Chapter 7
Mitochondrial Dysfunction as a Trigger of Inflammation in Cardiomyopathies

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Abstract Mitochondrial dysfunction and bioenergetic failure are a hallmark of heart failure, diabetic cardiomyopathy, and myocardial infarction. An inadequate supply of oxygen and nutrients triggers a cascade of events in which mitochondria are a critical mediator, particularly mitochondrial calcium overload, permeability transition pore opening, oxidative stress, and the release of mitochondrial components that interact with immune cell residents in the heart. Depending on the degree of mitochondrial dysfunction, cardiac cells lead to the activation of the inflammasome and other inflammation pathways. On the other hand, the activation of immune cells depends on their mitochondrial metabolism, and they potentially contribute to cardiac diseases. This chapter reviews the main mitochondrial molecular mechanisms that compromise the heart's immune activation and their potential involvement in acute myocardial infarction, sepsis, and myocarditis.

Keywords Cardiomyopathy · Heart failure · Mitochondria · Inflammation · Immunometabolism

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7.1 Introduction

Cardiac inflammation is currently recognized as a condition state that perpetuates heart damage and leads to cardiomyopathies (Castillo et al. 2020). Inflammatory stimuli are caused by either direct injury to the heart (e.g., myocarditis) or systemic soluble mediators (e.g., diabetic cardiomyopathy), and they alter cardiomyocyte functioning, activate resident cardiac-immune system cells, and stimulate the recruitment of other immune cells (Tschöpe et al. 2020). Mitochondria are biosynthetic and bioenergetic organelles that dictate cell function, modulating metabolism and signaling pathways by calcium buffering and ROS production (Burgoyne et al. 2012; Dedkova and Blatter 2013). Thus, mitochondria act as a link between metabolism and immune system activation, facilitating adequate heart function. In this context, prior research has shown that two transcription factors, nuclear factor κB (NFκB) and peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α), negatively regulate each other (Alvarez-Guardia et al. 2010). The former is a key regulator of inflammation, whereas PGC-1α is an essential regulator in mitochondrial dynamics and processes, as well as in metabolism (Schilling et al. 2011). This chapter reviews the mitochondrial regulatory processes that facilitate efficient heart function and how the disruption of these processes contributes to immune system activation, including the role played by immune system cells in the development of cardiomyopathies.

7.1.1 Mitochondrial Structure and Function

The primary process associated with mitochondrial function is its capacity to regulate energy conversion by generating adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). However, mitochondria also modulate cell signaling and cell death by buffering calcium and regulating the redox state of reactive nitrogen (RNS) and oxygen species (ROS) (Burgoyne et al. 2012; Dedkova and Blatter 2013). Therefore, the interconnection of mitochondria's fine-tuning mechanisms is essential to guarantee energy conversion (Gnaiger and Group MT 2020).

This organelle's unique feature is its two delimited inner and outer membranes, which are structurally and functionally distinct. While the outer mitochondrial membrane (OMM) allows the free transit of ions and small molecules, the inner mitochondrial membrane (IMM), consisting of cristae and inner boundary membranes, only enables their entry through specific transporters, and ion concentration gradients across the membrane create its membrane potential (Wolf et al. 2019). This characteristic allows physicochemical differences between the compartments associated with their particular functions in which the interaction among their components is crucial (van der Laan et al. 2016). The OXPHOS machinery (i.e., complexes of the respiratory chain and F1F0-ATP synthase) is anchored in the IMM cristae. The IMM surrounds the mitochondrial matrix, where mitochondrial DNA (mtDNA),

enzymes, and ions reside and the tricarboxylic acid cycle (TCA) occurs (Kühlbrandt 2015).

The space between the IMM and OMM contains various molecules, such as cytochrome c (Cyt c), which is essential for transporting electrons and, when released from mitochondria, acts as an apoptotic trigger (Zhao et al. 2019). Cyt c is released through the mitochondrial permeability transition pore (mPTP), which maintains proper membrane integrity, allowing only the passage of molecules <1.5 kDa (McCommis and Baines 2012). Although its structure is not yet well defined, the opening of the mPTP is triggered by calcium and regulated by adenine nucleotides and cyclophilin D (Cyp D) (Alves-Figueiredo et al. 2021).

7.1.2 Role of Mitochondria in the Heart

The heart is a demanding organ that needs large amounts of ATP to meet its bioenergetic requirements for rhythmic contractions and blood pumping. At high workloads, energy conversion can be completed in less than 10 s (Balaban 2009). Because mitochondria produce up to 90% of this ATP (Doenst et al. 2013), the mitochondrion comprises more than 30% of the volume of a cardiomyocyte, and various characteristics, such as its morphology, location, and interactions with other organelles, are crucial for proper functioning (Ventura-Clapier et al. 2011).

7.1.3 Metabolism

Although the heart can metabolize any substrate to produce energy, its primary fuel energy substrates are fatty acyl-CoA (fatty acids) and pyruvate (carbohydrates) (Kolwicz et al. 2013) to maintain a coordinated metabolic network and meet each heart contraction's energetic demands. Among them, fatty acids are the principal metabolic source (40–90%), and their utilization is controlled by the PPARα/PGC-1α/ERR (estrogen-related receptor) axis, from transport to oxidation (Duncan and Finck 2008). Fatty acid β-oxidation (FAO) provides higher energy yields than glycolysis, but more oxygen is required; thus, shifting mitochondrial oxidative metabolism from FAO to glucose oxidation increases energy efficiency. This shifting mechanism is employed by cardiomyocytes under certain pathological conditions, such as in hypertrophied hearts, to meet energetic needs (Sorokina et al. 2007). However, limiting fatty acid utilization results in detrimental heart function (Tuunanen et al. 2006). In contrast, if fatty acid utilization increases and surpasses the mitochondria's FAO capacity, lipids accumulate in the heart, which causes lipotoxicity (Nagoshi et al. 2011) and alterations in glucose transport, leading to mitochondrial dysfunction by impairing the redox state (Wright et al. 2009). Then, the increase in FAO and oxygen consumption increases the delivery of reducing equivalents to the electron transport chain (ETC), which decreases OXPHOS

capacity, ROS production, lipid peroxidation, and, in turn, cardiac energetic efficiency (Boudina et al. 2007). Thus, the exact coupling proportion of fatty acid and glucose oxidation is crucial to maintain the fine-tuning of energy versus ROS production for both ATP demands and signaling.

7.1.4 The Relevance of Mitochondrial Quality Control in Cardiomyocytes

As dynamic organelles, mitochondria continuously undergo morphological changes while forming continuous networks to adapt to environmental demands and achieve homeostasis. These morphological changes are called fusion and fission and are collectively known as mitochondrial dynamics. In conjunction with mitophagy and biogenesis, they maintain a healthy mitochondrial population (Fig. 7.1) by regulating mitochondrial quality control, and, therefore, cell survival (Ni et al. 2015). Additionally, a macrophage-dependent mechanism has recently been demonstrated, which involves the extrusion of autophagic vesicles with high mitochondrial content, also referred to as exophers, and incorporates the externalization of phosphatidylserine, which is an apoptotic cell recognition feature (Nicolás-Ávila et al. 2020) (Fig. 7.1). This process eliminates dysfunctional mitochondrial and avoids inflammation by preventing the activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome by a process that we will discuss in Sect. 7.1.6 of this chapter.

7.1.4.1 Mitochondrial Dynamics

Mitochondrial dynamics are essential in situations involving increased energetic demands, mitochondrial damage during development, stressful conditions, and aging (Chen et al. 2012; Ong et al. 2010; Piquereau et al. 2012). Remodeling through fission and fusion is necessary to conserve mitochondrial function and protect the heart's cellular homeostasis (Ikeda et al. 2015).

Fusion is a GTPase-regulated mechanism by which damaged mitochondria join with intact ones and redistribute their soluble and membrane proteins, lipids, and mtDNA to maintain an adequate membrane potential (Chen et al. 2010). Thus, mitochondrial fusion helps mitochondria to avoid mitophagy, regulates their morphology, and facilitates positive regulation of cellular contractility and respiration (Givvimani et al. 2015). Fusion is mediated by the transmembrane GTPases mitofusin 1 (Mfn1) and Mfn2, which are located in the OMM, interact, and create homotypic or heterotypic units, culminating in OMM fusion (Franco et al. 2016). Moreover, Mfn2 is directly related to contractility by modulating Ca^{2+} and K^{+} ionic fluxes (Givvimani et al. 2015), and dynamic-like GTPase optic atrophy 1 (Opa1) in the IMM collaborates with cardiolipin and modulates IMM fusion (Ban et al. 2017).

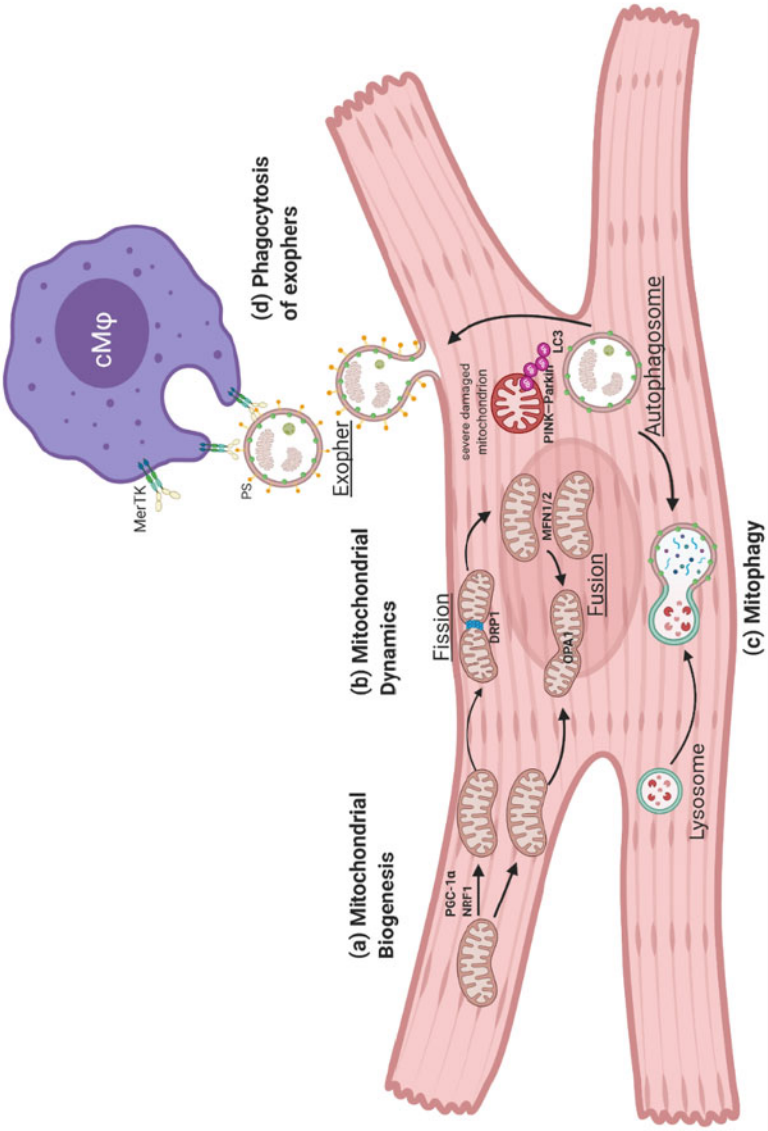

Fig. 7.1 Mechanisms of mitochondrial quality control in cardiomyocytes. (**a**) Mitochondrial biogenesis: a mitochondrion divides and gives two new renewal mitochondria. (**b**) Mitochondrial dynamics comprises fusion: lightly damaged mitochondria fuse with a healthy one to enhance mitochondrial function and fission: a senescent mitochondrion divides, giving up one healthy mitochondrion and other damage which is eliminated. (**c**) Mitophagy: allow the elimination of

Fig. 7.1 (continued) damaged mitochondria. (**d**) Phagocytosis of exophers: some autophagosomes are not eliminated within the cell and are extruded to the extracellular matrix to be engulfed. *cMφ* cardiac macrophages, *DRP1* dynamin-related protein 1, *LC3* microtubule-associated protein 1A/1B-light chain 3, *MerTK* Mer tyrosine kinase, *MFN1/2* mitofusin1/2, *NRF1* nuclear respiratory factor, *OPA1* dynamic-like GTPase optic atrophy, *Parkin* E3 ubiquitin ligase, *PGC-1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *PINK* PTEN-induced kinase 1, *PS* phosphatidylserine. (Created with BioRender.com)

In contrast, **fission** isolates nonfunctional mitochondrial fragments and is crucial in maintaining the quality of mitochondria (Youle and van der Bliek 2012). If the daughter mitochondrion has a normal membrane potential, it can undergo fusion. However, if it is impaired, it will be eliminated through mitophagy (Twig et al. 2008). On the other hand, increased fission impairs calcium handling in cardiomyocytes and Cyt c leakage (Givvimani et al. 2015). In conjunction with actin, the SR encircles the mitochondrion, marking the fission site and starting mitochondrial constriction (Korobova et al. 2013). Subsequently, cytosolic GTPase dynamin-related protein 1 (Drp1) migrates to the previously marked fission site. Its GTPase activity ends with OMM and IMM fission (Ji et al. 2015). In cardiomyocytes, the translocation of Drp1 to mitochondria depends on an increase in the cytosolic concentration of Ca^{2+} (Hom et al. 2010). Once Drp1 is translocated, it is recognized by the mitochondrial receptor fission 1 protein (Fis1), which is located in the OMM (Yoon et al. 2003).

7.1.4.2 Mitophagy

Mitophagy is an inherent process in quality control by which cardiomyocytes eliminate damaged mitochondria and retain functional ones, preventing heart failure and increasing survival (Kubli et al. 2013). As mentioned above, fission activation anticipates mitophagy (Twig et al. 2008). In the presence of low mitochondrial membrane potential, ROS increases production, or protein misfolding, and PTEN-induced kinase 1 (PINK1) accumulates in the OMM (Jin and Youle 2013). PINK phosphorylates Mfn2, blocking fusion, and activates Parkin; this cytosolic E3 ubiquitin ligase ubiquitinates the damaged mitochondria and associates with LC3, triggering the autophagic machinery (Kawajiri et al. 2010). Additionally, Parkin promotes mitochondrial biogenesis by the ubiquitination of PARIS (ZNF746), a Kruppel-associated box (KRAB), and zinc finger protein, which represses PGC-1α (Shin et al. 2011). As mitophagy requires mitochondrial depolarization, CypD, the mPTP regulator, acts as a crucial promoter (Carreira et al. 2010). Thus, assuring mitophagy prevents inflammation, as has been demonstrated that in the absence of Parkin-mediated mitophagy, NLRP-3 inflammasome is activated (He et al. 2019).

7.1.4.3 Mitochondrial Biogenesis

Considering that nuclear DNA encodes 99% of mitochondrial proteins, both nuclear DNA and mtDNA must be translated and transcribed to achieve mitochondrial biogenesis. Animal models have demonstrated that PGC-1α controls this process under stressful conditions but is nearly absent in steady-state cardiac conditions (Lehman et al. 2000). In adults, severe cardiac stress, such as starvation or ischemic conditions, causes mitochondria autophagy and, consequently, mitochondrial biogenesis (El-Sikhry et al. 2016; Huang et al. 2010). However, metabolic changes may also occur due to healthy lifestyle changes promoting metabolic flexibility, such as physical exercise (lactate) and fasting (ketone bodies), which confer cardioprotection (Kolwicz et al. 2013; Ismayil et al. 2005). Thus, mitochondrial turnover is associated with metabolic reprogramming, preconditioning, and cardioprotection (Gottlieb and Gustafsson 2011; McLeod et al. 2004).

Mechanistically, raising cytosolic calcium and the consequent Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activation and cAMP-response element binding (CREB) protein phosphorylation (Sun et al. 1994) promotes PGC-1α-mediated biogenesis while blocking the nuclear translocation of FoxO1 (Ozcan et al. 2012), preventing autophagy and oxidation by promoting FoxO3a (Olmos et al. 2013). PGC-1α is posttranscriptionally activated by sirtuin 1 (SIRT-1), an NAD^+-dependent protein deacetylase, allowing the transcription of nuclear respiratory factor 1 (NRF1) and NRF2. NRFs promote the expression of mitochondrial respiratory complexes, mtDNA transcription factors, and antioxidant defense genes (El-Sikhry et al. 2016; Olmos et al. 2013). They also regulate the transcription of SIRT-3 (Song et al. 2017), which controls the function of all these proteins within the mitochondria. In this context, SIRT-3 downregulation has been associated with mitochondrial and heart dysfunction related to metabolic changes in failing hearts (Castillo et al. 2019). Indeed, the concentration of the coenzyme NAD^+ is essential to prevent cell death (mPTP opening) (Castillo et al. 2019) and inflammation (NLRP3 activation) (Misawa et al. 2013); the latter in a SIRT-2 dependent manner (Misawa et al. 2013).

7.1.5 Calcium and ROS Regulation

Calcium is the second messenger responsible for many signal transductions in cells that respond to extracellular signals. In cardiac cells, such as cardiomyocytes, it controls contraction and cell death (Pérez-Treviño et al. 2020a). In immune cells, calcium determines the cells' activation and fate, including differentiation, replication, cytokine release, and cell death (Nunes and Demaurex 2010; Scharenberg et al. 2007). The regulation of Ca^{2+} within mitochondria facilitates the fine-tuning of calcium and ATP and ROS production (Görlach et al. 2015).

ATP synthesis is a calcium-dependent mechanism that results in ROS production, which is necessary to regulate cell signaling and perform the adequate contraction–

relaxation rhythm known as excitation–contraction coupling (ECC) (Burgoyne et al. 2012; Tarasov et al. 2012). During systole, the high influx of calcium, which facilitates contraction, depends on a mechanism of Ca^{2+}-induced Ca^{2+} release in which the L-type Ca^{2+} channel triggers Ca^{2+} release from the SR. This Ca^{2+} binds to troponin C, part of the contraction apparatus, and, consequently, heart contraction occurs (Altamirano and Bers 2007). Then, during the diastole or relaxation period, Ca^{2+} returns to the SR by sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), is exported from the cell through the Na^{+}/Ca^{2+} exchanger (Bers et al. 2006), and enters the mitochondria via the mitochondrial calcium uniporter (MCU). Ca^{2+} activates TCA cycle dehydrogenases in the mitochondria, ETC, and OXPHOS to produce ATP (Fernández-Sada et al. 2014).

As previously mentioned, OXPHOS takes place in the IMM, in which the ETC generates a proton gradient enabling the OXPHOS of ADP to ATP by F0/F1 ATP synthase. Due to FAO and glycolysis, Acetyl CoA enters the TCA cycle in the mitochondrial matrix. The resulting byproducts, nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$), are used in redox reactions by ETC complexes I and II. The generated electrons are then transferred through complexes III and IV, forming a proton gradient, which creates proton movement through F0/F1 ATP synthase, catalyzing the phosphorylation of ADP to ATP by restoring the electrochemical gradient. Consequently, the respiratory chain generates ROS (Hassanpour et al. 2018) (Fig. 7.2, Blue Box).

The process of fine-tuning regulation that allows ROS signaling includes crucial scavenging mechanisms. In the ETC, oxygen reduction generates superoxide anion radicals ($O_2^{\cdot-}$) in complexes I and III. The dismutation of these radicals to hydrogen peroxide (H_2O_2) is catalyzed primarily by manganese superoxide dismutase (MnSOD) (Holley et al. 2011). The final process that reduces H_2O_2 to water is performed by the enzymes catalase, glutathione peroxidase, and peroxiredoxin (Molavian et al. 2015). However, when ROS production overcomes the regulatory mechanisms, the frequency of oxidative posttranslational changes increases, limiting the reductive modifications' capacity. Consequently, important proteins that regulate calcium handling and ECC are compromised, which affects their function and leads to their constitutive activation, as is the case in calcium-calmodulin kinase II (CAMKII) and ryanodine receptor 2 (RyR2) (Burgoyne et al. 2012). As described previously, to prevent the entire cell from being compromised, highly damaged mitochondria are eliminated by mitophagy or even secreted into the extracellular space for elimination by macrophages (Nicolás-Ávila et al. 2020). However, if damage continues, ROS promotes several alterations within the cell, including the opening of mPTP, increasing ROS release, and, eventually, cell death and inflammation (Zorov et al. 2000).

In the heart, ATP cannot decrease, and ADP and Pi cannot increase during heavy workloads. Therefore, heart mitochondria balance the ATP production rate with the quality of utilization while maintaining ATP hydrolysis' energy-generating capacity, modulated by changes in the concentrations of mitochondrial Ca^{2+} in response to the increase in cytosolic Ca^{2+} (Yaniv et al. 2008). To achieve this balance, the MCU controls calcium buffering. However, under cardiac stress, such as severe metabolic

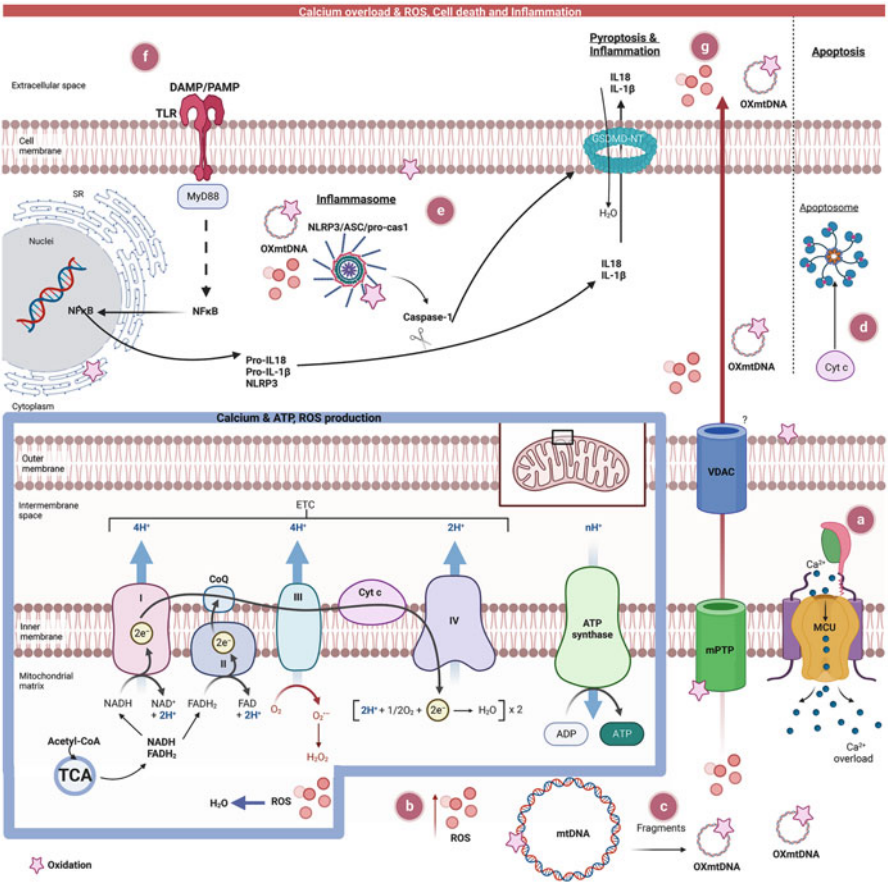

Fig. 7.2 Calcium and ROS regulation. Blue Box: oxidation of acetyl CoA produced NADH and $FADH_2$, which is further oxidated in the inner mitochondrial membrane by the ETC, generating a proton gradient and ROS. The proton gradient generates an electron force used by the ATP synthase to restore the electrochemical gradient and phosphorylation of ADP to ATP. (**a**) Under stress or pathological conditions, more Ca^{2+} enters the mitochondrial matrix by MCU transporter, promoting mitochondrial calcium overload and (**b**) ROS production increased. (**c**) Oxidative stress leads to mtDNA oxidation and fragmentation, and mPTP opening. (**d**) Cyt c is released into the cytoplasm, which interacts with other proteins to form the apoptosome and apoptosis cell death. (**e**) mtDNA and ROS activate NLP3 promoting caspase-1 activation (activation signal), which cleaves GSDMD producing NT-fragments and promotes maturation and release of IL-β and IL-18 through the GSDMD-NT pore leading to pyroptosis and cytokines released. (**f**) On the other hand, cardiomyocytes can also either be activated by extracellular DAMPs or PAMPS, which are recognized by TLRs and induce the synthesis of NLP3, pro-IL-1β, and pro-IL-18 (priming signal). These external activation signals by TLR also promote increased calcium and oxidative stress. (**g**) ROS and mtDNA are released from the cardiomyocyte and activate immune system cells such as macrophages, which recognized mtDNA as DAMPs. *ADP* adenosine diphosphate, *ASC* apoptosis-associated speck-like protein, *ATP* adenosine triphosphate, Ca^{2+} calcium, *Cyt c* cytochrome c, *DAMP* damage-associated molecular patterns, *ETC* electron transport chain, $FADH_2$ Flavin adenine dinucleotide, *GSDMD-NT* gasdermin D-N-terminal, H_2O_2 hydrogen peroxide, *IL* interleukin, *MCU* mitochondrial calcium uniporter, *mPTP* mitochondrial permeability transition pore, *NADH* nicotinamide adenine dinucleotide, *NFκB* nuclear factor κB, *NLRP3* NOD-like receptor pyrin domain-

changes (i.e., obesity) or ischemic conditions, mitochondrial overload occurs. Then, the balance between the production and detoxification of ROS is lost, leading to mPTP opening, the release of Cyt c, damage to mtDNA, cell death, and inflammation (Zhou and Tian 2018) (Fig. 7.2). It has been demonstrated that preventing mitochondrial calcium overload by targeting the MCU prevents all these mechanisms (de García-Rivas et al. 2006; Chapoy-Villanueva et al. 2019). Furthermore, it was recently documented that mitochondrial calcium overload could increase ROS production and cause membrane potential loss and energy decline. ROS can also affect critical proteins that control calcium handling, promoting unsolicited depolarization and pathological action potentials, which subsequently generate a suitable setting for arrhythmogenesis (Salazar-Ramírez et al. 2020).

7.1.6 *Mitochondrial Calcium Overload and ROS as Inflammation Triggers*

As previously mentioned, stressful conditions, such as ischemic and metabolic changes, promote calcium overload (Castillo et al. 2019; Oropeza-Almazán et al. 2017). Mitochondrial calcium overload or changes in the availability of adenine nucleotides or posttranslational modifications, such as oxidation, promotes the opening of mPTP and the release of Cyt c and other molecules, which initiate the formation of the apoptosome complex and results in apoptotic cell death (Carreira et al. 2010; Riojas-Hernández et al. 2015) (Fig. 7.2). Nonetheless, it has been suggested that mPTP opening may occur transiently during stress, such as in ischemic conditions, causing a mild depolarization of the IMM and resulting in a preconditioning mechanism; this mechanism prevents cell damage by favoring beneficial metabolic changes that increase mitochondria's capacity to respond to stress (Crescenzo et al. 2006).

However, when ischemic conditions promote excessive calcium overload and oxidative stress (Oropeza-Almazán et al. 2017), the increased mtROS induces mtDNA oxidation and specific fragments to be released through the mPTP (García et al. 2005; García and Chávez 2007). Unlike Cyt c, which promotes apoptotic cell death and prevents inflammation, oxidized mtDNA fragments lead to the activation of the NLRP3 inflammasome (Zhou et al. 2011) (Fig. 7.2). Upon activation, the NLRP3 forms a cytosolic complex with apoptosis-associated speck-like protein (ASC), which recruits the effector molecule pro-caspase-1 to form the NLRP3 inflammasome (NLRP3/ASC/pro-cas-1). NLRP3 belongs to the pattern recognition receptor (PRR) family, which recognizes a wide variety of specific motifs present on

Fig. 7.2 (continued) containing, O_2 oxygen, $O_2^{\cdot-}$ superoxide anion, *OxmtDNA* oxidized mitochondrial DNA, *PAMP* pathogen-associated molecular patterns, *Pro-cas1* procaspase 1, *ROS* reactive oxygen species, *TCA* tricarboxylic acid cycle, *TLR* Toll-like receptor, *VDAC* voltage-dependent anion channels. (Created with BioRender.com)

self and foreign antigens, triggering an innate immune system response. Both ROS and mtDNA are well-known NLRP3 activators that can activate the inflammasome within cardiomyocytes and then, when released, activate immune system cells (Pérez-Treviño et al. 2020b; Wu et al. 2019a).

It has recently been shown that ROS-associated mtDNA oxidation is partially mediated by proprotein convertase subtilisin/kexin type 9 (PCSK9) (Wang et al. 2020), which is secreted in response to inflammatory stimuli, such as LPS and ox-LDL, and increases in a pro-inflammatory milieu (Schlüter et al. 2017). On the cellular surface, both molecules are recognized by other PRRs, named toll-like receptors (TLRs), activating the NFκB transcription factor, which induces the synthesis of NLRP3, pro-IL-1β, and pro-IL-18, and providing the priming signal in NLRP3-mediated inflammation (Wu et al. 2019a) (Fig. 7.2). Moreover, TLR activation also contributes to increased Ca^{2+} and oxidative stress (Katare et al. 2017).

Once in the cytosol, damaged mtDNA activates the NLRP3 inflammasome, activating caspase-1 and promoting the maturation and release of pro-inflammatory cytokines IL-1β and IL-18 by a process called pyroptosis. Pyroptosis is a gasdermin (GSDMD)-mediated programmed necrosis that consists of the cleavage of GSDMD by caspase 1, generating N-terminal-GSDMD fragments that are oligomerized and form a pore in the cell membrane (Shi et al. 2017). mtDNA fragments and cytokines released by cardiomyocytes activate innate immune cells and induce immune cell recruitment, perpetuating cardiac inflammation. A recent study demonstrated that upon TLR activation, macrophages synthesize mtDNA for NLRP3 activation. Whereas pro-IL-1β and IL-18 synthesis is dependent on the NFκB pathway (Fig. 7.2), mtDNA is mediated by the IRF1 transcription factor (Zhong et al. 2018).

The mitochondrial-NLRP3-NFκB axis is a triggering factor for inflammation in many cardiomyopathies that lead to heart failure, whether due to sterile or pathogenic inflammation (Castillo et al. 2016). Moreover, its activation downregulates PGC-1α expression in both cardiomyocytes and macrophages (Kang et al. 2018; Palomer et al. 2009), which is involved in heart dysfunction via a direct association between the NFκB, p65 subunit and PGC-1α (Alvarez-Guardia et al. 2010). Therefore, as mitochondria modulate metabolic activity and immune function, mitochondrial dysfunction compromises immunometabolism and the cardiac-immune cells' relationship with heart function (Weinberg et al. 2015).

7.1.7 Role of Immune System Cells in Heart Function

Cardiac resident immune cells have been recognized as important regulators of heart function in steady-state conditions (Nicolás-Ávila et al. 2020; Adamo et al. 2020; Hulsmans et al. 2017). Cardiac-immune cells represent approximately 10% of all non-myocyte cardiac cells; Among them, macrophages are the largest immune population in the heart, comprising about 80%, followed by B cells, comprising 10% of all leukocytes (Pinto et al. 2016; Yu et al. 2016). In the atrioventricular node,

cardiac macrophages (cMφ) facilitate electrical conduction by direct contact with cardiomyocytes through connexin 43-gap junctions, which has been confirmed in patient biopsies (Hulsmans et al. 2017). Furthermore, connexin-43-gap junctions are also essential in the ventricle, where reduced levels are associated with fibrosis and ventricular dysfunction by aberrant mitophagy (Givvimani et al. 2014). Moreover, it was recently discovered that cMφ present in the ventricular myocardium are critical players in maintaining mitochondrial homeostasis, and, thus, healthy cardiac metabolism and function by phagocyting damaged mitochondria released by cardiomyocyte (Nicolás-Ávila et al. 2020). On the other hand, phagocytosis depends on bioenergetic production, which is finely tuned by the MCU. Recent data from a study of Mφ with MCU knock-down showed decreased pyruvate dehydrogenase activity, ROS production, and M2 polarization (Tedesco et al. 2019). These data reveal a new role for the MCU in alternative macrophage polarization and phagocytic activity. In this context, transgenic mice with dominant-negative MCU in macrophages showed a reduction in ROS and fatty acid oxidation and were protected from fibrosis. These findings suggest that macrophage MCU-mediated metabolic reprogramming is associated with fibrotic repair after lung injury (Gu et al. 2019). Notably, cardiac fibrosis and maladaptive remodeling in rodents are associated with MCU expression changes (Zaglia et al. 2017). However, the contribution of macrophage MCU in mediating fibrosis in the heart is not well understood.

Cardiac B cells (cB cells) are a B cell population that recirculates within the blood and spleen, delaying their heart transit. cB cells mostly remain intravascular and are located near the endothelium, which has been confirmed in patients with heart failure (Adamo et al. 2020). Although their exact function is not yet completely defined, the absence of cB cells also affects the recruitment of other immune cells and is associated with reduced cardiac mass and ventricular dysfunction. In this sense, cB cells are critical players in heart failure, several experimental therapeutics that target B cells are currently under examination (García-Rivas et al. 2020). Besides, immune synapse is crucial for B and T cell activation, and mitochondria have been shown a relevant role in this process by localizing nearly the immune synapse, regulating calcium signaling, and supplying energy locally. The interaction between B and T cells showed a significant mitochondrial depolarization after antigen exposure. Of note, antigen processing and antigen presentation were dependent on MCU activity (Bonifaz et al. 2015). Our group recently suggest that mitochondria participate during B cell activation through Ca^{2+} overload. Using primary murine B cells, we found that after BCR-independent stimulation, pretreatment with a mitochondrial antioxidant reduced B cell activation. It found that activated cells show higher mitochondrial calcium contents, suggesting that MCU participates in the B cell activation axis modulating mitochondrial ROS production (Torres-Quintanilla et al. 2017).

7.1.8 *Mitochondrial Dysfunction and Immune Cells Interplay in the Development of Cardiomyopathies*

As previously explained, mitochondria are exceptional organelles that regulate metabolism and immune function, and the interplay between cardiomyocytes and cardiac-immune cells is necessary to achieve ECC. In immune system cells, metabolic changes are indispensable to appropriate activation and polarization (Fracchia et al. 2013; Jang et al. 2015; Mills et al. 2016). During basal conditions, naïve/resting cells depend mainly on OXPHOS, but upon activation, their metabolism relies on aerobic glycolysis to directly produce ATP. This phenomenon is known as the Warburg effect (DeBerardinis and Chandel 2020) (Fig. 7.3). This shift increases

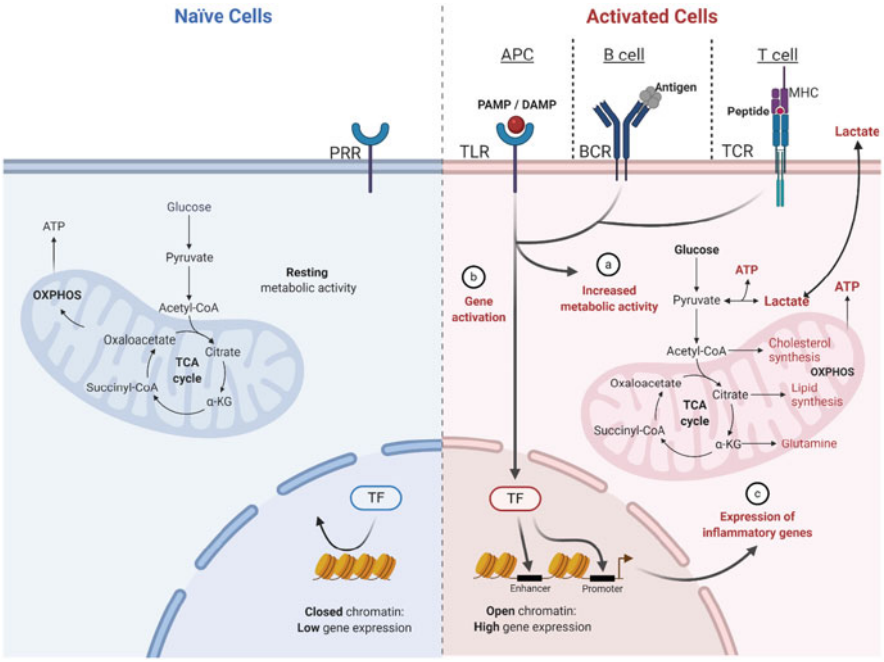

Fig. 7.3 Warburg effect: In the blue side, naïve or resting cells with resting metabolic activity producing ATP by OXPHOS after glycolysis fuels the TCA cycle. On the red side, immune cells become activated, APC, such as macrophages, by DAMPs or PAMPs recognition, B cell directly by the antigen and T cells by the antigenic peptide presented on the MHC-context by the APC. Either form of activation increases glucose utilization, and now cells also produce ATP directly by aerobic glycolysis, releasing lactate. *APC* antigen presenting cell, *ATP* adenosine triphosphate, *BCR* B cell receptor, *DAMP* damage-associated molecular patterns, *MHC* major histocompatibility complex, *OXPHOS* oxidative phosphorylation, *PAMP* pathogen-associated molecular patterns, *PPR* pattern recognition receptor, *TCA* tricarboxylic acid, *TCR* T cell receptor, *TF* transcription factor, *TLR* Toll-like receptor. (Created with BioRender.com)

the cell's bioenergetic capacity, allowing cytokines secretion, differentiation, and proliferation. However, the activation of polarization toward a regulatory cell, such as regulatory T cells or M2 macrophages, increases mitochondrial function by OXPHOS (Pålsson-McDermott and O'Neill 2020). Then, glucose metabolism in immune system cells changes over the duration of the immune response.

For instance, macrophages are the main population of immune system cells in the heart and are considered major players in cardiovascular homeostasis and disease (Lavine et al. 2018). In response to tissue injury, macrophages undergo M1 polarization. This pro-inflammatory phenotype produces TNF-α and relies on aerobic glycolysis to meet bioenergetic requirements, involving the downregulation of ETC genes. However, on subsequent days, a shift in tissue macrophages to the M2 phenotype promotes tissue reparation. This phenotype depends on OXPHOS by upregulating pyruvate metabolism and TCA cycle pathways (Rodríguez-Prados et al. 2010).

Cardiomyopathies can be triggered by either a direct insult to the heart, such as in acute myocardial infarction or myocarditis, or by indirect inflammatory processes that become chronic and systemic, such as in diabetic cardiomyopathy (Castillo et al. 2020). The trigger stimuli may also be sterile, associated with proper antigens, or pathogenic, associated with virus or bacteria. In this section, we will describe some of the previously described mechanisms in these types of cardiac disease.

7.1.9 Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a sterile, chronic, and inflammatory process that becomes systemic and affects heart metabolism and function. Despite their hyperglycemic status, diabetes mellitus (DM) insulin-dependent patients exhibit decreased cardiac glucose uptake (Avogaro et al. 1990). The mechanism may be mediated by impaired GLUT4 signaling, as demonstrated in animal models (Camps et al. 1992), limiting the ability to produce energy by glucose oxidation and forcing cardiomyocytes to increasingly rely on FAO, disrupting the balance in the utilization of these metabolic pathways. Thus, mitochondrial dysfunction, elevated ROS production, and increased apoptosis are involved in diabetic cardiomyopathy. Under diabetic conditions, cardiomyocytes have a decreased capacity to store calcium in the SR due to decreased SERCA2a activity and increased membrane leakage (Zarain-Herzberg et al. 2014), promoting mitochondrial Ca^{2+} overload (Chaube and Werstuck 2016).

Furthermore, mitochondrial fragmentation mediated by fission proteins increases ROS and activates cell death (Yu et al. 2008). However, when hyperglycemia becomes chronic, associated fusion proteins and autophagy are also decreased (Makino et al. 2010). In response to all these changes, cardiac-immune cells become

activated, releasing cytokines and chemokines that promote the chemotaxis and activation of circulating immune system cells within the heart (Tan et al. 2019).

In addition to systemic metabolic changes, the chronic systemic inflammatory state also affects the heart. Systemic inflammation associated with DM patients makes circulating immune system cells more susceptible to activation (van Oostrom et al. 2004; Zhai et al. 2016). In this context, mtDNA, ROS, and cytokines released into the extracellular milieu become available to activate immune system cells and promote cardiomyocytes' detrimental pathways, even if they were not primarily produced in the heart. For instance, IL-1β increases the propensity for arrhythmia by increasing CaMKII oxidation phosphorylation and SR calcium leakage (Monnerat et al. 2016). Additionally, several studies of diabetic cardiomyopathy have described high levels of IL-1β are associated with cardiac mitochondrial dysfunction. These results indicate that mitochondrial failure observed in diabetic cardiomyopathy is due to lower mitochondrial content and decreased mitochondrial respiration complexes (Yurre et al. 2020). Based on this idea, a recent study of glucose-intolerant rats found mitochondrial dysfunction and proneness to mPTP opening. This susceptibility was mediated by the hyperacetylation of Cyp D and an increase in mitochondrial oxidative stress (Fernández-Sada et al. 2017). The same model identified a significant increase in serum pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, and a nearly twofold incidence of ventricular fibrillation (Fernández-Sada et al. 2017).

7.1.10 Acute Myocardial Infarction

In contrast to diabetic cardiomyopathy, where the heart is exposed to a chronic stimulus, in acute myocardial infarction (AMI), cardiomyocytes are exposed to sudden and drastic metabolic changes, most notably a sharp decrease in the oxygen supply. Acute myocardial infarction is characterized by a strong inflammatory reaction in the necrotic myocardium, followed by tissue repair and fibrosis. Failure to keep inflammation in check results in inadequate tissue healing, adverse cardiac remodeling, and lower ejection fractions (Jia et al. 2019). Within the first day after AMI, significant macrophage recruitment occurs in the necrotic myocardium and non-infarcted myocardium as a remote ischemic event (Lee et al. 2012). Therefore, macrophages' metabolic activity may impact the healing of the necrotic myocardium and cardiac remodeling in the remaining viable myocardium. Local hypoxia promotes the expression of hypoxia-inducible factor 1 (HIF-1) in macrophages and a shift to glycolytic pro-inflammatory M1 macrophages (Mouton et al. 2018). When the oxygen supply is restored in a later phase, macrophages return to OXPHOS as their primary ATP source, changing their phenotype to M2 and thereby promoting inflammation resolution, fibrosis, and tissue healing (Mouton et al. 2018). However,

swelling, disruption of the cristae structure, and loss of density are observed in the cardiomyocyte's mitochondria, increasing fission (Tian et al. 2017). Fission augments mitochondrial permeability transition pore (mPTP) activity, which releases Cyt c and thereby promotes cell death (Ong et al. 2010).

7.1.11 Sepsis

Similarly, in sepsis, the classic activation of undifferentiated macrophages with LPS leads to M1 macrophage differentiation and is associated with metabolic reprogramming with lactate production (O'Neill and Pearce 2016). HIF-1 and mTORc1 mediate this metabolic shift (Sun et al. 2011). LPS-dependent HIF-1α activation is further stabilized by succinate accumulation (Tannahill et al. 2013) and pyruvate kinase M2 (PKM2), leading to increased glycolysis, inflammasome activation, and IL-1β expression (Palsson-McDermott et al. 2015). Both pharmacological inhibition and specific gene deletion in the macrophages of PKM2 reduce glycolysis and IL-1β production, contributing to decreased mortality in murine models of sepsis (Xie et al. 2016; Zhang et al. 2016).

The use of glycolysis as a direct source of ATP production allows the engagement of fatty acid synthesis, which may be used to synthesize pro-inflammatory mediators (O'Neill and Pearce 2016). The ETC however remains crucial during the early pro-inflammatory phase, as inhibition of complex II leads to reduced IL-1β serum levels, increased anti-inflammatory IL-10 levels, and a higher bacterial load (Garaude et al. 2016). Late sepsis is characterized by a shift towards M2 cells, which marks an immunosuppressed state (Watanabe et al. 2016). IL-10 promotes M2 differentiation by immunometabolic effects, suppressing glycolysis and stimulating OXPHOS. These actions are mediated by suppressing mTORc1, increasing mitophagy, and reducing ROS production (Ip et al. 2017). Instead of relying on glucose, M2 macrophages depend on FAO (Huang et al. 2014). The low glycolytic rate in M2 macrophages allows the glycolytic enzyme GAPDH to bind to TNF-α mRNA and suppress its translation by ribosomes (Millet et al. 2016). While M2 macrophages can oxidize glucose to drive fatty acid synthesis (Huang et al. 2016), M1 macrophages suffer from mitochondrial dysfunction. Therefore, it could be possible to reprogram M2 macrophages to an M1 phenotype, but the conversion from M1 to M2 would pose a more significant challenge (Van den Bossche et al. 2016).

7.1.12 Myocarditis

Myocarditis is characterized by a strong T CD4+ response that requires increased glycolysis. T cells from human patients with dilated cardiomyopathy (80% of whom had a previous diagnosis of myocarditis) were characterized by an increased

glycolytic rate, either during the basal condition or upon maximal metabolic stimulation, as assessed by the extracellular acidification rate (ECAR), without impairment in the oxygen consumption rate (OCR) (Wu et al. 2019b). The injection of exosomes from mice with experimental autoimmune myocarditis (EAM) into naïve mice induced cardiac damage associated with increased levels of Th1 and Th17 cells, as well as a reduction in T-reg cells. The predominance of Th1/Th17 cells was related to the increased glycolytic rate and lactate production. Further analysis identified the microRNA miR-142 as a key component in the ability of exosomes from EAM mice to induce disease. Inhibition of miR-142 blocked the increase in glycolysis and the proliferation of CD4+ T cells (Sun et al. 2020). Beyond the identification of miR-142 as a potential target in treating myocarditis, these findings highlight the relevance of glycolysis upregulation in T cell-mediated disease. During myocarditis, DRP1 is translated from the cytoplasm to mitochondria. Consequently, mitochondrial fission is stimulated (Lin et al. 2017) with the downregulation of OPA1-associated TNF-α and ROS in a TLR4-dependent activation, resulting in disorganized, fragmented mitochondria and damaged mitochondrial cristae in the cardiomyocytes of mice with dilated cardiomyopathy (Wu et al. 2018).

7.2 Conclusion and Prospects

As previously discussed, mitochondria are essential to maintaining cellular function by not only providing energy but also regulating the bioenergetic source, which dictates cellular fate. Thus, the regulation of mitochondrial biogenesis is critical for cell survival. In this chapter, we described how immune system cells contribute to this process by eliminating dysfunctional mitochondria released into the extracellular space, avoiding inflammation and allowing cardiomyocytes to meet their metabolic and mechanical demands (Nicolás-Ávila et al. 2020). Although we do not entirely understand the interplay between immune and cardiac cells, evidence has shown that imbalance among these cells has a detrimental effect on cardiac function and even proper heart development (Adamo et al. 2020; Hulsmans et al. 2017). However, when inflammation occurs, whether sterile or pathogenic, chronic or acute, immune system cells release soluble mediators that alter mitochondrial function in cardiomyocytes by altering calcium handling and favoring glycolysis (Palomer et al. 2009; Palsson-McDermott et al. 2015). This change in the bioenergetic source of cardiomyocytes promotes mitochondria fragmentation, as well as increases ROS production, protein oxidation, mPTP opening, and cell death (Boudina et al. 2007). However, the activation of cardiac-immune cells also promotes glycolysis, which facilitates the proliferation and production of cytokines (Tedesco et al. 2019), compromising the relationship between cardiac-immune cells and cardiomyocytes that exist in a steady state (Adamo et al. 2020; Hulsmans et al.

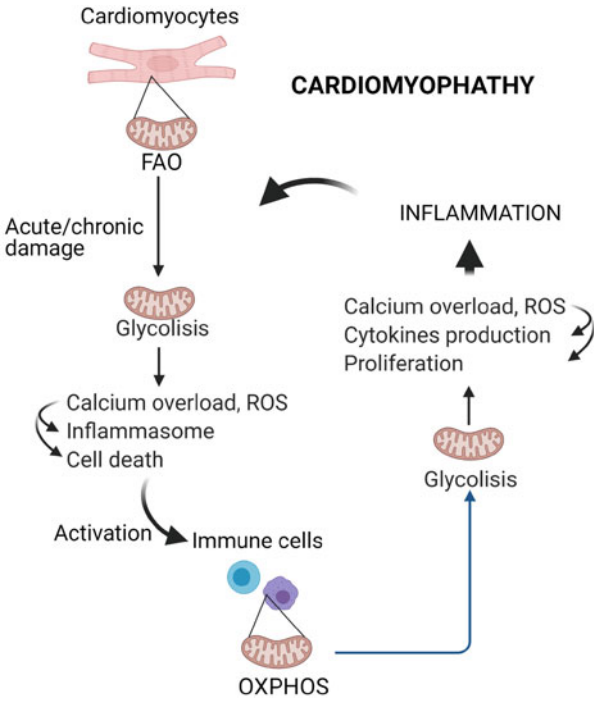

Fig. 7.4 Mitochondrial dysfunction as a trigger of inflammation in cardiomyopathies. When alterations in mitochondria promote bioenergetic changes that relay in glycolysis, it increases ROS production leading to inflammasome activation, cell death, and immune cell activation. To become activated, immune systems cells must change their bioenergetic source from oxidative to glycolytic, increasing the inflammatory milieu, and perpetuating cardiomyocyte dysfunction that leads to cardiomyopathies. (Created with BioRender.com)

2017). Therefore, mitochondrial dysfunction compromises immunometabolism and the cardiac-immune cell relationship, leading to cardiomyopathies (Fig. 7.4).

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