Published in final edited form as:

Mitochondrion. 2018 July ; 41: 37–44. doi:10.1016/j.mito.2017.12.001.

Mitochondrial Dysfunction and Damage Associated Molecular Patterns (DAMPs) in Chronic Inflammatory Diseases

Charles S. Dela Cruz^{1,*} and Min-Jong Kang^{1,*}

¹Section of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520-8057

Abstract

Inflammation represents a comprehensive host response to external stimuli for the purpose of eliminating the offending agent, minimizing injury to host tissues and fostering repair of damaged tissues back to homeostatic levels. In normal physiologic context, inflammatory response culminates with the resolution of infection and tissue damage response. However, in a pathologic context, persistent or inappropriately regulated inflammation occurs that can lead to chronic inflammatory diseases. Recent scientific advances have integrated the role of innate immune response to be an important arm of the inflammatory process. Accordingly, the dysregulation of innate immunity has been increasingly recognized as a driving force of chronic inflammatory diseases. Mitochondria have recently emerged as organelles which govern fundamental cellular functions including cell proliferation or differentiation, cell death, metabolism and cellular signaling that are important in innate immunity and inflammation-mediated diseases. As a natural consequence, mitochondrial dysfunction has been highlighted in a myriad of chronic inflammatory diseases. Moreover, the similarities between mitochondrial and bacterial constituents highlight the intrinsic links in the innate immune mechanisms that control chronic inflammation in diseases where mitochondrial damage associated molecular patterns (DAMPs) have been involved. Here in this review, the role of mitochondria in innate immune responses is discussed and how it pertains to the mitochondrial dysfunction or DAMPs seen in chronic inflammatory diseases is reviewed.

Keywords

Mitochondria; DAMPs; Chronic Inflammation; Innate Immunity

*Corresponding Author: Min-Jong Kang, M.D., Ph.D., Department of Internal Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, PO BOX 208057, New Haven, CT 06520-8057, min-jong.kang@yale.edu, Phone 1-203-737-6343; Fax 1-203-785-3763 Or Charles S. Dela Cruz, M.D., Ph.D., Department of Internal Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, PO BOX 208057, New Haven, CT 06520-8057, Charles.delacruz@yale.edu, Phone 1-203-737-4181; Fax 1-203-785-5952.

*Equally contributed for the work

AUTHOR CONTRIBUTIONS

Conceived the idea and designed the experiments (CDC, MJK); Provided scientific insight (CDC, MJK); Drafted the manuscript (CDC, MJK); All of the authors reviewed the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

I. INTRODUCTION

Inflammation is classically defined as a response of vascularized tissues to infections and damaging stimuli that brings cells and molecules of host defense from the circulation to the sites where they are needed, in order to eliminate the offending agents (Kumar V, 2015). Host inflammation has a functional role as the body's immediate response to damage to its cells and tissues by pathogens or noxious stimuli such as chemicals or physical injury. Recent conceptual advances in innate immunity have shed new light on our understanding of inflammation, revealing that inflammation is closely related to innate immunity, the first line of the host defense system. Inflammation can be acute with its short-term response that usually results in healing: leukocytes infiltrate the damaged region, remove the noxious stimulus and repair the damaged tissue. Chronic inflammation, by contrast, is a prolonged, dysregulated and maladaptive response that involves persistent inflammation and, often, tissue destruction (Kumar V, 2015).

Mitochondria have recently emerged as important signaling organelles where intracellular perturbations are integrated and, consequently, intracellular signaling pathways are modulated to execute appropriate cellular functions (Bhola and Letai, 2016; Chandel, 2015; West et al., 2011). In addition, studies over the past two or three decades have expanded mitochondrial roles as important players in regulating cell proliferation or differentiation, cell death, redox and calcium homeostasis and others. Hence, considering that mitochondrial function and behavior are fundamental to the physiology of cellular and organismal health, it is not surprising "mitochondrial dysfunction" has been implicated in a wide range of diseases that encompass all aspects of health and disease (Cloonan and Choi, 2016; Dromparis and Michelakis, 2013; Nunnari and Suomalainen, 2012; Sack and Finkel, 2012; Wallace, 2012; Weinberg et al., 2015). Certainly, recent advancements on mitochondrial biology have enabled us to rethink of mitochondrial role in chronic inflammation and its related disorders (Lopez-Armada et al., 2013). In this review, current understanding of mitochondrial dysfunction is discussed in the context of various chronic inflammatory disorders.

II. INFLAMMATION & MITOCHONDRIA

A. Inflammation – an overview

As evident in the description of the four cardinal signs of inflammation, *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain), which is noted in the writing of a Roman encyclopedist, Aulus Cornelius Celsus (c. 25 BC – c. 50 AD), inflammation is an ancient concept noted far earlier than modern medicine (Kumar V, 2015). Since then, numerous studies have added knowledge about functional characteristics and their underlying mechanisms contributing to inflammatory response. Mediators of inflammation include phagocytic leukocytes, antibodies, and complement proteins. In addition, components of other innate immunity including natural killer cells, dendritic cells, and epithelial cells are also active participants in inflammation. The process of inflammation delivers these cells and proteins to damaged or necrotic tissues and foreign invaders, such as microbes, and activates the recruited cells and molecules, which then function to get rid of the harmful or unwanted substances (Kumar V, 2015). As such, inflammation comprises a diverse range of

processes that has become too large and amorphous to fit into a single discipline (Medzhitov, 2010).

Although inflammation is such a comprehensive term which include diverse range of normal physiology and pathology, it should be noted that inflammation has been continuously re-illuminated in the perspective of innate immunity. Indeed, these recent advances in innate immunity has revealed that inflammatory responses share many features of innate immunity and, conceptually, the line cannot be clearly drawn to differentiate these two terminologies. Here in this review, inflammation or innate immune response is used interchangeably in accordance with the context.

B. Functional Role of Mitochondria in Inflammation and Innate Immunity

During four billion years of evolution, prokaryotes have never been evolved to achieve morphological complexity beyond the rudimentary form. All complex organism is composed of eukaryotic cells. Why is that? A school of evolutionary biologists argue that the origin of mitochondria and the eukaryotic cell was plausibly the same event, which arose from prokaryotes just once four billion years ago via endosymbiosis; and, the acquisition of mitochondria was the critical step towards the origin of eukaryotes (Lane, 2015; Lane and Martin, 2010). In other words, the acquisition of mitochondria was prerequisite to eukaryote complexity and the key innovation *en route* to the development of multicellular life. Given this evolutionary history, it is no wonder that mitochondrial functions are inseparably integrated with fundamental cellular physiology, and thus, mitochondria are connected to every aspect of inflammatory and innate immune responses to keep cellular or organismal physiology in homeostasis. The functional role of mitochondria in association with chronic inflammation and its related disorders is summarized below, focusing on recently emerged conceptual advances (Figure 1).

B.1. Mitochondrial Regulation of Inflammasomes—Since the concept of inflammasomes was introduced nearly a decade ago, inflammasomes have been increasingly recognized as a central player in innate immune and inflammatory responses (reviewed in the reference (Strowig et al., 2012)). Inflammasomes-activated caspase-1 is used for the activation of pro-inflammatory cytokines IL-1 β and IL-18, and release of these cytokines results in the recruitment of effector cell populations important in inflammation and tissue repair. Under normal circumstances, the activation of the inflammasomes culminates in the resolution of infection or inflammation and contributes to homeostatic processes. However, in a pathologic context, the perpetuation of inflammasome activation occurs and this leads to a variety of chronic inflammatory disorders such as metabolic disorders, tumorigenesis and autoimmune diseases (Davis et al., 2011; de Zoete et al., 2014; Schroder and Tschopp, 2010; Strowig et al., 2012). In this regards, multiple studies have demonstrated a key role for mitochondria or mitochondrial function in the regulation of inflammasomes-mediated signaling (reviewed in (Gurung et al., 2015; Mills et al., 2017; Tschopp, 2011)). Mitochondrial dysfunction or damage causes the following individually or simultaneously: mitochondrial reactive oxygen species (mtROS), aberrant calcium mobilization, reduction in cytoplasmic levels of NAD⁺, potassium (K⁺) efflux, as well as extracellular ATP. These mitochondrial-related changes have been shown to be involved in NLRP3 inflammasomes

activation. It is important to note, however, that it has not been identified yet how the various aspects of mitochondrial dysfunction converge as a common pathway to activate NLRP3 inflammasomes (Gurung et al., 2015). In addition, mitochondrial-dependent regulation of inflammasome activation seems to be specific to NLRP3 inflammasomes. Other types of inflammasomes such as the NLRC4, AIM2, and NLRP1b inflammasomes have not been dependent on mitochondria. Currently, it is not clear why mitochondria is specifically involved in the regulation of NLRP3 inflammasomes but not in others (Gurung et al., 2015; Lamkanfi and Dixit, 2014).

B.2. Mitochondria as signaling hubs—Mitochondria have recently emerged as important signaling organelles where intracellular perturbations are integrated and, consequently, intracellular signaling pathways are modulated to execute appropriate cellular functions (Bohovych and Khalimonchuk, 2016; Butow and Avadhani, 2004). Multiple mechanisms have been identified by which a variety of signals from the extracellular milieu or cytoplasmic perturbations are conveyed to mitochondria where these events are collectively interpreted, and, as a consequence, metabolic, regulatory, or stress-related pathways are adjusted with altered mitochondrial states (Bohovych and Khalimonchuk, 2016; Chandel, 2015). For example, under conditions of mitochondrial damage, decreased ATP production results in depletion of intracellular ATP, which leads to increased intracellular concentrations of adenosine monophosphate (AMP) or its subsequent derivative, adenosine. The latter nucleotide directly binds to the γ subunit of the energy-sensing adenosine monophosphate-activated protein kinase (AMPK) complex, which plays as a key metabolic sensor in the cell and its activation initiates multiple signaling events (Wu et al., 2014). In addition, mitochondrial biosynthetic intermediates such as acetyl coenzyme A, succinate and others play as important signaling molecules (Chandel, 2015). Physiological amounts of free radicals have also been identified to be required to mediate a number of normal cellular processes including signaling pathways such as hypoxic signaling (Shadel and Horvath, 2015). Furthermore, mitochondria play an important role in the regulation of major elements of innate immune receptor signaling pathways such as RIG-I-like helicases receptors (RLR), Toll-like-receptors (TLR), and Nuclear oligomerization domain (NOD)-like receptors (NLR) (Cloonan and Choi, 2013). As such, it seems obvious that mitochondria have important roles as centrally positioned signaling hubs in regulating inflammatory and immune responses (West et al., 2011).

C. Mitochondrial DAMPs in Inflammation/ Innate Immunity

Given the evolutionary history, it is not surprising that mitochondria can work as a double-edged sword in regulating innate immune and inflammatory responses. The innate immune system evolved to recognize conserved bacterial molecules that are largely foreign to host cells. As mitochondria are considered to have originated from α -proteobacteria through endosymbiosis (Archibald, 2015), many similarities exist between mitochondrial and bacterial constituents. Thus, it has been hypothesized that mitochondrial constituents might play as damage-associated molecular patterns (DAMPs) that could trigger innate immune responses during pathological insults (Krysko et al., 2011). In other words, when mitochondria are stressed or functionally impaired, they may produce a variety of mitochondrial DAMPs which function as drivers of the inflammatory responses, and in

certain situation could be pathologic. Recent information is summarized about mitochondrial DAMPs which are being actively studied in inflammation and inflammatory disorders (Figure 1).

C.1. Mitochondrial DNA (mtDNA)—Mitochondrial DNA (mtDNA) is increasingly recognized as an agonist of the innate immune system that influences antimicrobial responses and inflammatory pathology. It has been demonstrated that fragments of mtDNA are released from mitochondria upon opening of the mitochondrial permeability transition pore (Patrushev et al., 2004). On entering the cytoplasm, extracellular space or circulation, mtDNA can engage multiple pattern-recognition receptors in cell-type- and context-dependent manners to trigger pro-inflammatory and type I interferon responses (reviewed in reference;(West and Shadel, 2017)). Like bacterial genome, mtDNA has numerous regions of nonmethylated DNA (CpG islands). Indeed, it has been demonstrated that mtDNA released into circulation by traumatic injury cause inflammatory responses via Toll-like receptor 9 (TLR9)-dependent stimulation of polymorphonuclear cells (Zhang et al., 2010). Accumulation of mtDNA in the cytosol has been identified to cause activation of an antiviral immune response (West et al., 2015). In addition, oxidized mtDNA released during programmed cell death appears to activate nucleotide-binding domain leucine-rich repeat family, pyrin domain containing 3 (NLRP3) inflammasomes and the consequent IL-1 β production (Shimada et al., 2012). Interestingly, a recent study has demonstrated that autophagy, a major cellular homeostatic program for organelle and protein turnover, regulates innate immune responses by inhibiting the release of mtDNA which is mediated by the NLRP3 inflammasomes activation (Nakahira et al., 2011).

C.2. N-formyl Peptides (NFP)—Just like in bacteria, the initiation of mitochondrial translation requires N-formylmethionine-tRNA (Ott et al., 2016). Similar to their bacterial homologs, mitochondrial NFPs has been identified to attract neutrophils in earlier studies (Carp, 1982). Later studies have revealed that mitochondrial NFPs are recognized by high-affinity formyl peptides receptors (FPRs) (Dahlgren et al., 2016). FPRs constitute a small group of 7-transmembrane domain, G-protein-coupled receptors that are expressed not only on neutrophils, monocytes and dendritic cells but also on hepatocytes, endothelial cells and cells of the nervous system (He and Ye, 2017). Indeed, a recent study has suggested a pathogenic role of mitochondrial NFPs in human disease (Dorward et al., 2017). In this study, mitochondrial NFPs appear to be increased in the intra-alveolar space of lungs and circulation of patient with acute respiratory distress syndrome (ARDS) and mitochondrial NFPs-driven formyl peptide receptor 1 signaling seems to mediate an important role in the pathogenesis of sterile lung inflammation (Dorward et al., 2017).

C.3. Cardiolipin—Cardiolipin is the signature phospholipid of mitochondria. As a principal lipid component of the inner mitochondrial membrane, cardiolipin is normally confined to mitochondria. In certain contexts of mitochondrial stress or mitochondrial dysfunction, however, it undergoes oxidation and is released into the extracellular milieu as a mitochondrial DAMP (Claypool and Koehler, 2012). A recent study has demonstrated that cardiolipin can play as a potent immunogenic factor to activate NLRP3 inflammasomes via its direct binding to NLRP3 (Iyer et al., 2013). Interestingly, inflammatory insults caused by

infection or noxious agents such as silica appear to cause the translocation of cardiolipin from the inner mitochondrial membrane to the cytosol-facing outer membrane, allowing NLRP3 recruitment and activation and leading to the production of the important pro-inflammatory cytokine IL-1 β (Iyer et al., 2013). This observation may provide another evidence to support the role of misplaced mitochondrial molecule which act as a mitochondrial danger signal. In this regard, the hydrophobic portions of biological molecules, which are considered to be part of an evolutionarily ancient alert system, have been implicated to act, when exposed, as universal DAMPs to initiate inflammatory and immune responses (Seong and Matzinger, 2004). Cardiolipin might play such a functional role as a hydrophobic danger signal. Further studies are required to address these intriguing questions.

C.4. Cytochrome C—Cytochrome *c* is a small soluble electron carrier heme protein found loosely associated with the mitochondrial inner membrane. Under normal conditions, cytochrome *c* transfers electrons from complex III to complex IV to facilitate cell energy production. Upon apoptotic stimuli, the release of cytochrome *c* into the cytoplasm has been identified to be a critical event to trigger non-inflammatory process of cellular death. In contrast, when translocated into the extracellular space, cytochrome *c* may function as a mitochondrial DAMP to trigger inflammation and its level could be used as a marker of mitochondrial damage (Eleftheriadis et al., 2016). For example, serum levels of cytochrome *c* were found increased in patients with myocardial infarction, hepatic inflammation, multiple types of cancers and systemic inflammatory response syndrome. The measurement of cytochrome *c* has been suggested to be a clinically useful marker for diagnosing and assessing the severity of these pathologic entities (reviewed in reference; (Eleftheriadis et al., 2016)).

D. Role of Mitochondrial in Immunometabolism

Different immune cells should adopt distinct metabolic configurations to balance its requirements for energy and molecular biosynthesis as they respond to immunological challenges. As a natural consequence, immunometabolism, the interface of immune and metabolic responses in health and disease, has emerged as a novel theme in studies of chronic inflammatory pathologies (Loftus and Finlay, 2016; Schertzer and Steinberg, 2014). Given mitochondria are at the core of metabolic adaptation to the changing environment, it is not surprising the close interaction between mitochondrial metabolism and immune signaling has been highlighted recently (Sancho et al., 2017). These mitochondrial components include electron transfer chain (ETC) system, tricarboxylic acid (TCA) cycle or fatty acid oxidation metabolic pathways, which influence innate and adaptive immune responses via various ways (Bohovych and Khalimonchuk, 2016). For example, metabolic intermediates such as acetyl coenzyme A (ac-CoA) can be used for DNA or protein modification which influence epigenetic regulation. Mitochondrial dysfunction perturbs alteration of adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ration, which, in turn, activates adenosine monophosphate-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis. Indeed, a highly ordered interactions between immune and metabolic responses have been demonstrated in multiple studies, identifying the

complex immunometabolic signaling networks and the cellular and molecular events which underlie the development of chronic inflammatory diseases (Hotamisligil, 2017).

E. Mitochondrial Quality Control and Inflammation/ Innate Immunity

In keeping with the importance of mitochondrial health, a number of mechanisms are now known to contribute to mitochondrial quality control, a term used to describe the integrated coordination of mechanisms operating in order to protect mitochondria against stress, monitor mitochondrial damage and ensure the selective removal of dysfunctional mitochondrial proteins or organelles (Fischer et al., 2012; Szklarczyk et al., 2014). Mitophagy, a selective form of autophagy in which damaged or dysfunctional mitochondria are specifically targeted for lysosomal degradation, constitutes an important arm of mitochondrial quality control (Tan et al., 2016). Indeed, a defect of mitophagy in macrophages causes pronounced accumulation of damaged mitochondria and excessive IL-1 β -dependent inflammation (Zhong et al., 2016). Therefore, it seems that mitophagy orchestrates a self-limiting host response that maintains homeostasis and favors tissue repair. Our understanding remains limited, however, about how the pathways or molecules of mitophagy/mitochondrial quality control play a role in the pathogenesis of chronic inflammatory diseases.

III. RECENT ADVANCES – MITOCHONDRIAL DYSFUNCTION/DAMPs AND CHRONIC INFLAMMATORY DISEASES

A. Cardiovascular Disorders and Mitochondria

Atherosclerosis is an arterial disease process characterized by the accumulation of lipoproteins, immune and inflammatory cells as well as extracellular matrix in subendothelium (Tabas and Lichtman, 2017). The lipoproteins which function as a DAMP trigger innate immune responses and the ongoing inflammatory response contributes significantly to the development of arterial damage and thrombotic complications (Tabas and Lichtman, 2017). Markers of inflammation such as C-reactive protein have become *bone fide* risk factors for the complications of atherosclerosis. Mitochondrial dysfunction is associated with atherosclerosis, and the increased production of ROS in mitochondria and mitochondrial DNA damage accumulation can lead to atherosclerosis (Madamanchi and Runge, 2007). In addition, many contributors of atherogenesis in addition to inflammation such as hypercholesterol, hyperglycemia, hypertriglyceridemia, aging can result in mitochondrial dysfunction. Pancreatic beta-islet cells are damaged with excessive mitochondrial ROS and can lead to increased LDL oxidation and endothelial cell dysfunction which all can promote atherosclerosis. Mitochondrial dysfunction can result in apoptosis, favoring plaque rupture. Atherosclerosis also requires normal vascular cell growth which requires mitochondrial integrity, and the increased mitochondrial stress seen in atherosclerosis can result in abnormal endothelial structure and function, and vascular smooth muscle aberrant proliferations. Low aerobic capacity as manifested as poor exercise tolerance is associated with increased risk of cardiovascular death (Kodama et al., 2009). Mitochondrial dysfunction impairs aerobic capacity and endothelial cell function, and contribute to vascular smooth muscle proliferation and apoptosis resulting to the

development of atherosclerosis. Many of the factors that contribute to atherogenesis causes varying degrees of oxidative damages to mitochondrial proteins which can lead to progressive mitochondrial dysfunction (Ballinger et al., 2002). Studies are underway to determine if mitochondrial dysfunction itself directly results in atherogenesis, or if mitochondrial dysfunctions are responses to atherosclerosis as currently this is not clear.

Studies have shown that mtDNA, itself are inflammatogenic, are found in complex with antimicrobial peptide LL37 in atherosclerotic plaques and plasma (Zhang et al., 2015). Mitochondrial structural changes and mitochondrial DNA damage are seen in mitochondrial aging and cell senescence, and atherosclerosis is a typical aged degenerative pathology characterized by dysfunctional mitochondria (Sobenin et al., 2015). Cholesterol themselves as crystals are important metabolic signals that can induce sterile inflammation as seen in atherosclerosis, especially with the known role of cholesterol crystals in activating IL-1 production (Freigang et al., 2013).

The heart is one of the highest ATP-consuming organs in the body, turning over more than its weight in ATP per day. Approximately 95% of ATP is produced by the mitochondrion and thus, mitochondria play a crucial bioenergetics role in healthy heart function. Indeed, the failing heart from the patients with heart failure is characterized by a complex interplay of defective mitochondrial proteins, oxidative damage and althered signaling pathways, resulting in insufficient energy production in myocardium (Sheeran and Pepe, 2017). In addition, mitochondrial diseases preferentially affect the heart, as impaired cardiac conditions are associated with mitochondrial dysfunction due to defects in either OXPHOS or ETC (Lee and Han, 2017). Accordingly, novel pharmacological approaches are recently being endeavored to target the mitochondria and preserve or restore their function for the treatment of cardiovascular disorders (von Hardenberg and Maack, 2017). In this regard, a recent study has demonstrated that spermidine, a natural polyamine, exerts cardioprotective effects via, at least, enhancement of cardiac autophagy, mitophagy and mitochondrial respiration in aged mice (Eisenberg et al., 2016).

B. Pulmonary Disorders and Mitochondria

Many pulmonary disorders have recently been linked with mitochondrial dysfunction given the fact that many of these pulmonary disorders such as COPD and fibrosis are linked fundamentally with aberrant lung inflammatory and repair responses to external stimuli. The role of mitochondrial function has been an active area of investigation in pulmonary medicine. For example, COPD is a pulmonary disorder characterized by chronic inflammation and aberrant tissue remodeling in response to cigarette smoke exposure and other external stimuli. Studies have shown mitochondrial dysfunction in patients with COPD and have implicated several mitochondrial related genes such as MAVS and NLRX1 in its pathogenesis (Kang and Shadel, 2016; Kang et al., 2015; Yoon et al., 2016).

COPD is also characterized by exercise intolerance and skeletal muscle mitochondrial dysfunction, alteration of mitochondrial DNA content and reduced mitochondrial densities in these patients (Puate-Maestu et al., 2011; Puate-Maestu et al., 2009; Rabinovich et al., 2007). Mitochondrial fission as mediated by a specific cathepsin has been shown to be associated in lung models of lung tissue destruction as in emphysema (Zhang et al., 2014).

Mitochondrial associated autophagy (or mitophagy) as well as iron-mediated mitochondria regulation have been shown to be important in COPD pathogenesis (Cloonan et al., 2016; Mizumura et al., 2014). Alveolar macrophages from COPD patients have impaired bacterial clearance due to failure to induce mitochondrial ROS in the macrophages in response to infection (Bewley et al., 2017).

Pulmonary fibrosis, a disease associated with aging, has been shown to have altered mitochondria (reviewed in (Mora et al., 2017)). Dysfunctional mitochondria in alveolar epithelial cells in IPF has been linked to reduced expression of PINK1 (a regulator of mitochondrial homeostasis) (Bueno et al., 2015; Patel et al., 2015). Other pulmonary disease such as asthma, cystic fibrosis and pulmonary hypertension have been reported to have mitochondrial dysfunction (Dromparis and Michelakis, 2013; Dromparis et al., 2013; Iyer et al., 2017; Valdivieso and Santa-Coloma, 2013).

C. Hepatic Disorders & Mitochondria

Mitochondrial dysfunction plays an important role in many liver diseases including drug-induced liver injury, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD) and others. Among these, NAFLD is the most common cause of chronic liver disease in adults, increasing in parallel with that of obesity and diabetes (Rinella, 2015). It encompasses diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NSAH), fibrosis, and cirrhosis (Samuel and Shulman, 2017). Although the underlying pathophysiologic mechanism that contribute to the development and progression of NAFLD and NASH are complex (Samuel and Shulman, 2017), the activation of the innate immune system in association with chronic inflammation has been highlighted as an important feature of its pathogenesis (Arrese et al., 2016). Furthermore, maladaptation of mitochondrial oxidative flux has been indicated as a central feature of simple steatosis to NASH transition (Sunny et al., 2017). The liver is the hub of intermediary metabolism supporting key anabolic pathways and, in the setting of obesity and hepatic insulin resistance, continuous maladaptation of mitochondrial energetics, gene expression and morphology seems to play a key role in the pathogenesis (Koliaki et al., 2015).

D. Cancer-related inflammation & Mitochondria

Inflammation and dysregulated cellular energetics are important hallmarks of cancer. Many cancers arise from sites of infection, chronic irritation and inflammation. Cancers rely on many mitochondrial activities that include oxidative phosphorylation for cell growth and survival, suppression of mitochondria-mediated apoptosis and synthesis of nucleotide and amino acids. The host relies on the mitochondria protective responses to limit tumorigenesis. The tumor environment is an important contributor to the neoplastic process that can foster cell proliferation, survival and migration that is important for cancer development and progression with metastases (Shalapour and Karin, 2015). Tumor-associated inflammation can also result in immunosuppressive effects allowing for unchecked tumor growth but recent successful advances have taken advantage of using important immune checkpoint inhibitors in the treatment of many solid tumors (Nishino et al., 2017).

Somatic mutations in the mtDNA of human cancers are common events. It has been suggested that somatic mutations and decreased copy number of mtDNA in tumors cells can lead to mitochondrial dysfunction and cancer progression (Lee et al., 2005). However, how the specific mtDNA mutations regulate tumorigenesis is not clear. Mitochondrial enzyme defects, mtDNA mutations and or altered oncogenes/tumor suppressors in cancer result in mitochondrial dysfunctions and these dysfunctions are associated with deregulated cellular energetics as commonly seen in tumorigenesis (Petros et al., 2005; Shidara et al., 2005). Moreover, mitochondrial dysfunction promote cancer progression to cancer phenotypes that are apoptosis-resistant and or chemo-resistant with invasive properties (Higuchi et al., 2006; Ishikawa et al., 2008; Singh et al., 2009). More and more is being discovered how mitochondrial dysfunction influence inflammatory responses and cellular metabolisms, which are all important in all aspects of cancer biology.

E. Neuroinflammation & Mitochondrial dysfunction/DAMPs

Since the word ‘neuroinflammation’ was first coined in the 1980s to describe the accumulation of leukocytes in degenerating myelin and brain vessels in multiple sclerosis, the concept of ‘neuroinflammation’ has been extended to other neurodegenerative disorders including Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis and other neurological disorders (Masgrau et al., 2017; Ransohoff, 2016). Inflammation, which is characterized by the presence of immune and inflammatory cells, is indeed observed in these pathologies. Additional evidence of neuroinflammation can encompass the activation of inflammatory pathways, increased expression of cytokines or chemokines, and in some cases, disruption of the blood–brain barrier (BBB) accompanied by infiltration of peripheral immune cells (such as T cells) (Schwartz and Deczkowska, 2016). Because signs of neuroinflammation and neurodegeneration represent a ubiquitous pathological finding during the course of multiple neurodegenerative diseases, and, importantly, mitochondria may exert a crucial role in the pathogenesis of both inflammatory and neurodegenerative central nervous system disorders, there has been a consensus in which neuroinflammation and mitochondrial impairment may synergistically trigger a vicious cycle ultimately leading to neuronal death (Di Filippo et al., 2010; Wilkins et al., 2017; Witte et al., 2010). It is true, however, that the nature of neuroinflammation and the immunologic features of each neurodegenerative disorders are distinct and strikingly different among these conditions (Schwartz and Deczkowska, 2016). Furthermore, neuroinflammation has been difficult to define its pathogenic roles in relation to most neurodegenerative diseases (Ransohoff, 2016). Thus, it should be noted that the designations inflammation and neuroinflammation are not interchangeable and the term, ‘neuroinflammation,’ should be carefully and specifically applied (Filiou et al., 2014; Masgrau et al., 2017).

F. Aging, Inflammaging & Mitochondrial dysfunction

Aging is characterized by a progressive loss of physiologic and cellular integrity, leading to impaired function and increased vulnerability to death (Lopez-Otin et al., 2013). Although aging is a multifactorial process influenced by genetic factors, environmental influence, nutrition, lifestyle, and others, multiple lines of evidence in model organisms and humans have continuously demonstrated that the impaired mitochondrial function is one of

characteristic features of age-associated disease phenotypes and aging (Kauppila et al., 2017).

Recently, the presence of a pro-inflammatory phenotype in aged mammals has been increasingly appreciated. These observations include (a) increased expression of genes linked to inflammation and immune responses in the tissues of old humans and rodents; (b) higher levels of cytokines in serum, e.g. IL-6 and TNF- α ; and (c) activation of NF- κ B signaling which is the master regulator of inflammatory responses. To describe this concept of age-associated pathologic inflammation, a term called inflammaging has been proposed (Franceschi et al., 2000). In short, inflammaging refers to a low-grade pro-inflammatory phenotype which accompanies aging in mammals (Franceschi and Campisi, 2014; Salminen et al., 2012). Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis (Franceschi and Campisi, 2014).

Given both mitochondrial dysfunction and inflammaging are characteristic features of aging, several interesting questions are raised: (a) do any interconnection between mitochondrial dysfunction and inflammaging exist?; (b) if there is, what is the underlying mechanism to interconnect these two important features of aging?; and (c) overall, how does this interconnection contribute to age-associated disease phenotypes and aging? Numerous forms of endogenous and environmental stressors may disrupt mitochondrial function by impacting critical processes in mitochondrial homeostasis, such as mitochondrial redox system, oxidative phosphorylation, biogenesis, and mitophagy (Fivenson et al., 2017; Lerner et al., 2016). In this regard, it is intriguing that mitochondrial dysfunction is causally resulted from defects of DNA repair mechanisms which have been identified to accelerate aging process (Fang et al., 2014). Emerging evidence suggests a crucial role of nuclear-mitochondrial crosstalks for the mitochondrial health and physiologic aging (Fang et al., 2014; Fang et al., 2016). Thus, mitochondrial function may decline progressively in association with physiologic aging, leading to the release of multiple mitochondrial DAMPs including mitochondrial reactive oxygen species (mtROS), mtDNA, and oxidized mitochondrial molecules. These misplaced or altered mitochondria-originated molecules which are increased over aging subsequently may trigger innate immune responses and result in the onset or progression of inflammaging and aging-associated chronic diseases. The specific and precise roles of how mitochondrial DAMPs contribute to inflammaging or aging-associated diseases, however, remain poorly understood. Clearly, the dissection of this interconnection between mitochondrial dysfunction and inflammaging will provide us enhanced understanding of the aging biology.

IV. CONCLUSION/FUTURE PERSPECTIVE

There is growing evidence for the importance of the mitochondria with inflammatory and immune cell function. Given the evolutionary significance of the mitochondria in contributing to the genesis of eukaryotic complexity, it is not surprising to see the how integral the mitochondria are when it comes to the cellular metabolic, immune signaling and survival responses to external stimuli. A “healthy” cellular mitochondrial system is important to maintain health and homeostasis, and the host innate immunity relies on an

intact and robust mitochondrial system to respond to various cellular stresses. Many chronic diseases are result of chronic inflammation such as atherosclerosis, chronic lung diseases, neurodegenerative disorders, cancer, infectious diseases and aging itself.

The mitochondria are fundamentally important in the establishment of a balanced cellular function and an impaired and declined mitochondrial function is important in many of the pathological inflammatory processes seen in chronic inflammatory diseases and in aging. As a result of excessive or chronic inflammation which are characteristics of many of the inflammatory diseases, oxidative stresses and damages to the mitochondria may lead to progressive dysfunctional and dysregulated mitochondrial machinery. Impaired mitochondrial function may itself lead to unchecked inflammatory response through excessive mtDNA, inflammasomes activation and other pro-inflammatory immune signaling engagements. Therefore, the mitochondria exert many effects on the inflammatory signaling, and the inflammatory proteins themselves can modulate mitochondrial function, which can feed into potentially damaging inflammatory cycle that result in many of the chronic diseases described above. Strategies are much needed at stopping the damaging inflammatory cycle and or dampening the excessive oxidative stress within the mitochondria. Pharmacological agents that preserve mitochondrial function and or control levels of mitochondrial ROS and or mtDNA can potentially contribute to the management and control of many inflammation-driven diseases. However, more studies are needed to show that this is achievable in a specific and safe manner given how the mitochondria is integrally important in many basic cellular functions. There is also no reason to ignore the role of non-immune cells with their own mitochondrial dysfunctions and their contribution to the inflammatory process in chronic inflammatory diseases and aging. This is an exciting time in science and medicine since the initial description of “inflammation” by Celsus given the emerging interest of an evolutionarily-important organelle, the mitochondrion, and their integral role in inflammation and inflammatory-related diseases.

Acknowledgments

We apologize for the vast number of outstanding publications that could not be cited because of space limitations.

Funding Sources: This work was supported by NHLBI R01HL130283 (MJK), NIA R01AG053495 (MJK) and NHLBI R01HL126094 (CDC).

References

- Archibald JM. Endosymbiosis and Eukaryotic Cell Evolution. *Curr Biol*. 2015; 25:R911–921. [PubMed: 26439354]
- Arrese M, Cabrera D, Kalergis AM, Feldstein AE. Innate Immunity and Inflammation in NAFLD/ NASH. *Digestive diseases and sciences*. 2016; 61:1294–1303. [PubMed: 26841783]
- Ballinger SW, Patterson C, Knight-Lozano CA, Burow DL, Conklin CA, Hu Z, Reuf J, Horaist C, Lebovitz R, Hunter GC, McIntyre K, Runge MS. Mitochondrial integrity and function in atherogenesis. *Circulation*. 2002; 106:544–549. [PubMed: 12147534]
- Bewley MA, Preston JA, Mohasin M, Marriott HM, Budd RC, Swales J, Collini P, Greaves DR, Craig RW, Brightling CE, Donnelly LE, Barnes PJ, Singh D, Shapiro SD, Whyte MKB, Dockrell DH. Impaired Mitochondrial Microbicidal Responses in Chronic Obstructive Pulmonary Disease Macrophages. *Am J Respir Crit Care Med*. 2017

- Bhola PD, Letai A. Mitochondria-Judges and Executioners of Cell Death Sentences. *Molecular cell*. 2016; 61:695–704. [PubMed: 26942674]
- Bohovich I, Khalimonchuk O. Sending Out an SOS: Mitochondria as a Signaling Hub. *Front Cell Dev Biol*. 2016; 4:109. [PubMed: 27790613]
- Bueno M, Lai YC, Romero Y, Brands J, St Croix CM, Kamga C, Corey C, Herazo-Maya JD, Sembrat J, Lee JS, Duncan SR, Rojas M, Shiva S, Chu CT, Mora AL. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *J Clin Invest*. 2015; 125:521–538. [PubMed: 25562319]
- Butow RA, Avadhani NG. Mitochondrial signaling: the retrograde response. *Molecular cell*. 2004; 14:1–15. [PubMed: 15068799]
- Carp H. Mitochondrial N-formylmethionyl proteins as chemoattractants for neutrophils. *J Exp Med*. 1982; 155:264–275. [PubMed: 6274994]
- Chandel NS. Evolution of Mitochondria as Signaling Organelles. *Cell metabolism*. 2015; 22:204–206. [PubMed: 26073494]
- Claypool SM, Koehler CM. The complexity of cardiolipin in health and disease. *Trends in biochemical sciences*. 2012; 37:32–41. [PubMed: 22014644]
- Cloonan SM, Choi AM. Mitochondria: sensors and mediators of innate immune receptor signaling. *Current opinion in microbiology*. 2013; 16:327–338. [PubMed: 23757367]
- Cloonan SM, Choi AM. Mitochondria in lung disease. *J Clin Invest*. 2016; 126:809–820. [PubMed: 26928034]
- Cloonan SM, Glass K, Lacho-Contreras ME, Bhashyam AR, Cervo M, Pabon MA, Konrad C, Polverino F, Siempos II, Perez E, Mizumura K, Ghosh MC, Parameswaran H, Williams NC, Rooney KT, Chen ZH, Goldklang MP, Yuan GC, Moore SC, Demeo DL, Rouault TA, D'Armiento JM, Schon EA, Manfredi G, Quackenbush J, Mahmood A, Silverman EK, Owen CA, Choi AM. Mitochondrial iron chelation ameliorates cigarette smoke-induced bronchitis and emphysema in mice. *Nat Med*. 2016; 22:163–174. [PubMed: 26752519]
- Dahlgren C, Gabl M, Holdfeldt A, Winther M, Forsman H. Basic characteristics of the neutrophil receptors that recognize formylated peptides, a danger-associated molecular pattern generated by bacteria and mitochondria. *Biochem Pharmacol*. 2016; 114:22–39. [PubMed: 27131862]
- Davis BK, Wen H, Ting JP. The inflammasome NLRs in immunity, inflammation, and associated diseases. *Annu Rev Immunol*. 2011; 29:707–735. [PubMed: 21219188]
- de Zoete MR, Palm NW, Zhu S, Flavell RA. Inflammasomes. *Cold Spring Harbor perspectives in biology*. 2014; 6:a016287. [PubMed: 25324215]
- Di Filippo M, Chiasserini D, Tozzi A, Picconi B, Calabresi P. Mitochondria and the link between neuroinflammation and neurodegeneration. *Journal of Alzheimer's disease : JAD*. 2010; 20(Suppl 2):S369–379. [PubMed: 20463396]
- Dorward DA, Lucas CD, Doherty MK, Chapman GB, Scholefield EJ, Conway Morris A, Felton JM, Kipari T, Humphries DC, Robb CT, Simpson AJ, Whitfield PD, Haslett C, Dhaliwal K, Rossi AG. Novel role for endogenous mitochondrial formylated peptide-driven formyl peptide receptor 1 signalling in acute respiratory distress syndrome. *Thorax*. 2017
- Dromparis P, Michelakis ED. Mitochondria in vascular health and disease. *Annual review of physiology*. 2013; 75:95–126.
- Dromparis P, Paulin R, Sutendra G, Qi AC, Bonnet S, Michelakis ED. Uncoupling protein 2 deficiency mimics the effects of hypoxia and endoplasmic reticulum stress on mitochondria and triggers pseudohypoxic pulmonary vascular remodeling and pulmonary hypertension. *Circulation research*. 2013; 113:126–136. [PubMed: 23652801]
- Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, Harger A, Schipke J, Zimmermann A, Schmidt A, Tong M, Ruckstuhl C, Dammbrueck C, Gross AS, Herbst V, Magnes C, Trausinger G, Narath S, Meinitzer A, Hu Z, Kirsch A, Eller K, Carmona-Gutierrez D, Buttner S, Pietrocola F, Knittelfelder O, Schrepfer E, Rockenfeller P, Simonini C, Rahn A, Horsch M, Moreth K, Beckers J, Fuchs H, Gailus-Durner V, Neff F, Janik D, Rathkolb B, Rozman J, de Angelis MH, Moustafa T, Haemmerle G, Mayr M, Willeit P, von Frieling-Salewsky M, Pieske B, Scorrano L, Pieber T, Pechlaner R, Willeit J, Sigrist SJ, Linke WA, Muhlfeld C, Sadoshima J,

- Dengjel J, Kiechl S, Kroemer G, Sedej S, Madeo F. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med.* 2016; 22:1428–1438. [PubMed: 27841876]
- Eleftheriadis T, Pissas G, Liakopoulos V, Stefanidis I. Cytochrome c as a Potentially Clinical Useful Marker of Mitochondrial and Cellular Damage. *Frontiers in immunology.* 2016; 7:279. [PubMed: 27489552]
- Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. *Cell.* 2014; 157:882–896. [PubMed: 24813611]
- Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, Bohr VA. Nuclear DNA damage signalling to mitochondria in ageing. *Nat Rev Mol Cell Biol.* 2016; 17:308–321. [PubMed: 26956196]
- Filiou MD, Arefin AS, Moscato P, Graeber MB. 'Neuroinflammation' differs categorically from inflammation: transcriptomes of Alzheimer's disease, Parkinson's disease, schizophrenia and inflammatory diseases compared. *Neurogenetics.* 2014; 15:201–212. [PubMed: 24928144]
- Fischer F, Hamann A, Osiewacz HD. Mitochondrial quality control: an integrated network of pathways. *Trends in biochemical sciences.* 2012; 37:284–292. [PubMed: 22410198]
- Fivenson EM, Lautrup S, Sun N, Scheibye-Knudsen M, Stevnsner T, Nilsen H, Bohr VA, Fang EF. Mitophagy in neurodegeneration and aging. *Neurochemistry international.* 2017; 109:202–209. [PubMed: 28235551]
- Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci.* 2000; 908:244–254. [PubMed: 10911963]
- Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2014; 69(Suppl 1):S4–9.
- Freigang S, Ampenberger F, Weiss A, Kanneganti TD, Iwakura Y, Hersberger M, Kopf M. Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1 α and sterile vascular inflammation in atherosclerosis. *Nat Immunol.* 2013; 14:1045–1053. [PubMed: 23995233]
- Gurung P, Lukens JR, Kanneganti TD. Mitochondria: diversity in the regulation of the NLRP3 inflammasome. *Trends in molecular medicine.* 2015; 21:193–201. [PubMed: 25500014]
- He HQ, Ye RD. The Formyl Peptide Receptors: Diversity of Ligands and Mechanism for Recognition. *Molecules.* 2017:22.
- Higuchi M, Kudo T, Suzuki S, Evans TT, Sasaki R, Wada Y, Shirakawa T, Sawyer JR, Gotoh A. Mitochondrial DNA determines androgen dependence in prostate cancer cell lines. *Oncogene.* 2006; 25:1437–1445. [PubMed: 16278679]
- Hotamisligil GS. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. *Immunity.* 2017; 47:406–420. [PubMed: 28930657]
- Ishikawa K, Takenaga K, Akimoto M, Koshikawa N, Yamaguchi A, Imanishi H, Nakada K, Honma Y, Hayashi J. ROS-generating mitochondrial DNA mutations can regulate tumor cell metastasis. *Science.* 2008; 320:661–664. [PubMed: 18388260]
- Iyer D, Mishra N, Agrawal A. Mitochondrial Function in Allergic Disease. *Curr Allergy Asthma Rep.* 2017; 17:29. [PubMed: 28429306]
- Iyer SS, He Q, Janczy JR, Elliott EI, Zhong Z, Olivier AK, Sadler JJ, Knepper-Adrian V, Han R, Qiao L, Eisenbarth SC, Nauseef WM, Cassel SL, Sutterwala FS. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. *Immunity.* 2013; 39:311–323. [PubMed: 23954133]
- Kang MJ, Shadel GS. A Mitochondrial Perspective of Chronic Obstructive Pulmonary Disease Pathogenesis. *Tuberc Respir Dis (Seoul).* 2016; 79:207–213. [PubMed: 27790272]
- Kang MJ, Yoon CM, Kim BH, Lee CM, Zhou Y, Sauler M, Homer R, Dhamija A, Boffa D, West AP, Shadel GS, Ting JP, Tedrow JR, Kaminski N, Kim WJ, Lee CG, Oh YM, Elias JA. Suppression of NLRX1 in chronic obstructive pulmonary disease. *J Clin Invest.* 2015; 125:2458–2462. [PubMed: 25938787]
- Kauppila TE, Kauppila JH, Larsson NG. Mammalian Mitochondria and Aging: An Update. *Cell metabolism.* 2017; 25:57–71. [PubMed: 28094012]

- Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009; 301:2024–2035. [PubMed: 19454641]
- Koliaki C, Szendroedi J, Kaul K, Jelenik T, Nowotny P, Jankowiak F, Herder C, Carstensen M, Krausch M, Knoefel WT, Schlensak M, Roden M. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. *Cell metabolism*. 2015; 21:739–746. [PubMed: 25955209]
- Krysko DV, Agostinis P, Krysko O, Garg AD, Bachert C, Lambrecht BN, Vandenabeele P. Emerging role of damage-associated molecular patterns derived from mitochondria in inflammation. *Trends Immunol*. 2011; 32:157–164. [PubMed: 21334975]
- Kumar, VAA., Aster, JC. Inflammation and Repair, Robbins and Cotran Pathologic Basis of Disease. 9. Saunders; Philadelphia PA: 2015. p. 69–111.
- Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. *Cell*. 2014; 157:1013–1022. [PubMed: 24855941]
- Lane, N. The Vital Question: Energy, Evolution, and the Origins of Complex Life. W. W. Norton & Company; New York, NY: 2015.
- Lane N, Martin W. The energetics of genome complexity. *Nature*. 2010; 467:929–934. [PubMed: 20962839]
- Lee HC, Yin PH, Lin JC, Wu CC, Chen CY, Wu CW, Chi CW, Tam TN, Wei YH. Mitochondrial genome instability and mtDNA depletion in human cancers. *Ann N Y Acad Sci*. 2005; 1042:109–122. [PubMed: 15965052]
- Lee SR, Han J. Mitochondrial Mutations in Cardiac Disorders. *Advances in experimental medicine and biology*. 2017; 982:81–111. [PubMed: 28551783]
- Lerner CA, Sundar IK, Rahman I. Mitochondrial redox system, dynamics, and dysfunction in lung inflammation and COPD. *Int J Biochem Cell Biol*. 2016; 81:294–306. [PubMed: 27474491]
- Loftus RM, Finlay DK. Immunometabolism: Cellular Metabolism Turns Immune Regulator. *J Biol Chem*. 2016; 291:1–10. [PubMed: 26534957]
- Lopez-Armada MJ, Riveiro-Naveira RR, Vaamonde-Garcia C, Valcarcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*. 2013; 13:106–118. [PubMed: 23333405]
- Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013; 153:1194–1217. [PubMed: 23746838]
- Madamanchi NR, Runge MS. Mitochondrial dysfunction in atherosclerosis. *Circulation research*. 2007; 100:460–473. [PubMed: 17332437]
- Masgrau R, Guaza C, Ransohoff RM, Galea E. Should We Stop Saying 'Glia' and 'Neuroinflammation'? *Trends in molecular medicine*. 2017; 23:486–500. [PubMed: 28499701]
- Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell*. 2010; 140:771–776. [PubMed: 20303867]
- Mills EL, Kelly B, O'Neill LAJ. Mitochondria are the powerhouses of immunity. *Nat Immunol*. 2017; 18:488–498. [PubMed: 28418387]
- Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, Glass K, Owen CA, Mahmood A, Washko GR, Hashimoto S, Ryter SW, Choi AM. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. *J Clin Invest*. 2014; 124:3987–4003. [PubMed: 25083992]
- Mora AL, Bueno M, Rojas M. Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. *J Clin Invest*. 2017; 127:405–414. [PubMed: 28145905]
- Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, Choi AM. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat Immunol*. 2011; 12:222–230. [PubMed: 21151103]
- Nishino M, Ramaiya NH, Hatabu H, Hodi FS. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. *Nat Rev Clin Oncol*. 2017

- Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell*. 2012; 148:1145–1159. [PubMed: 22424226]
- Patel AS, Song JW, Chu SG, Mizumura K, Osorio JC, Shi Y, El-Chemaly S, Lee CG, Rosas IO, Elias JA, Choi AM, Morse D. Epithelial cell mitochondrial dysfunction and PINK1 are induced by transforming growth factor-beta1 in pulmonary fibrosis. *PLoS One*. 2015; 10:e0121246. [PubMed: 25785991]
- Patrushev M, Kasymov V, Patrusheva V, Ushakova T, Gogvadze V, Gaziev A. Mitochondrial permeability transition triggers the release of mtDNA fragments. *Cellular and molecular life sciences : CMLS*. 2004; 61:3100–3103. [PubMed: 15583871]
- Petros JA, Baumann AK, Ruiz-Pesini E, Amin MB, Sun CQ, Hall J, Lim S, Issa MM, Flanders WD, Hosseini SH, Marshall FF, Wallace DC. mtDNA mutations increase tumorigenicity in prostate cancer. *Proc Natl Acad Sci U S A*. 2005; 102:719–724. [PubMed: 15647368]
- Puente-Maestu L, Lazaro A, Tejedor A, Camano S, Fuentes M, Cuervo M, Navarro BO, Agusti A. Effects of exercise on mitochondrial DNA content in skeletal muscle of patients with COPD. *Thorax*. 2011; 66:121–127. [PubMed: 21097816]
- Puente-Maestu L, Perez-Parra J, Godoy R, Moreno N, Tejedor A, Gonzalez-Aragoneses F, Bravo JL, Alvarez FV, Camano S, Agusti A. Abnormal mitochondrial function in locomotor and respiratory muscles of COPD patients. *Eur Respir J*. 2009; 33:1045–1052. [PubMed: 19129279]
- Rabinovich RA, Bastos R, Ardite E, Llinas L, Orozco-Levi M, Gea J, Vilaro J, Barbera JA, Rodriguez-Roisin R, Fernandez-Checa JC, Roca J. Mitochondrial dysfunction in COPD patients with low body mass index. *Eur Respir J*. 2007; 29:643–650. [PubMed: 17182653]
- Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science*. 2016; 353:777–783. [PubMed: 27540165]
- Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *Jama*. 2015; 313:2263–2273. [PubMed: 26057287]
- Sack MN, Finkel T. Mitochondrial metabolism, sirtuins, and aging. *Cold Spring Harbor perspectives in biology*. 2012;4.
- Salminen A, Kaarniranta K, Kauppinen A. Inflammaging: disturbed interplay between autophagy and inflammasomes. *Aging*. 2012; 4:166–175. [PubMed: 22411934]
- Samuel VT, Shulman GI. Nonalcoholic Fatty Liver Disease as a Nexus of Metabolic and Hepatic Diseases. *Cell metabolism*. 2017
- Sancho D, Enamorado M, Garaude J. Innate Immune Function of Mitochondrial Metabolism. *Frontiers in immunology*. 2017; 8:527. [PubMed: 28533780]
- Schertzer JD, Steinberg GR. Immunometabolism: the interface of immune and metabolic responses in disease. *Immunol Cell Biol*. 2014; 92:303. [PubMed: 24613974]
- Schroder K, Tschopp J. The inflammasomes. *Cell*. 2010; 140:821–832. [PubMed: 20303873]
- Schwartz M, Deczkowska A. Neurological Disease as a Failure of Brain-Immune Crosstalk: The Multiple Faces of Neuroinflammation. *Trends Immunol*. 2016; 37:668–679. [PubMed: 27616557]
- Seong SY, Matzinger P. Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol*. 2004; 4:469–478. [PubMed: 15173835]
- Shadel GS, Horvath TL. Mitochondrial ROS signaling in organismal homeostasis. *Cell*. 2015; 163:560–569. [PubMed: 26496603]
- Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest*. 2015; 125:3347–3355. [PubMed: 26325032]
- Sheeran FL, Pepe S. Mitochondrial Bioenergetics and Dysfunction in Failing Heart. *Advances in experimental medicine and biology*. 2017; 982:65–80. [PubMed: 28551782]
- Shidara Y, Yamagata K, Kanamori T, Nakano K, Kwong JQ, Manfredi G, Oda H, Ohta S. Positive contribution of pathogenic mutations in the mitochondrial genome to the promotion of cancer by prevention from apoptosis. *Cancer research*. 2005; 65:1655–1663. [PubMed: 15753359]
- Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, Rentsendorj A, Vargas M, Guerrero C, Wang Y, Fitzgerald KA, Underhill DM, Town T, Arditi M. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012; 36:401–414. [PubMed: 22342844]

- Singh KK, Ayyasamy V, Owens KM, Koul MS, Vujcic M. Mutations in mitochondrial DNA polymerase-gamma promote breast tumorigenesis. *J Hum Genet.* 2009; 54:516–524. [PubMed: 19629138]
- Sobenin IA, Zhelankin AV, Sinyov VV, Bobryshev YV, Orekhov AN. Mitochondrial Aging: Focus on Mitochondrial DNA Damage in Atherosclerosis - A Mini-Review. *Gerontology.* 2015; 61:343–349. [PubMed: 25531813]
- Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature.* 2012; 481:278–286. [PubMed: 22258606]
- Sunny NE, Bril F, Cusi K. Mitochondrial Adaptation in Nonalcoholic Fatty Liver Disease: Novel Mechanisms and Treatment Strategies. *Trends Endocrinol Metab.* 2017; 28:250–260. [PubMed: 27986466]
- Szklarczyk R, Nooteboom M, Osiewicz HD. Control of mitochondrial integrity in ageing and disease. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences.* 2014; 369:20130439. [PubMed: 24864310]
- Tabas I, Lichtman AH. Monocyte-Macrophages and T Cells in Atherosclerosis. *Immunity.* 2017; 47:621–634. [PubMed: 29045897]
- Tan T, Zimmermann M, Reichert AS. Controlling quality and amount of mitochondria by mitophagy: insights into the role of ubiquitination and deubiquitination. *Biological chemistry.* 2016; 397:637–647. [PubMed: 27145142]
- Tschopp J. Mitochondria: Sovereign of inflammation? *Eur J Immunol.* 2011; 41:1196–1202. [PubMed: 21469137]
- Valdivieso AG, Santa-Coloma TA. CFTR activity and mitochondrial function. *Redox Biol.* 2013; 1:190–202. [PubMed: 24024153]
- von Hardenberg A, Maack C. Mitochondrial Therapies in Heart Failure. *Handbook of experimental pharmacology.* 2017; 243:491–514. [PubMed: 28181010]
- Wallace DC. Mitochondria and cancer. *Nature reviews Cancer.* 2012; 12:685–698. [PubMed: 23001348]
- Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. *Immunity.* 2015; 42:406–417. [PubMed: 25786173]
- West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, Bestwick M, Duguay BA, Raimundo N, MacDuff DA, Kaech SM, Smiley JR, Means RE, Iwasaki A, Shadel GS. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature.* 2015; 520:553–557. [PubMed: 25642965]
- West AP, Shadel GS. Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nat Rev Immunol.* 2017; 17:363–375. [PubMed: 28393922]
- West AP, Shadel GS, Ghosh S. Mitochondria in innate immune responses. *Nat Rev Immunol.* 2011; 11:389–402. [PubMed: 21597473]
- Wilkins HM, Weidling IW, Ji Y, Swerdlow RH. Mitochondria-Derived Damage-Associated Molecular Patterns in Neurodegeneration. *Frontiers in immunology.* 2017; 8:508. [PubMed: 28491064]
- Witte ME, Geurts JJ, de Vries HE, van der Valk P, van Horssen J. Mitochondrial dysfunction: a potential link between neuroinflammation and neurodegeneration? *Mitochondrion.* 2010; 10:411–418. [PubMed: 20573557]
- Wu SB, Wu YT, Wu TP, Wei YH. Role of AMPK-mediated adaptive responses in human cells with mitochondrial dysfunction to oxidative stress. *Biochim Biophys Acta.* 2014; 1840:1331–1344. [PubMed: 24513455]
- Yoon CM, Nam M, Oh YM, Dela Cruz CS, Kang MJ. Mitochondrial Regulation of Inflammasome Activation in Chronic Obstructive Pulmonary Disease. *Journal of innate immunity.* 2016; 8:121–128. [PubMed: 26536345]
- Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010; 464:104–107. [PubMed: 20203610]
- Zhang X, Shan P, Homer R, Zhang Y, Petrache I, Mannam P, Lee PJ. Cathepsin E promotes pulmonary emphysema via mitochondrial fission. *Am J Pathol.* 2014; 184:2730–2741. [PubMed: 25239563]

- Zhang Z, Meng P, Han Y, Shen C, Li B, Hakim MA, Zhang X, Lu Q, Rong M, Lai R. Mitochondrial DNA-LL-37 Complex Promotes Atherosclerosis by Escaping from Autophagic Recognition. *Immunity*. 2015; 43:1137–1147. [PubMed: 26680206]
- Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, He F, Boassa D, Perkins G, Ali SR, McGeough MD, Ellisman MH, Seki E, Gustafsson AB, Hoffman HM, Diaz-Meco MT, Moscat J, Karin M. NF-kappaB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. *Cell*. 2016; 164:896–910. [PubMed: 26919428]

Figure 1.

Role of mitochondria in the pathogenesis of chronic inflammatory disorders. A schematic diagram is illustrated to depict pathogenic roles of mitochondrial dysfunction which contribute to the development of multiple chronic inflammatory disorders. Mitochondrial physiology is integrated with fundamental biologic functions at the cellular level. When the mitochondrial physiology is perturbed, dysfunctional mitochondria instigate or propagate inappropriate and persistent inflammation via multiple mechanisms including inflammasomes activation, dysregulation of immune signaling, alteration of immunometabolism and the release of mitochondrial damage-associated molecular patterns (DAMPs), which, in consequence, lead to chronic inflammatory disorders in affected organs or systemically.