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Faas, M M; de Vos, P

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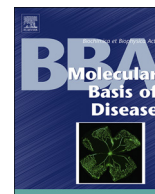
Mitochondrial function in immune cells in health and disease

M.M. Faas[a,b,*], P. de Vos[a]

[a] *Immunoendocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University of Groningen and University Medical Centre Groningen, Groningen, the Netherlands*
[b] *Department of Obstetrics and Gynecology, University of Groningen and University Medical Centre Groningen, the Netherlands*

A B S T R A C T

One of the main functions of mitochondria is production of ATP for cellular energy needs, however, it becomes more recognized that mitochondria are involved in differentiation and activation processes of immune cells. Upon activation, immune cells have a high need for energy. Immune cells have different strategies to generate this energy. In pro-inflammatory cells, such as activated monocytes and activated T and B cells, the energy is generated by increasing glycolysis, while in regulatory cells, such as regulatory T cells or M2 macrophages, energy is generated by increasing mitochondrial function and beta-oxidation.

Except for being important for energy supply during activation, mitochondria also induce immune responses. During an infection, they release mitochondrial danger associated molecules (DAMPs) that resemble structures of bacterial derived pathogen associated molecular patterns (PAMPs). Such mitochondrial DAMPS are for instance mitochondrial DNA with hypomethylated CpG motifs or a specific lipid that is only present in prokaryotic bacteria and mitochondria, i.e. cardiolipin. Via release of such DAMPs, mitochondria guide the immune response towards an inflammatory response against pathogens. This is an important mechanism in early detection of an infection and in stimulating and sustaining immune responses to fight infections. However, mitochondrial DAMPs may also have a negative impact. If mitochondrial DAMPs are released by damaged cells, without the presence of an infection, such as after a trauma, mitochondrial DAMPs may induce an undesired inflammatory response, resulting in tissue damage and organ dysfunction. Thus, immune cells have developed mechanisms to prevent such undesired immune activation by mitochondrial components.

In the present narrative review, we will describe the current view of mitochondria in regulation of immune responses. We will also discuss the current knowledge on disturbed mitochondrial function in immune cells in various immunological diseases.

1. Introduction

The mitochondrion is a double membrane organelle present in almost all cells. Evolutionary, it is suggested that mitochondria are derived from bacteria merging with proto-eukaryotic cells [1]. A major function of mitochondria is the supply of ATP for cellular energy needs [1]. However, it is becoming more and more apparent that mitochondria have various other important roles in the cells, such as for instance regulating apoptosis [2] and also regulating immune responses which protect the body against infections and cancer [3]. Mitochondria are able to affect immune cell function in various ways, such as for instance by production of reactive oxygen species (ROS), which are generated by mitochondria via the electron transport chain [4]. ROS function as second messengers in various signaling pathways in immune cells, for instance in the Ca^{2+}-NFAT signaling pathway, which is critical in T cell activation [5]. ROS can also damage bacterial pathogens, but if produced excessively it can also undesirably damage the producing cell or neighboring cells. The role of other mitochondrial products, such as mitochondrial DNA and proteins, in triggering and maintaining immune responses has also been recently recognized [6]. Not only via mitochondrial components but also via the generation of energy mitochondria are essential for inducing and regulating immune responses [7]. As recent discoveries have given timely and new insights in how mitochondrial processes might contribute to forming pro- or regulatory immune responses, we have decided to write this narrative review. The review will focus on the various functional roles of mitochondria in immune cells and in activating immune responses and will shortly discuss the function of mitochondria in immune cells in some immunological diseases.

2. Mitochondrial metabolism

One of the main functions of mitochondria is to accomplish oxidative phosphorylation and produce ATP [8]. Oxidative phosphorylation is a highly efficient mechanism for ATP production and uses an electron transfer chain driven by oxidation of various substrates [9]. The movement of electrons down the mitochondrial electron transport chain is associated with the transport of protons across the mitochondrial membrane. This creates an electrochemical gradient (mitochondrial membrane potential), which is used to phosphorylate ADP to ATP [10]. NADH2 and FADH2 are used by the electron transport chain to generate electrons. NADH and FADH are refueled by the tricarboxylic acid (TCA) cycle. The TCA cycle is fed by various substrates, such as fatty acids and pyruvate, which are converted to acetyl-CoA by beta-oxidation and pyruvate dehydrogenase, respectively, before entering the TCA cycle [11]. Pyruvate is produced via glycolysis, in which glucose is converted to pyruvate. Pyruvate can be used by the TCA, but can also be reduced to lactate (aerobic glycolysis), which results in quick, but relatively inefficient ATP production, and production of lactate [12]. Glycolysis also fuels the Pentose Phosphate Pathway, which efficiently synthesizes nucleotides and NADPH [7]. Amino acids, such as glutamine can also be used by the TCA, after conversion through glutaminolysis to alpha-ketoglutarate [7]. Depending on the metabolic state of the cell, the TCA cycle fuels the electron transport chain or TCA intermediates are transported out of the mitochondria into the cytosol, where they may be used for building fatty acids or nucleotides or function as important signaling molecules. ROS are such signaling molecules [13] and are produced at various sites in the mitochondria [4]. (See "resting immune cells" in Fig. 1). Since excessive ROS production can also damage cells, important ROS scavenging systems are present in the cells, such as superoxide dismutase (SOD) or catalase [4]. Changes in either mitochondrial activity, such as changes in the mitochondrial membrane potential, or changes in the ROS scavenging system determine mitochondrial ROS production [4].

Differences in mitochondrial function are linked to dynamics in mitochondrial morphology [14]. Mitochondrial morphology is regulated by so-called fusion and fission events, which in their turn are regulated independently by a complex protein machinery. The fusion of the outer membrane between 2 adjacent mitochondria is mediated by mitofusin 1 and 2 [15]. After outer membrane fusion, the dynamin-like GRPase optic atrophy (OPA) mediates fusion of the inner membrane [15]. The other protein important for inner membrane fusion is Cardiolipin [16]. Mitochondrial fission of the outer membrane is dependent on dynamin-related protein 1 [17]. It remains unclear whether fission of the outer membrane is sufficient to drive fission of the inner membrane but two inner membrane proteins, i.e. mitochondrial protein 18 (MTP18) and short Optic Atrophy −1 (OPA1), are probably important [18]. Fusion of mitochondria is important for maintenance of mitochondrial DNA integrity and for cellular respiration [19]. Fission of the mitochondria is important to allow inheritance of mitochondria by daughter cells during cell division [20]. Fission is also important when mitochondria are damaged and deleted, since the segregation of damaged mitochondria facilitates their removal by mitophagy [21]. Mitochondrial fission and fusion processes are responsible for dynamics in mitochondrial morphology, which can vary significantly between tissues and cells. For example in activated T cells the fission and fusion processes result in more fragmented mitochondria while in neurons it induces formation of more tubular mitochondria [22,23]. Notably, however, fission and fusion processes occur also in response to various extra- or intracellular changes, such as changes in nutrient supply or in energy or redox status, but also during cell differentiation in a cell-type dependent manner. This is for instance seen when comparing effector T cells and memory T cells. Active effector T cells have more fragmented mitochondria, while long-lived, less active memory T cells have a more fused mitochondrial network [22]. Moreover, various disease are associated with fragmented mitochondria [24] which might be an important indicator and target for management of disease.

Mitochondria are not only important as energy suppliers and for functioning of immune cells, they also have a role in antiviral signaling. Mitochondria control signaling pathways to restrain viral infections [25]. A major role is played by the mitochondrial antiviral signaling (MAVS) protein, which is localized in the mitochondrial membrane [26]. Viral RNA is sensed by the retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), which are present in the cytosol [27]. Following RNA binding, RIG-I and melano differentiation associated gene 5, two members of this family, oligomerize and activate the downstream MAVS [28]. MAVS induces via various pathways the expression of type I and II interferons, important for clearing of the virus, and the activation of Nuclear Factor-kB (NF-kB), important for activating the innate and adaptive immunity [29].

3. Mitochondrial function in immune cells

Upon activation of immune cells, immune cell function alters, since for instance large amounts of cytokines and chemokines need to be produced or immune cells need to migrate to inflamed tissues. Such processes demand large amounts of energy and adaptations of the energy producing mechanisms. Immediate fuel of cellular energy can be induced by increasing glucose uptake and upregulation of glycolysis, which is used by for instance monocytes [30] and M1 macrophages [31]. Often these immune cells do not use all pyruvate for the TCA cycle and mitochondrial oxidation, but use it for aerobic glycolysis, producing ATP, albeit in low amounts [32]. Mitochondrial oxidation can also be upregulated upon activation of immune cells, but this requires mitochondrial biogenesis, which takes longer [33]. Glutamine is also often used as an energy source for activated immune cells [34]. These changes in metabolism in activated immune cells will be described in more detail for various immune cells below.

The mechanistic target of rapamycin (mTOR) is an evolutionary conserved signaling pathway that senses and integrates various stimuli, such as pathogen associated molecular patterns (PAMPs), growth factors and cytokines, to coordinate metabolic adaptations and regulate growth,proliferation and function of immune cells [35]. The ser/thr kinase mTOR exists in two mTOR complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTOR C2) [36,37]. Both can be activated by various immunological stimuli, such as growth factors, Toll-like receptor ligands or LPS, but also by intracellular stimuli, such as amino acids [38]. Such stimuli result in activation of phosphoinositide 3-kinase (PI3K), which directly, mTORC2, or via Akt (Protein Kinase B), mTORC1, activates mTOR [39]. The central function of mTORC1 is to induce cellular growth and proliferation, while mTORC2 is involved in Th polarization and actin cytoskeleton dynamics, which are important for cellular movement [39]. MTORC1 promotes amongst others translation of metabolic enzymes necessary for cell proliferation and the synthesis of transcription factors HIF1α and Myc, which are important for programming the metabolism in activated immune cells, and positively regulate glycolysis [40]. MTORC2 can also enhance glycolysis [41].

3.1. Mitochondrial function in innate immune cells

The immune system is important in the body's defense against infection and cancer. The immune system consists of 2 arms: the adaptive immune system and the innate immune system [3]. The innate immune system is the first line of defense against infections [3]. Cells of the innate immune response are monocytes, macrophages/dendritic cells, granulocytes (neutrophils, eosinophils and basophils), but also innate lymphocytic cells (ILCs), including natural killer (NK) cells [3]. Their main functions are cytokine production, phagocytosis, lysis of infected cells, or presenting antigens to T cells [3]. Innate immune cells recognize structures specific for microbes such as so called microbe or Pathogen associated molecular patterns (PAMPs), which are microbial
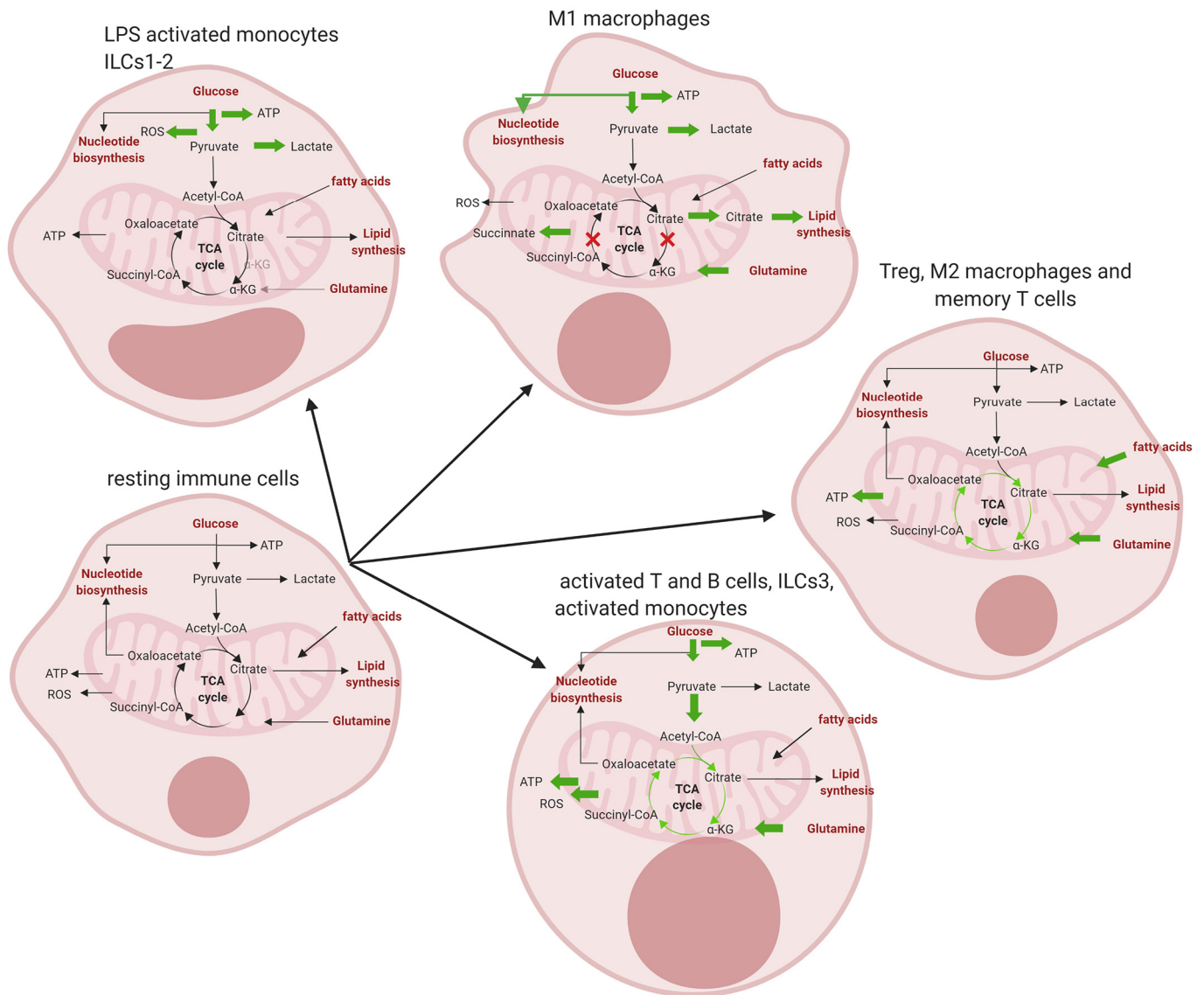
Fig. 1. Mitochondrial metabolism in resting immune cells and in activated monocytes, M1 macrophages, M2 macrophages, Treg cells and memory cells, and in activated T and B cells.

In pro-inflammatory cells, like activated monocytes, ILCs1, M1 macrophages and activated T and B cells the high demand for energy is fueled by increasing glycolysis. However, the role of mitochondrial function differs between these pro-inflammatory cells, since little changes in mitochondrial function are observed in LPS activated monocytes, while a deficient TCA cycle is observed in M1 macrophages and increased mitochondrial function is characteristic for activated T and B cells and monocytes activated by other stimuli, such as TLR2 ligands. Regulatory cells and long-lived cells (M2 macrophages, Treg cells and memory T cells) mainly rely on beta-oxidation and increased mitochondrial function.

molecules, such as LPS or flagellin [42]. They also recognize eu-karyote's own cell derived molecules, such as damage associated mo-lecular patterns (DAMPS), amongst which is mitochondrial DNA. For recognition of PAMPs and DAMPs, the innate immune cells have spe-cific receptors, Pattern Recognition Receptors (PRRs), the most well-known being Toll-like Receptors (TLR) [42].

3.1.1. Monocytes

Blood monocytes arise from precursors in the bone marrow and about 5–10% of all circulating blood leukocytes is monocyte [43].They circulate in the blood for 24–48 h., after which they migrate into tissues to become macrophages or dendritic cells [43]. They are important for regulating immune responses, inflammation and tissue repair. They produce cytokines, are phagocytotic and present antigens to cells of the adaptive immune system [43]. Three subsets of monocytes are cur-rently distinguished: classical monocytes (CD14 + +/CD16low),

intermediate monocytes (CD14 + +/CD16 +) and non-classical mono-cytes (CD14low/CD16 +) [44]. Classical monocytes (80–90% of all monocytes) are phagocytes, produce reactive oxygen species and pro-duces cytokines in response to TLR activation. Non-classical monocytes (5–10% of all monocytes) are efficient producers of pro-inflammatory cytokines; they have been shown to be increased in various in-flammatory conditions [44]. The function of intermediate monocytes is less clear and it is thought that they may have an intermediate function between classical and non-classical monocytes [44].

Various studies have focused on mitochondrial function in mono-cytes but it is unknown whether there are differences in mitochondrial function between the three subsets of monocytes. Most studies in monocytes have been done in the total monocyte population, which consists mainly of classical monocytes. Monocytes, like other immune cells, upregulate their metabolism after activation to meet the high energy demands of activation [30]. Common pro-inflammatory

monocyte stimuli, such as LPS, induce a glycolytic burst and reduce oxidative phosphorylation, and upregulate lactate, which is similar to the Warburg effect seen in cancer cells [30,45,46] (see Fig. 1). This increased glycolysis increases ROS production in monocytes [45]. However, at sites of inflammation, glucose concentration often decreases, after which monocytes shift their metabolism to oxidative phosphorylation, fueled by fatty acid oxidation. Fatty acids are derived from the lipid droplets insight the cell [46].

Other stimuli than LPS, can induce oxidative phosphorylation in monocytes. The upregulation of glycolysis and downregulation of oxidative phosphorylation, as described above, appears to be specific for LPS engaging the TLR4, since stimulation of monocytes with for instance TLR2 ligands, such as Pam3CysSK4, increased glycolysis but also increased oxidative phosphorylation [47]. Similarly, stimulation of human monocytes with the yeast *Candida albicans* or the live attenuated Bacillus Clamette-Guerin (BCG) vaccine increased glycolysis but also oxidative phosphorylation [48,49]. Stimulation of monocytes with fungal components, like B-glucans, induced glycolysis and decreased oxidative phosphorylation, like LPS [50]. These data indicate that metabolic changes in activated monocytes may depend on the stimulus.

Some studies suggest an important role for early oxidative stress and increased mitochondrial respiratory activity in monocytes in immune paralysis during sepsis [51]. Sepsis is a serious condition caused by an inflammatory response triggered by PAMPs, such as LPS, during an infection [52]. The important role of monocytes in sepsis is well-known [53]. Monocytes are activated in sepsis followed by subsequent immune paralysis [53]. A recent study into activation of the monocytic cells (THP-1 cells) by LPS showed that the immune paralysis is associated with early oxidative stress and increased mitochondrial respiratory activity [51]. The authors also demonstrated increased autophagy of mitochondria (mitophagy) as well as an increased mitochondrial synthesis and upregulation of antioxidant defenses during immune paralysis [51]. These data suggest occurrence of mitochondrial dysfunction during immune paralysis and replacement of dysfunctional mitochondria in order to inhibit oxidative stress and increase mitochondrial respiratory activity [51]. Unfortunately, not many studies on mitochondrial function in septic patients have been performed. One study showed increased mitochondrial enzyme activity of the electron transport system, indicating increased ATP production in septic monocytes. However, ATP content did not increase, suggesting an increased metabolic demand and thus ATP consumption [54]. A few studies have looked at mitochondrial function in monocytes in other conditions. It has been shown that ageing, which is associated with a low grade inflammatory response, called inflammaging [55], decreased mitochondrial function in classical monocytes and possibly also in non-classical monocytes [56], by impairing mitochondrial respiratory capacity [55]. Both type 2 diabetes and obesity were associated with decreased monocyte mitochondrial function [57,58].

Activation of monocytes by TLR ligands induces the activation of mTORC1 and mTORC2, which enhance not only glycolysis [45], but also the production of chemokines and cytokines [59]. Activation of mTORC1 increases proinflammatory cytokine production, while inhibition of mTORC1 inhibits proinflammatory cytokine production [60].

Recently, it was shown that not only adaptive immune cells develop memory, but that also innate immune cells develop memory, called trained immunity [61]. Trained immunity has been shown for various innate immune cells, including monocytes, and can be induced by stimuli like β-glucan or the Bacillus Calmette-Guérin (BCG) vaccine [61]. Trained memory allows innate immune cells to respond stronger and more rapidly upon subsequent triggers [61]. The mechanisms inducing trained immunity have mainly been studied in monocytes in vitro. Trained immunity seems to result from epigenetic changes, induced by metabolic pathways [61]. Recently, Arts et al. showed that increased glycolysis, glutaminolysis and cholesterol synthesis pathways are needed to induce trained memory in monocytes [62].

3.1.2. Macrophages

Macrophages are tissue resident cells, which are important in detecting, phagocytosing and processing foreign material, such as bacteria or dead cells [43]. Macrophages play an important role in inflammatory processes in tissues, but they also have anti-inflammatory or regulatory properties, with which they are involved in resolution of inflammation [43]. Like for monocytes, several macrophages subtypes have been described. Macrophages can be classified into M1 macrophages, which are microbicidal and pro-inflammatory, or M2 macrophages, which are anti-inflammatory or immunomodulatory and can induce resolution of inflammation [43]. M1 macrophages secrete many pro-inflammatory molecules, such as IL-12, TNF-alpha and nitric oxide (NO) [63]. They are implicated in the clearance of various types of microbial infections [63]. M2 macrophages produce molecules that modulate inflammation and promote tissue repair and are involved in responses to helminth parasites [63]. These populations, however, may be the extreme ends of polarization, since various subtypes in between M1 and M2 macrophages have been described [63].

Macrophages stimulated with LPS differentiate into M1 macrophages, while macrophages stimulated with IL-4 or IL-13 differentiate into M2 macrophages [64]. It has recently become recognized that not only LPS or cytokines can mediate differentiation towards macrophage phenotypes, also the cellular metabolism is very important for determining macrophage phenotype [65]. Similar to monocyte activation by LPS as described above, stimulation of macrophages with LPS (i.e. differentiation towards M1 macrophages), increases glucose uptake and glycolysis [31] (see Fig. 1). This increased glycolysis seems to be the result of an upregulation of the enzyme ubiquitous 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (uPFK2), inducing high concentrations of fructose-2,6-bisphosphate, which potentiates glycolysis [31]. This is associated with the production of HIF1α, which induces pro-inflammatory IL-1β production and upregulation of several enzymes involved in glycolysis [66]. Not only glycolysis, but also the Pentose Phosphate Pathway is increased in M1 macrophages. This is the result of downregulation of the enzyme carbohydrate kinase-like protein (CARKL) [66], which inhibits this Pentose Phosphate Pathway [67]. The Pentose Phosphate Pathway generates nucleotides and NADPH [7], the latter is important for mitochondrial ROS production [67]. M1 macrophages also increase glutamine metabolism, which is used as alpha-ketoglutarate in the TCA cycle after glutaminolysis [66]. This stimulates succinate accumulation [66]. Succinate stabilizes HIF1α [66]. M1 macrophages have an impaired TCA cycle, with two deficient steps [66,68]. The first deficiency results in accumulation of citrate in the cytosol of the cell [68,69]. This citrate can be used for synthesis of lipids (prostaglandins), nitric oxide or ROS [70], which are important for M1 macrophage function. The other break in the TCA cycle leads to accumulation of succinate [66] (see Fig. 1).

Relatively little is known about the cellular metabolism in M2 macrophages. In contrast to M1 macrophages, which largely depend on glycolysis due to the upregulation of uPFK2, M2 macrophages do not upregulate uPFK2, and therefore do not increase glycolysis [31]. M2 macrophages are thought to be dependent on beta-oxidation [71,72]. Beta-oxidation in IL-4 activated macrophages is upregulated by induction of the nuclear receptors PPAR-γ and PPAR-δ [71,73,74]. Exogenous lipoproteins are used as a source for fatty acids in M2 macrophage, which are taken up by CD36 and broken down to fatty acids in the lysosome [72]. Enhanced beta-oxidation is associated with an increased TCA, increased respiratory capacity, and thus with an increased capacity to produce ATP by oxidative phosphorylation. Whether this is important for M2 macrophage function, such as for production of various M2 specific regulatory factors or factors associated with tissue repair, and/or for longevity remains to be established. M2 macrophages also upregulate consumption of glutamine [68]. In contrast to M1 macrophages, in M2 macrophages, this is mainly used in the hexosamine pathway and upregulates N-glycosylation, which is important for several M2 markers [68].

Activation of Akt and mTOR in M1 macrophages is important for inducing HIF1α and therefore inducing glycolysis [50]. It is also important for the balance of pro- and anti-inflammatory cytokine production, as well as for macrophage polarization: inhibition of mTORC1 with rapamycin increased M1 macrophage polarization [75], while in M2 macrophages, activation of mTORC1 is a negative regulator of induction of M2 macrophages, while mTORC2 is critical for M2 macrophage induction [76]. In M1 macrophages, it has been shown that mTORC1 inhibition increases the production of proinflammatory cytokines, and inhibits the production of the anti-inflammatory IL-10 [60], while on the other hand mTORC1 activation enhanced the production of IL-10 and decreased the production of the proinflammatory cytokines [60]. mTORC1 limits the production of proinflammatory cytokines by inhibiting the activation of NF-kB [60,76].

Trained immunity can also be observed in macrophages [61]. This is associated with changes in mTOR activity [50]. After in vitro stimulation of monocytes derived macrophages with β-glucan, macrophages respond with exaggerated proinflammatory cytokine production following a subsequent stimulus with β-glucan or a TLR agonist [62]). This trained immunity is associated with the Warburg effect (i.e. increased glycolysis and reduced oxidative phosphorylation) as well as an increased Pentose Phosphate Pathway and cholesterol metabolism [62]. It is also associated with an increased expression of mTOR, mainly mTORC1 [62,50], and the downstream targets of mTOR, such as HIF1α [50]. This latter upregulation results from epigenetic changes at promotors in the mTOR pathway [50].

3.1.3. Innate lymphocytic cells

ILCs are the innate counterpart of T cell subsets. They are lymphocyte like cells, since they are derived from the common lymphoid precursors, but they lack expression of antigen receptors found on T or B cells, such as CD3 or CD19 [77]. They are primarily tissue resident cells, and can be found in lymphoid tissue and non-lymphoid tissue [78]. They play key roles in immune responses to pathogens in all organs, since they can rapidly secrete cytokines, but they are particularly important at mucosal tissues and play a key role in mucosal immunity [79]. Three types of ILCs can be distinguished: ILCs1, ILCs2 and ILCs3. ILCs1 are comprised of NK cells and other ILCs1 cells and are dependent on the T-box transcription factor Tbet for development and function and they produce interferon-gamma (IFNγ); ILCs2 are dependent on the transcription factors GATA binding protein 3 (GATA3) and RAR-related orphan receptor α (RORα) and produce type 2 cytokines, such as IL5 and IL13; ILCs3 are dependent on the transcription factor RAR-related orphan receptor gamma T (RORγT) and produce IL-17 and IL-22 [77].

Mitochondrial function in ILCs has recently been reviewed by Rolot et al. [80]. Like other immune cells, naïve quiescent ILCs mainly use glycolysis and oxidative phosphorylation to provide ATP for energy requirements [81]. Upon activation, different ILCs use different energy generating strategies. NK cells, as part of the ILC1 group, upregulate glycolysis to provide for the increased demand for amino acids, lipids and nucleotides during activation and proliferation [81]. ILCs2 can also increase glycolysis upon activation, this, however, depends on arginase-1 activity, which metabolizes L-arginine to polyamines (derived from ornithine) to fuel glycolysis [82]. ILCs2 can also take up long chain fatty acid and use fatty acid oxidation for proliferation and function [83]. ILCs3 can increase glycolysis and fatty acid oxidation as well increase the mitochondrial respiratory function [84].

3.2. Mitochondrial function in adaptive immune cells

The adaptive immune system consists of T lymphocytes and B lymphocytes. B lymphocytes upon stimulation can develop into plasma cells, which are antibody producing cells [3]. B lymphocytes are also professional antigen presenting cells and they can secrete cytokines [3]. T lymphocytes are identified by their T cell receptor. Two T lymphocyte subsets can be distinguished: CD4+ T helper cells and CD8+ cytotoxic

T cells. Cytotoxic T cells act mainly by killing cells through cell-cell interaction [3]. T helper cells produce cytokines upon antigen stimulation, thereby coordinating the immune response [3]. T helper cells can be divided into various subpopulations, based on their effector function. The main and most studied subpopulations are T helper 1 (Th1), Th2, Th17 and regulatory T cells (Treg). Th1 cells are involved in cell-mediated immunity and characterized by production of Th1 cytokines, such as IFNγ. Th2 cells are involved in humoral immunity and produce Th2 type cytokines, such as interleukin 4 (IL-4). Th17 cells produce IL-17, and are involved in mucosal immunity and inflammation. These subsets are called effector T cells [3]. Treg cells are identified by the expression of the transcription factor Forkhead box P3 (FOXP3). Treg cells can suppress other immune cells, such as other T cells, but also macrophages and dendritic cells, thereby controlling both innate and adaptive immune responses [85]. An important feature of adaptive immunity is their ability to generate long-lived memory cells, that are able to respond more rapidly upon reinfection [3].

3.2.1. B lymphocytes

Antigen specific B lymphocytes become activated upon encountering a cognate antigen and with co-stimulation of T cells. [3]. They then migrate to secondary lymphoid tissues and start proliferating [86]. They undergo immunoglobulin class switching and differentiate into plasma cells producing large amounts of antibodies [3,86]. Upon activation, B lymphocytes upregulate both oxidative phosphorylation and glycolysis [87] (see Fig. 1). Activated B lymphocytes also have increased mitochondrial mass as well as increased ROS production compared to resting cells [88,89]. ROS production in B lymphocytes is necessary for B cell activation [88]. Upon differentiation to plasma cells, glycolysis and oxidative phosphorylation is further upregulated [87], and upon further differentiation into long-lived plasma cells, the maximal capacity for oxidative phosphorylation is even further increased [90]. This is due to increased glucose uptake and mitochondrial pyruvate import [90]. Upregulation of glycolysis in activated B lymphocytes is induced by phosphoinositide 3 kinase (PI3K) and upregulation of mTOR [91]. It has been shown the mTORC1 is important for B cell development and survival [92]. Both mTORC1 and mTORC2 have been shown to be important for antibody class switching [93,94].

3.2.2. Effector T cells

Resting naïve T cells have a low rate of nutrient uptake and rely on oxidative phosphorylation to generate ATP for their survival. This is fueled by oxidation of glucose, glutamine and fatty acids [95]. Upon activation, effector T cells immediately increase glucose uptake and glycolysis to rapidly produce ATP [95] (see Fig. 1). In contrast to activated innate immune cells, in which oxidative phosphorylation is relatively inhibited and pyruvate is used in aerobic glycolysis and the Pentose Phosphate Pathway, in effector T cells oxidative phosphorylation is increased upon activation [96]. This is associated with an increase in mitochondrial mass and mitochondrial DNA levels in the first hours of activation [96,97]. This increase in oxidative phosphorylation is indispensable for T cell proliferation upon activation, since blocking the electron transport chain reduces T cell proliferation [97]. The increase in oxidative phosphorylation in activated T cells is also important for production of ROS, which is required for intracellular signaling during activation of T cells [98]. Oxidative phosphorylation in effector T cells is supported by glutamine uptake, which through glutaminolysis is converted to alpha-ketoglutarate and used in the TCA cycle for oxidative phosphorylation [99]. Glutamine uptake seems to be essential for effector T cells, since restriction of glutamine converts naïve T cells into Treg cells [100].

Although the above-described mitochondrial metabolism in effector T cells is general for these cells, within the effector T cells subpopulations, there are differences in mitochondrial metabolism. For instance, mitochondrial dysfunction in T cells induced by depletion of mitochondrial transcription factor A (TFAM) (one of the mitochondrial
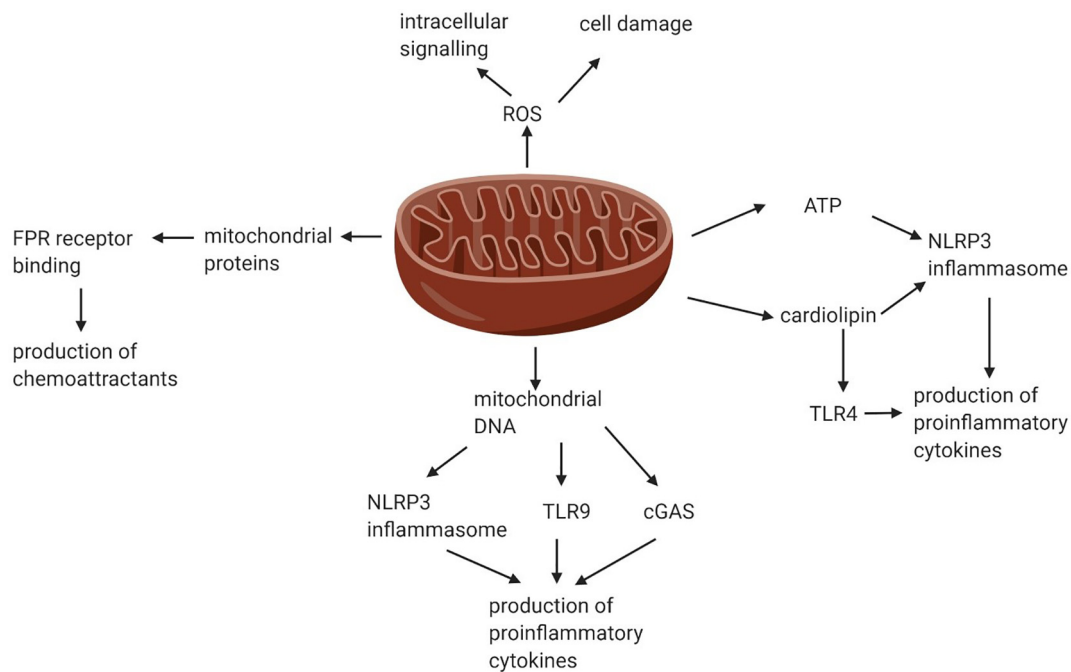
Fig. 2. Effects of mitochondrial DAMPs on immune responses.
Various mitochondrial DAMPs can be released into the cell cytosol or into the extracellular space and circulation. Mitochondrial proteins may bind to FRP receptors inducing the production of chemoattractants. Mitochondrial ROS are important for intracellular signaling, although excess ROS production may damage cells. Mitochondrial ATP and cardiolipin may activate the NLRP3 inflammasome or TLR4 and induce the production of pro-inflammatory cytokines. Mitochondrial DNA may activate TLR9, NLRP3 inflammasomes or the cGAS pathway resulting in production of pro-inflammatory cytokines.

genes) induces an increased glycolysis and differentiation towards Th1 cells and not towards the other subpopulations [97], suggesting the Th1 cells depend less on mitochondrial respiration than the other subtypes.

The dependence of effector T cells on glycolysis is associated with a role of mTOR in these cells. Activation of mTOR is important for the development of Th subsets, such as Th1, Th2 and Th17 [101]. mTORC1 is important for Th1 and Th17 cell differentiation [101]; mTORC2 may play a role in Th1 cells [102] and in Th2 cell differentiation [102].

3.2.3. Regulatory T cells

The metabolism of Treg cells is different from the metabolism of effector T cells and unfortunately, less is known about mitochondrial function in Treg cells. Treg cells use fatty acid oxidation and oxidative phosphorylation, rather than glycolysis, to induce Treg specific differentiation such as expression of FOXP3 and sustain their immunoregulatory function [103–105]. Treg stability is further achieved by FOXP3 specific suppression of glycolysis and Myc signaling [106], and enhanced oxidative phosphorylation and NAD+ generation [103] (See Fig. 1). The fact that Treg cells do not need glycolysis for their induction is in line with the finding that activation of mTORC1 is not necessary for Treg induction [40], and both loss of mTORC1 and mTORC2 induces Treg differentiation in T cells [101]. However, mTORC1 does play a role in Tregs: activation of mTORC1 induces proliferation in these cells while inhibiting the suppressive activity [107]. Indeed, activation of Tregs with TLR ligands promotes glycolysis and proliferation of Treg cells and inhibits suppressive activity via the mTOR pathway [108]. This findings are in line with the findings that Treg cell proliferation depends on glycolysis [105].

3.2.4. Memory T cells

After an active infection, T cells undergo contraction and a small population survives to become memory T cells [3]. Memory T cells are long-lived cells that can quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen [3]. During memory T cell development glycolysis is reduced, while mitochondrial

metabolism fueled by fatty acid oxidation is enhanced [109,110] (see Fig. 1). This may be an important adaptation for memory cells, since enhanced mitochondrial metabolism may be necessary for expediting responses of memory T cells upon restimulation with the cognate antigen [109]. To increase fatty acid oxidation, memory T cells increase the expression of the enzyme carnitine palmitoyl transferase 1, which is a rate limiting enzyme in fatty acid oxidation [110]). The importance of the increase of this enzyme is shown by the fact that inhibition of the enzyme reduced fatty acid oxidation and oxidative phosphorylation [110]. This specific mitochondrial metabolism in memory T cells is associated with distinct changes in mitochondrial morphology [22]. Memory T cells have a more fused network of mitochondria, which is associated with improved oxidative phosphorylation, while effector T cells have more isolated mitochondria [22]. These mitochondrial changes are mediated by enhance expression of dynamin-related protein 1 and OPA1 [22].

In memory T cells, mTOR is less important since the central function of mTOR is induction of cellular growth and proliferation. In memory T cells, another protein kinase is important, adenosine monophosphate-activated kinase (AMPK). This is, like mTOR, an intracellular nutrient sensor, but it increases fatty acid oxidation and oxidative phosphorylation [111]. mTOR may negatively regulate memory T cell development, since inhibiting mTOR increases antigen specific CD8 memory T cells in mice with lymphocyte choriomeningitis infection and in primates vaccinated against vaccinia virus [112].

4. Mitochondrial DAMPs

The sections above describe the importance of mitochondria and mitochondrial metabolism in immune cell functioning. Mitochondria, being of bacterial origin and still sharing several features with bacteria [1], also release DAMPs that just like bacterial derived PAMPS, may activate and sustain immune responses. Such DAMPs arise for instance from the mitochondrial membrane in which specific phospholipids are present that are unique to mitochondria and prokaryotes and are not

found in eukaryotes [113]. One such lipid, prominently present in the inner mitochondrial membrane is cardiolipin [114]. Moreover, mitochondria have their own DNA, which is circular with hypomethylated CpG motifs, while mitochondrial proteins have a formylated methionine at the N-terminus, which is specific for mitochondria and bacteria [115,116] (see Fig. 2). These mitochondrial products may act as DAMPs when released into the cytosol or extracellular space and circulation.

4.1. Innate immune recognition of DAMPs

Innate immune cells, but also adaptive immune cells [117], have various Pattern Recognition receptors (PPRs) to detect PAMPs and DAMPs. The most well-known PPR are Toll-like receptors (TLR). TLR are membrane bound or intracellular receptors, expressed by all innate immune cells, which detect DAMPs or PAMPs [118]. TLR4 for instance detects lipopolysaccharide (LPS) a membrane component of gram-negative bacteria; TLR2 detects cell wall components such as lipopeptides and peptidoglycan, from gram-positive bacteria. TLR9, detects unmethylated CpG DNA motifs [119].

Cardiolipin is a phospholipid present in the inner mitochondrial membrane [114]. Cardiolipin is highly enriched in linoleic acids, with double bonds and therefore is susceptible to oxidation [120]. In healthy individuals, cardiolipin is not oxidized [121]. During disease, cardiolipin may become oxidized after which it promotes its own release from mitochondria and can be found in the circulation [122,123]. Oxidized cardiolipin is a TLR4 agonist and promotes pro-inflammatory cytokine production, production of leukotrienes in macrophages and it also induces activation of endothelial cells [122,123]. Also, mitochondrial DNA can stimulate TLRs. Mitochondrial DNA contains hypomethylated CpG motifs, which are recognized by TLR 9 in the endolysosomal compartment of the cell [124]. The signaling pathway of TLR9 results in activation of Mitogen-activated Protein Kinases (MAPK) and NF-kB to trigger pro-inflammatory cytokine production and inflammatory responses [125]. In various inflammatory diseases, it has now been shown that mitochondrial DNA is increased in the circulation [126]. Mitochondrial proteins have formylated methionine at the N-terminus, which are recognized by Formyl Peptide receptors (FPR). Binding of these peptides to FPR results in production of chemoattractants, and therefore recruitment of immune cells to the site of infection [127].

Another route by which mitochondrial DAMPS can contribute to immune responses is by activating inflammasomes, mainly the NLRP3 inflammasomes. Inflammasomes are cytoplasmic protein complexes, consisting of receptor and sensor molecules, an adaptor protein and caspase 1 [128]. The NLRP3 inflammasome, containing the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) is activated by a wide range of mitochondrial ligands, such a ATP, mitochondrial DNA, mitochondrial ROS but also by mitochondrial dysfunction and cardiolipin [128]. Upon activation of NLRP3, caspase-1 is recruited to the inflammasome by an adaptor protein apoptosis-associated speck-like protein, which contains a caspase recruitment domain [128]. Upon activation of caspase-1, it cleaves pro-interleukin-1β and pro-interleukin 18 to their biological forms [128].

Mitochondrial DNA could also affect immune responses by the cGAS (cyclic AMP-GMP synthase) pathway [129]. The cGAS pathway is part of the innate immune system that detects the presence of DNA in the cytosol and in response triggers type I interferon inflammatory responses [129]. cGAS and its second messenger cyclic GMP-AMP (cGAMP) and the sensor of cGAMP, stimulator of interferon genes (STING) is a major sensing pathway for cytosolic DNA [130]. Stimulation of this pathway by viral DNA leads to induction of type I interferons, which prevents viral replication, assembly and release, and NF-kB activation and induction of proinflammatory cytokines [130,131]. NF-kB controls the transcription of proinflammatory cytokines and chemokines [132]. The cGAS-STING pathway is linked to autophagy pathways and cell-death pathways [133–136]. Also mitochondrial DNA can activate the cGAS-STING pathway [137–139].

4.2. Mitochondrial DAMPs and inflammation

Since circulating mitochondrial DNA is increased in various infections, mitochondrial DAMPS are suggested to be an important mechanism in detection of an infection and stimulating and maintaining immune responses against pathogens [140,141]. However, on the other hand, the sensing of mitochondrial DAMPs may also stimulate undesired immune responses in case of traumatic tissue damage and may result in unwanted inflammation. To prevent undesired inflammation under physiological conditions, cells have various mechanisms to scavenge the DAMPs during cell damage. One of these mechanisms is mitophagy. Mitophagy is the process of autophagy of mitochondria [142]. During mitophagy, damaged mitochondria are taken up by the autophagosome and the mitochondrial DNA is degraded by DNase II nuclease activity [143,144]. Another mechanism is to prevent leakage of mitochondrial products into the cell. To do so, mitochondrial membrane permeabilization is tightly regulated. The outer mitochondrial membrane is permeable for metabolites involved in oxidative phosphorylation [145]. The inner mitochondrial membrane is impermeable [146]. Various specific transporters and exchangers exist to transport molecules over the inner mitochondrial membrane [146]. In certain physiological and pathophysiological conditions, mitochondrial membrane permeability may change. In mitochondrial permeability transition, the mitochondrial inner membrane becomes permeable, leading to mitochondrial depolarization, failure of oxidative phosphorylation and as a consequence mitochondrial swelling and cell death is induced [147,148]. Another mechanism protecting cells from undesired immune activation by mitochondria is that in situations of increased mitochondrial membrane permeabilization, caspase-9 dependent mechanisms are triggered to silence the cGAS pathway [137].

In conditions of massive cell damage, such as during traumatic injury or cardiac disease, the protective mitochondrial mechanisms may not be working or may be overwhelmed and mitochondrial DAMPs may be released into the cytosol and the circulation [149]. This may trigger an unwanted pro-inflammatory response. Even in the absence of an infection, such a pro-inflammatory response may be as severe as seen during septic shock in uncontrolled infections. The role of mitochondria in such a sterile inflammation is illustrated in studies demonstrating increased levels of mitochondrial DNA in the circulation of patients with major trauma (without infection) [150,151]. Also in a mouse model of pressure overload, which is not associated with infections, it has been demonstrated that mitochondrial DNA is increased leading to inflammation and damage of heart muscle cells, thereby inducing abnormalities in cardiac structure and function and finally inducing heart failure [144]. Also, injecting exogenous mitochondrial extracts into experimental animals induced an inflammatory response like in septic shock [151].

5. Mitochondrial dysfunction in immune cells in immunological diseases

5.1. Systemic lupus erythematosus (SLE)

SLE is a systemic autoimmune disease, which is characterized by the production of pathogenic autoantibodies by immune cells, inducing injuries in multiple organs [152]. Various studies have recently shown that mitochondrial dysfunction in immune cells may play a role in the pathogenesis of SLE. SLE is characterized by abnormal T cell activation, with overproduction of ROS in the mitochondria of these cells [153,154]. This, together with a decreased antioxidant capacity [154,155], may explain the higher levels of ROS in plasma and urine of SLE patients [154,155]. Since increased oxidative stress may arise from increased ROS production due to mitochondrial dysfunction, various groups have now studied mitochondrial function in immune cells in SLE. Mitochondria in T cells of SLE patients have a high mitochondrial membrane potential and decreased ATP production, indicating

mitochondrial damage [156]. Peripheral blood mononuclear cells (PBMC) from SLE patients show low basal mitochondrial oxygen consumption rates [157]. Lee et al. showed a decrease in glycolytic enzymes and mitochondrial related proteins in leukocytes of SLE patients [155], while Wahl et al. showed that mitochondria of T cells of SLE patients only showed decreased glycolysis [158] but not impaired mitochondrial respiration. These contradicting observations show disturbances in mitochondrial metabolism in immune cells in SLE, but at the same time indicate that further research is necessary into mitochondrial function in immune cells in SLE. A role for mitochondria in T cells of SLE patients can also be observed from the findings that mTOR is activated in T cells in SLE patients [159]. Inhibition of the mTOR by rapamycin in lupus prone mice inhibits SLE [160,161]. Moreover, promising effects of a clinical trial of rapamycin treatment in patients with active SLE have been shown [162]. Recently, Lee et al. showed that in SLE mitochondrial dysfunction was associated with oxidative damage and cytokine production [163] and suggested that mitochondrial dysfunction is implicated in the pathophysiology of SLE. The available evidence so far thus suggests that mitochondrial dysfunction in immune cells in SLE may play a role in the pathogenesis of SLE.

5.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the synovium [164]. Various types of autoantibodies, which play an important role in the induction of the disease, can be found in the plasma of RA patients [164]. Mitochondrial DNA has also been found to be increased in the plasma of RA patients. This mitochondrial DNA may act as a DAMP and induce or maintain inflammatory responses in RA [165]. T cells play an important role in the production of antibodies by B cells [3] and CD4 positive naïve T cells from patients with RA show various defects, amongst which mitochondrial dysfunction: mitochondria in T cells in RA have defective DNA repair mechanisms, which is associated with low mitochondrial oxygen consumption and ATP production [166]. Activated T cells in RA suppress glycolysis [167] but enhance the activity of the Pentose Phosphate Pathway [168]. Decreased glycolysis and low pyruvate production will slow down the TCA cycle, resulting in transportation of citrate into the cytoplasm, where it is used to synthesize fatty acids [169]. Also, the decreased beta-oxidation in mitochondria of RA in T cells, results in fatty acids accumulation in the cytoplasm [170]. Indeed, it has been shown that T cells in RA patients have upregulated lipogenesis [170]. These fatty acids are stored in lipid droplets in the cell and can be used for building new cells and for T cell invasion machinery, enabling proliferation and invasion of T cells into the synovium [171].

5.3. Diabetes

Type 1 diabetes is an autoimmune disease in which beta cells in the pancreas are destroyed by an autoimmune process [172]. Immunologically, Type 1 diabetes is characterized by a Th1 type immune response involving adaptive and innate immune cells [173]. Also, in type 1 diabetes, mitochondrial dysfunction has been shown, such as mitochondrial membrane hyperpolarization in T cells [174]. This mitochondrial membrane hyperpolarization is associated with increased mitochondrial ROS production and increased IFNγ production in T helper cells and with increased cytotoxicity in cytotoxic T cells in diabetes type 1 [174]. Moreover, T cells isolated from type 1 diabetic patients show decreased ATP production, also indicating mitochondrial dysfunction [174]. Since this mitochondrial dysfunction was only observed in type 1 diabetes and not in type 2 diabetes [174], it is assumed that mitochondrial dysfunction in type 1 diabetes does not result from metabolic abnormalities and that this mitochondrial dysfunction may play a role on the pathogenesis of type 1 diabetes.

Although in type 2 diabetes mitochondrial dysfunction was not observed in T cells, increased levels of circulating mitochondrial DNA were observed in type 2 diabetes patients [175]. This suggests that this mitochondrial DNA does not arise from T cells but from other sources. Since mitochondrial DNA may activate TLR9, thereby activating inflammatory cells, this mitochondrial DNA could be involved in activating and maintaining the inflammatory responses characterizing type 2 diabetes [176].

5.4. Pregnancy

In order to accept the semi-allogeneic fetus, pregnancy is associated with various changes in the immune response, such as a shift away from a Th1 immune response towards a Th2 immune response [177–180], increased numbers of Treg cells and decreased numbers of Th17 cells [181,182]. Moreover, there is a generalized mild activation of the inflammatory response [183,184]. Various factors are suggested to be involved in inducing these immunological changes during pregnancy, such as hormonal changes [185], factors produced by the placenta [186–188] and pertinent changes in the gut microbiome favoring a tolerogenic immune response [189]. In view of the recent knowledge on the role of mitochondria in immune cell function, we would expect changes in mitochondrial function in immune cells during pregnancy. However, to the best of our knowledge, there are no data on mitochondrial (dys) function in immune cells during pregnancy. Recently, however, it was shown that circulating mitochondrial DNA was increased during pregnancy [190]. This paper measured absolute mitochondrial DNA and contradicted another study which found decreased mitochondrial DNA in plasma during pregnancy [191]. In this latter study, however, mitochondrial DNA was normalized to nuclear DNA and the correlation between mitochondrial DNA and nuclear DNA may vary during pregnancy [190]. The question arises whether, next to all other mechanisms known to affect the maternal immune response, also circulating mitochondrial DNA, is involved as DAMP in inducing the immunological changes during pregnancy. Further research is necessary to be able to answer this question.

Various pregnancy complications are associated with immunological changes, such as preeclampsia [192] and gestational diabetes mellitus [193], which are the main pregnancy complications. Unfortunately, nothing is known about differences in mitochondrial function in immune cells between healthy pregnancy and preeclampsia. Gestational diabetes mellitus which is defined as glucose intolerance developing during pregnancy [194], is characterized by generalized inflammation in the maternal circulation [193,195]. Recently Qu et al. showed that mitochondrial function in monocytes was reduced in gestational diabetes mellitus, resulting in increased oxidative stress [196]. They showed higher mitochondrial superoxide and ROS production, as well as a decreased mitochondrial membrane potential [196]. Also, in gestational diabetes mellitus the role of mitochondria in immune cell function needs to be further explored.

In preeclampsia, mitochondrial DNA has been shown to be further increased as compared with healthy pregnancy [197–199] and may activate TLR9 on immune cells [200]. This mitochondrial DNA was suggested to play a role in the pathogenesis of preeclampsia, since it was already increased in early pregnancy before the onset of preeclampsia [199,201]. Further research is necessary to implicate a role for mitochondrial DNA in the pathogenesis of preeclampsia, but also to identify the source of mitochondrial DNA. It may be speculated that the placenta is the source of the increased circulating mitochondrial DNA during preeclampsia, since mitochondrial dysfunction has been shown in the placenta of women with preeclampsia [202].

6. Conclusions

It is clear from currently available literature that there is a link between immune cell activation and immune cell metabolism. It is now

generally accepted that increased glycolysis is mostly associated with a pro-inflammatory phenotype in immune cells (such as in monocytes and M1 macrophages), while oxidative phosphorylation and fatty acid oxidation is more associated with a regulatory phenotype and induction of long-living immune cells (such as in Treg cells, M2 macrophages and memory T cells). Although our knowledge on immunometabolism is increasing, there is still little knowledge on the role of mitochondrial function in immunological diseases. We are starting to unravel mitochondrial dysfunctions in various autoimmune diseases, such as RA, SLE and diabetes, however, the causal relationship between mitochondrial dysfunction and disease induction or maintenance is still unclear. Also, the role of mitochondrial function during pregnancy and its complications is unclear currently.

Further unraveling of the role of mitochondrial dysfunction in autoimmune diseases, especially studying mitochondrial function in the various subtypes of immune cells in these diseases, may lead to new treatment options based on improving mitochondrial function in one or more immune cell subsets. Focus should not only be on the mitochondria itself, but also on the mTOR pathway and other pathways that affect mitochondrial function and which could be inhibited or activated in order to stimulate or inhibit certain immune cells. Little is known about these pathways in immune cells of patients with autoimmune diseases. Some examples show promising effects of therapeutic approaches affecting the mTOR pathway: inhibition of mTOR may enhance vaccination efficiency [112] and may also have beneficial effects on immune senescence in elderly people [203]. Moreover, promising effects of a clinical trial of rapamycin treatment in patients with active SLE have been shown [162]. Further insight into role of mitochondria and mTOR and its downstream pathways could lead to more personalized medicine, based on improving mitochondrial function in one or more immune cell subsets in different patients' groups.

Future studies should not only focus on mitochondrial function in immune cells in immunological/inflammatory diseases, it is also important to focus further on the role of mitochondrial DAMPs in immunological/inflammatory diseases. Such mitochondrial DAMPs have a specific structure and have been shown to reach high levels during severe undesired inflammatory events such as during traumatic injury or cardiac disease. Further insight into the role of mitochondrial DAMPS in various diseases, but also during pregnancy, might provide new personalized management strategies to control these disorders by inhibition of release of mitochondrial DAMPs or neutralizing these DAMPs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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