autophagic lysosomes. Also, phosphatase and PINK1 are translocated to mitochondria, where they activate PARKIN, which ubiquitinates proteins in the outer membrane of mitochondria. The ubiquitinated mitochondria interact with LC3 on the surface of lysosomes forming autophagosomes. Additionally, BNIP3 and NIX encompassing LC3 interaction motifs directly bind LC3, consequently promoting the formation of autophagic lysosomes. In the later stages of mitophagy, biogenesis of mitochondria occurs. The principal regulatory agent PGC1α, promotes transcription of Tfam by inducing the activity of Nrf-1/2. BNIP3, BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3; Drp1, dynamin-1-like protein; FIS1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing 1; LC3, an autophagosome marker; MMP, mitochondrial membrane potential; Mff, mitochondrial fission factor; NIX, BH3-only family signaling protein; Mfn1/2, mitofusin-1/2; Nrf 1/2, nuclear respiratory factors 1/2; OPA1, dynamin-like 120 kDa protein; PARKIN, 465-amino acid residue E3 ubiquitin ligase; PGC1α, peroxisome proliferator-activated receptor alpha; PINK1, tensin homolog-induced putative kinase 1; Tfam, mitochondrial transcription factor A.

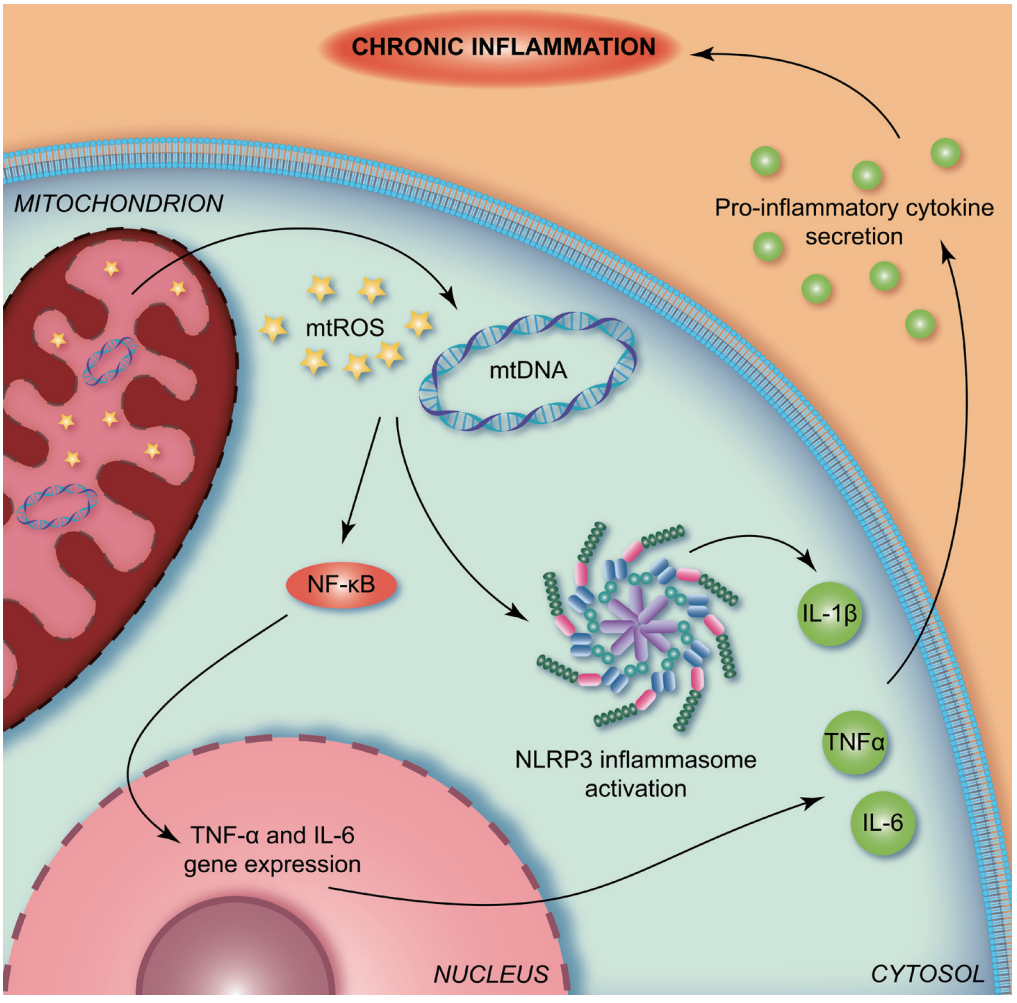


Fig. 2. Interplay between defective mitophagy and chronic inflammation. IL, interleukin; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor-kappa B; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; TNF-α, tumor necrosis factor-alpha.

demonstrated that failed mitophagy can lead to the accumulation of damaged proteins and lipids, which can initiate the activation of the NLRP3 inflammasome, a multiprotein complex that promotes the production of pro-inflammatory cytokines and the development of inflammatory disease.[121,122] Other studies in animal models showed that promoting mitophagy reduced inflammation and prevented the development of inflammatory disease. In a mouse model of atherosclerosis, enhancing mitophagy reduced the accumulation of inflammatory cells in the arterial wall and prevented the development of atherosclerosis, the chronic inflammatory condition.[123,124]

Several studies demonstrated that enhancing mitophagy using pharmacological or genetic approaches can reduce inflammation and improve outcomes in different inflammatory disease models, including diabetes, neurodegenerative diseases, and atherosclerosis. Thus, including mitophagy, rapamycin can reduce inflammation and prevent the development of Parkinson's disease in *in vitro* model cells.[125] Similarly, enhancing mitophagy, urolithin A has been shown to reduce inflammation and improve insulin sensitivity in obese mice.[126] Also, enhancing mitophagy can reduce inflammation and improve outcomes in atherosclerosis. In a mouse model of atherosclerosis, enhanced mitophagy reduced the accumulation of inflammatory cells in the arterial wall and prevented the development of atherosclerosis.[127] In addition, physical exercise, by enhancing the targeting of mitochondria for mitophagy and increasing autophagy and mitophagy flux, reduced inflammation in murine animal models.[128] The schematic representation of the direct link between defective mitophagy and the development of chronic inflammation is presented in Figure 2.

Defective mitophagy can lead to the accumulation of damaged/dysfunctional mitochondria, which can produce excessive mtROS and release mtDNA into the cytoplasm. Mitochondrial ROS and mtDNA can activate the NF-κB signaling pathway, which can increase the transcription of pro-inflammatory cytokines, such as IL6 and tumor necrosis factor-alpha. A release of mtROS and mtDNA can contribute to the activation of the NLRP3 inflammasome, leading to the production and secretion of pro-inflammatory cytokine IL1β. When ROS are produced by dysfunctional mitochondria, they can activate the NLRP3 inflammasome by inducing the production of ROS-sensitive proteins. These proteins can interact with the inflammasome and promote its activation. Similarly, mtDNA can also induce the NLRP3 inflammasome by serving as a damage-associated molecular pattern. These processes are believed to play central roles in the development and progression

of chronic inflammatory diseases, for example, atherosclerosis.[127]

Overall, accumulated evidence suggests that defects in mitophagy can disrupt the inflammatory response and aid in the development of chronic inflammation, the key feature of many inflammatory diseases. Moreover, the increase in mitophagy can reduce inflammation, as shown in experimental models of inflammatory diseases. When mitophagy is enhanced, dysfunctional mitochondria are efficiently removed, which reduces the secretion of pro-inflammatory molecules and attenuates the inflammatory response. Mitophagy modulation may, therefore, have therapeutic potential for the treatment of inflammatory diseases. It is important to note that the modulation of mitophagy can be challenging, therefore, the enhancing mitophagy optimal strategies that would help to achieve therapeutic benefits have to be identified.

Future directions

To obtain rigorous evidence confirming that defective mitophagy is responsible for the disruption of the inflammatory response, the following research can be carried out: (1) Gene-editing experiments using clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) technology that can modify, delete, or correct precise regions in mitophagy-related genes. This approach will allow testing of the effects of altered mitophagy on the inflammatory response. For this, animal models of inflammation can be used; (2) Further animal studies using mitophagy-modulating pharmacological agents, such as rapamycin and urolithin A, to test whether these drugs can reduce inflammation in animal models of inflammation; (3) Translational experiments using human tissue samples obtained from patients with inflammatory diseases that would help to determine whether the association between mitophagy and inflammation observed in animal models extends to humans; (4) *in vitro* studies using cell lines derived from patients with inflammatory diseases to test the after-effects of mitophagy modulation on the production of pro-inflammatory cytokines.

Defective mitophagy and mtDNA mutations

Mitochondria have their own independent genome known as mtDNA. Mitochondrial DNA encodes essential proteins involved in oxidative phosphorylation, the process through which mitochondria generate chemical energy, which is accumulated in ATP molecules. One unique feature of mtDNA is maternal inheritance. It is inherited only from the mother, *i.e.,* passed down from mother to offspring. This means that mtDNA mutations, which can be random or arise due to genetic predisposition or the influence of environmental factors, can be transmitted from generation to generation. Unlike nuclear DNA, mtDNA is more susceptible to mutations and damage because of (1) its vicinity to the site of ROS production; (2) the lack of protective histone proteins, and (3) the failure of the complex DNA repair system.[129]

Mitochondrial DNA mutations can be homoplasmic, where both mutated and wild-type mtDNA are present in the cell or heteroplasmic, where only mutated species are present in the cell. Studies of mtDNA obtained from patients with atherosclerosis showed the presence of mtDNA mutations with different levels of heteroplasmy in atherosclerotic lesions.[130] Mutations were found in the mitochondrial genes encoding rRNA12S, tRNA-Leu (UUR recognition codon), tRNA-Leu (CUN recognition codon), subunits of 1, 2, 5, and 6 NADH-dehydrogenase, and cytochrome B.[131–133] It was also found that, in atherosclerosis, homoplasmic mutations of mtDNA, such as A1811G and G9477A, and heteroplasmic mutations, such as G14459A, A1555G, and G12315A, are linked to the pro-inflammatory activation of circulating human monocytes.[134] This study proposed that in atherosclerosis certain mtDNA mutations can alter monocyte macrophage activation via mitochondrial dysfunction. Also, 4977 bp deletion in mtDNA was detected in blood cells and atherosclerotic lesions of patients with coronary artery disease, which links this mtDNA damage with mitochondrial dysfunction.[135,136] However, whether the degree of damage observed in atherosclerosis is sufficient for the manifestation of mitochondrial dysfunction remains unclear. The continuing loss of mitochondrial function occurs with aging or it can be accelerated by the oxidative stress caused by modified low-density lipoproteins during the process of atherogenesis.[137] Furthermore, a large amount of evidence indicating that mtDNA mutations can impair the normal function of mitochondria, leading to mitochondrial dysfunction that, in turn, can disrupt mitophagy, has been reviewed.[138,139] Mitochondrial DNA mutations can be responsible for defects in mitochondrial respiratory chain complexes, leading to reduced ATP production, increased production of ROS, and altered mitochondrial membrane potential. A study using cybrid cell lines with some point mutations in mtDNA suggested that aging-related mtDNA mutations can lead to mitochondrial dysfunction by altering the oxidative phosphorylation mechanism.[140] Supporting the action of ATP synthase, variants of mtDNA, such as m.3256C>T, m.12315G>A, and m.13513G>A, were also identified.[127] Mitochondrial DNA mutations have key roles in pathological processes, affecting the genes encoding components of mitochondrial electron transport chains or mitochondrial tRNA genes. Thus, numerous mtDNA variants associated with inflammation and mitochondrial dysfunction have been identified.[127] Our experiments showed a direct relationship between the presence of mtDNA variants, such as del562G, m.3256C>T, m.12315G>A, m.13513G>A, and m.14459G>A, and an increased proton leakage and oxygen consumption, resulting in the excessive generation of ROS and the development of mitochondrial dysfunction, under the conditions of uncoupling of oxidative phosphorylation *in vitro*.[127] The level of the pro-inflammatory response was assessed by the expression of the pro-inflammatory cytokine IL1β gene using reverse transcriptase polymerase chain reaction. On day 1, the addition of lipopolysaccharide was accompanied by upregulation of the IL1β gene, indicating the occurrence of an inflammatory response both in control cells and in the presence of mitophagy inhibitors. On day six, repeated addition of lipopolysaccharide resulted in a lower pro-inflammatory response in control cells, indicating the presence of immune tolerance. Upon mitophagy inhibition, a continuous inflammatory response was perceived in cells, whereas immune tolerance was not observed. These experiments emphasize the important role of mtDNA mutations in the development of the innate immune response and the manifestation of chronic inflammation. In addition, a study showed that altered aminoacylation of tRNAHis caused by the m.12201T>C mutation may lead to mitochondrial translational defects and respiratory deficiency.[141] Disrupted tRNA metabolism is accountable for the failure of mitochondrial protein synthesis and oxidative phosphorylation, an increased ROS production, and a marked decrease in membrane potential.[142]

Impaired mitophagy due to mitochondrial dysfunction leads to a buildup of damaged mitochondria within cells.[143] Defective mitophagy due to mtDNA mutations can disrupt cellular energy metabolism and homeostasis, leading to cellular stress and dysfunction. In this way, defective mitophagy caused by mtDNA

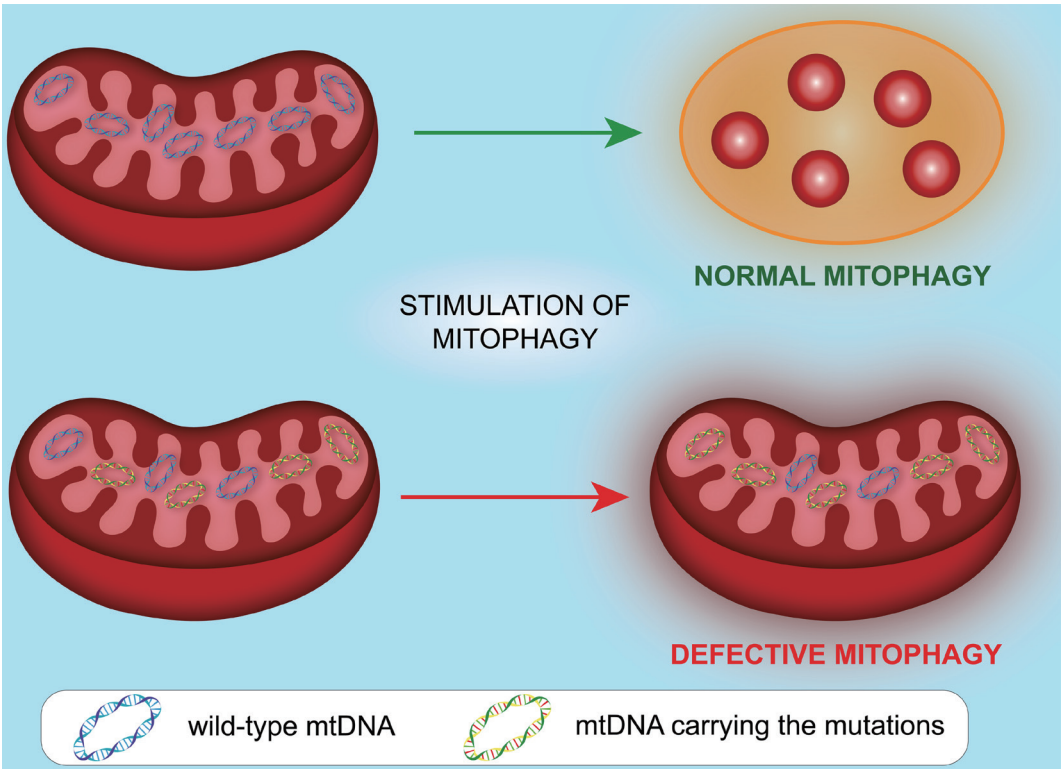


Fig. 3. Hypothetical causal role of mutations in mitochondrial DNA in developing defective mitophagy that induces an excessive and continuous inflammatory response. mtDNA, mitochondrial DNA.

mutations may contribute to the development of chronic diseases, including cancers, neurodegenerative diseases, and metabolic disorders.[144–146] Therefore, it is important to understand the relationship between mutations in mtDNA, mitochondrial dysfunction, and mitophagy defects. Mitochondrial DNA mutations were found to be associated with atherosclerosis.[119] A direct relationship between the presence of some mtDNA mutations and defective mitophagy was also established in chronic inflammation-associated atherosclerotic disease.[147] Therefore, it is possible to suggest that mitochondrial mutations can be the cause of defective mitophagy (Fig. 3), which, in turn, can disrupt the immune response, leading to the development of local chronic inflammation and the formation of an atherosclerotic lesion in the arterial wall, as observed in atherosclerosis.

The schematic representation of the development of chronic inflammation during atherogenesis and atherosclerotic lesion formation in the arterial wall, which is associated with defective mitophagy due to mtDNA mutations, is shown in Figure 4. The hypothesis about the possible role of mitochondrial mutations in the occurrence of defective mitophagy stimulated research using the mitochondrial genome editing approach.[148] In particular, the causal role of the G15059A mutation in the mitochondrially encoded cytochrome B gene was established by using CRISPR/Cas9 technique.[148] The mitoCAS9 vector and two single guide RNAs to the G15059A mutation were used to eliminate the mutation from cybrid cytoplasmic Thp1Cybrid-High Sum Mutation Antiatherogenic Mutation 1(TC-HSMAM1) macrophage-like cells (Fig. 5). As a result, initially defective mitophagy in intact TC-HSMAM1 macrophage-like cells was restored to its normal activity. In these cells, the mitophagy was dysfunctional under the same conditions. Thus, the G15059A mutation causes the disruption of cellular mitophagy processes, preserving dysfunctional mitochondria in cells.

Conclusion

It is clear that mitochondria, apart from playing a crucial role in a variety of cellular processes, such as energy production, metabolism, and cell signaling, are also involved in regulating inflammation, a complex immune response to tissue injury or infection. Independent research groups have established a connection between dysfunctional mitochondria and the chronification of inflammation. In particular, mitophagy defects caused by mtDNA mutations have been found to be associated with disrupted immune response. Dysfunctional mitophagy can lead to the accumulation of damaged mitochondria within cells, resulting in the production of ROS and the release of pro-inflammatory molecules. These molecules can cause and sustain a lengthy stimulation of the inflammatory response, leading to the chronification of inflammation. The chronification of inflammation associated with dysfunctional mitophagy and mtDNA mutations can contribute to the pathogenesis of many inflammatory diseases, such as neurodegenerative disorders, cardiovascular diseases, and metabolic and autoimmune disorders. In recent years, the mechanisms that prevent the clearance of dysfunctional mitochondria and determine the development of chronic inflammation have become the subject of important biomedical research as one of the main medical problems. Understanding these processes may provide insights into developing therapeutic strategies to restore mitochondrial health and mitigate chronic inflammation.

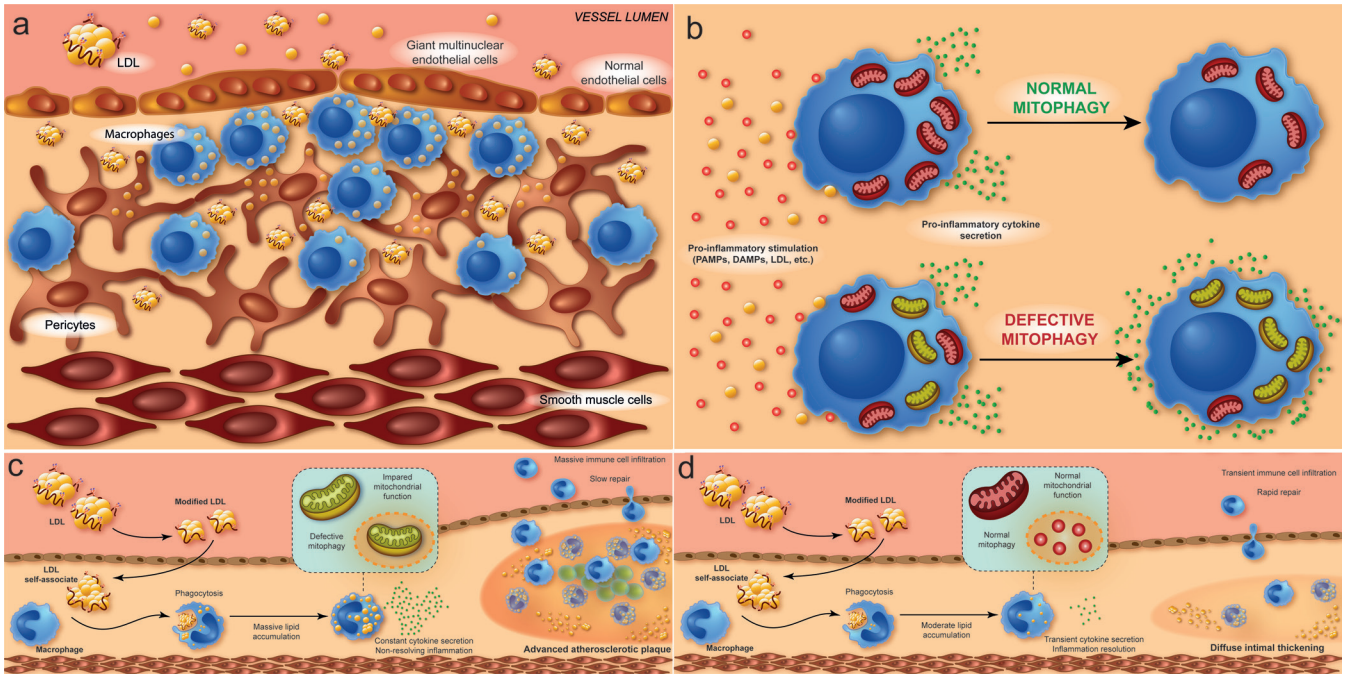


Fig. 4. Proposed mechanisms of chronic inflammation development in the arterial wall during atherogenesis and atherosclerotic lesion formation, which is associated with defective mitophagy due to mtDNA mutations. (a) Accumulation of circulating immune cells and LDL is taking place predominantly in areas with a great number of giant multinucleated endothelial cells. (b) Pro-inflammatory signaling initiated in response to pro-inflammatory stimuli or uptake of modified LDL can become persistent due to defective mitophagy. (c) Chronification of inflammation and (d) Inflammation resolution in the arterial wall can lead either to persistent inflammation or diffuse thickening and atherosclerotic plaque formation. DAMPs, damage-associated molecular patterns; LDL, low-density lipoprotein; PAMPs, pathogen-associated molecular patterns.

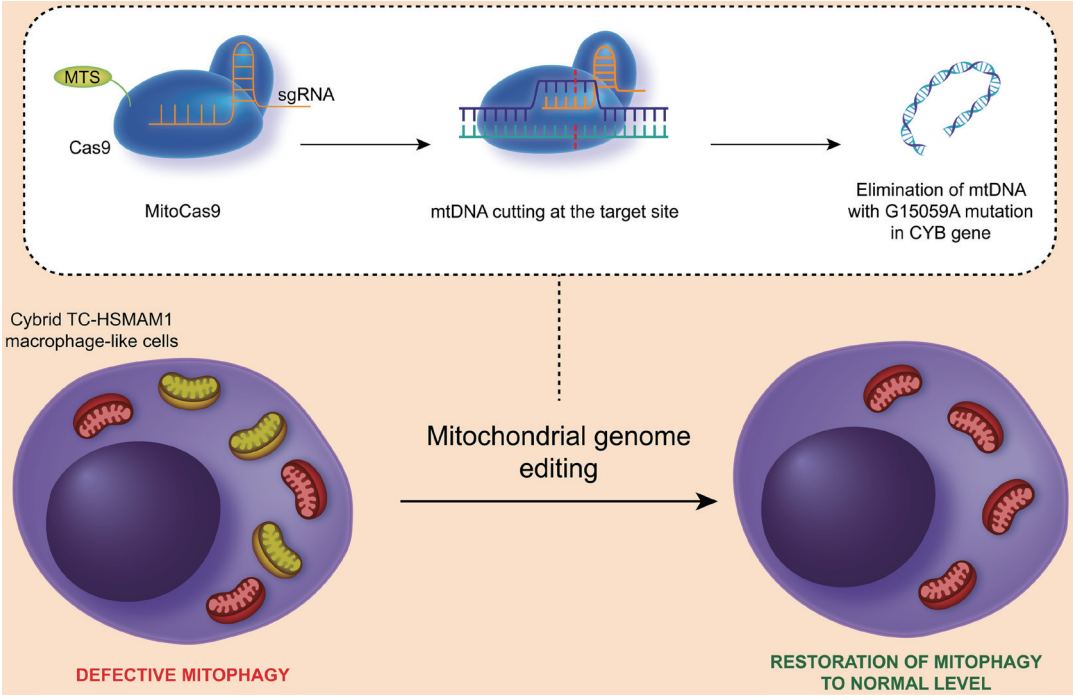


Fig. 5. Schematic representation of functional recovery of defective mitophagy caused by the presence of the G15059A mutation in mtDNA in cybrid TC-HSMAM1 macrophage-like cells, elucidated by using the mitochondrial genome editing approach, the CRISPR/Cas9 technique. CRISPR-Cas9, clustered regularly interspaced short palindromic repeats; mtDNA, mitochondrial DNA; MTS, mitochondrial targeting sequence; sgRNA, single guide RNA; TC-HSMAM1, Thp1 Cybrid-High Sum Mutation Antiatherogenic Mutation 1.

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There is nothing to declare.

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Conflict of interest

ANO has been an editorial board member of *Gene Expression* since June 2023. The authors declare there are no other conflict of interests related to this study.

Author contributions

Wrote the draft of the manuscript and provided the figures with legends (ANO), contributed to the concept of the manuscript (VAK, MAP, JKU, VNS), and conducted the final review and editing of the manuscript (VIS). All authors have read and approved the final version of the manuscript.

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