Seminars in Immunology 69 (2023) 101808

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Mitochondria during T cell aging

Jose Ignacio Escrig-Larena [a], Sandra Delgado-Pulido [b], María Mittelbrunn [a,*]

[a] Consejo Superior de Investigaciones Científicas (CSIC), Centro de Biología Molcular Severo Ochoa (CSIC-UAM), Universidad Autónoma de Madrid (UAM), Madrid, Spain

[b] Departamento de Biología Molecular, Facultad de Ciencias (UAM), Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Universidad Autónoma de Madrid (UAM), Madrid, Spain

ARTICLE INFO

Keywords:
Mitochondria
Lymphocyte
Inflammaging
T cells
Aging
MtDNA
Mitokines
Mitochondrial dynamics
ROS
Calcium homeostasis
Apoptosis
Mitophagy

ABSTRACT

Mitochondrial dysfunction is a hallmark of aging that contributes to inflammaging. It is characterized by alterations of the mitochondrial DNA, reduced respiratory capacity, decreased mitochondrial membrane potential and increased reactive oxygen species production. These primary alterations disrupt other interconnected and important mitochondrial-related processes such as metabolism, mitochondrial dynamics and biogenesis, mitophagy, calcium homeostasis or apoptosis. In this review, we gather the current knowledge about the different mitochondrial processes which are altered during aging, with special focus on their contribution to age-associated T cell dysfunction and inflammaging.

1. Introduction

Mitochondria are dynamic organelles responsible for the production of energy through metabolic pathways such as oxidative phosphorylation (OXPHOS) or fatty acids oxidation (FAO). In addition, mitochondria are also implicated in multiple cellular processes such as lipid synthesis, apoptosis and calcium (Ca^{2+}) homeostasis. Due to their prokaryotic origin, the release of mitochondrial molecules to the cytosol activates different inflammatory pathways, situating mitochondria as a hub of inflammation [1]. This inflammatory role links mitochondria with the low-grade, chronic sterile inflammatory state, known as inflammaging, that underlies a wide variety of age-associated diseases [2,3]. Therefore, mitochondrial dysfunction has direct consequences in essential signaling cascades, alters cellular and tissue homeostasis and, importantly, it has been postulated as one of the main hallmarks of aging [4].

Age-associated mitochondrial dysfunction is mainly characterized by mutations in the mitochondrial DNA (mtDNA), diminished respiratory capacity, decreased mitochondrial membrane potential (MMP) and increased reactive oxygen species (ROS) production [4,5]. These features lead to the progressive accumulation of alterations in mitochondrial morphology, activity and signaling functions that are closely related to the aging process (Fig. 1) [4,5]. Mitochondrial dysfunction occurs in many cell types of the organism, with special emphasis on immune cells as it contributes to the decline of the immune function during aging, termed as immunosenescence, which is featured by an increased vulnerability to infections, autoimmune diseases and cancer, together with a lower vaccination efficiency and inflammaging [4,6].

T cells are specialized immune cells whose function highly relies on their metabolism [7,8]. Indeed, the field of immunometabolism has been developed in order to decipher how to modulate the immune response by rewiring the metabolism either to achieve a correct activation or to elude an excessive inflammatory or autoimmune response [9]. The correct function of T cells is intimately linked to mitochondrial metabolism and signaling [10]. Alterations in mitochondrial biogenesis and dynamics (e.g., fission and fusion), recycling through mitophagy or transport result in deep functional modifications in T cells. In addition, altered concentrations of several signaling molecules produced or regulated by mitochondria, such as ROS or Ca^{2+}, have a capital impact in the activation of T cells. In this regard, T cells from mice suffering physiological stress show mitochondrial alterations and the transfer of $CD4^{+}$ from these stressed mice to recipient mice induces anxiety, depression and social disorders in the recipients, highlighting the

* Corresponding author.
E-mail address: mmittelbrunn@cbm.csic.es (M. Mittelbrunn).

https://doi.org/10.1016/j.smim.2023.101808
Received 13 April 2023; Received in revised form 30 June 2023; Accepted 10 July 2023
Available online 18 July 2023

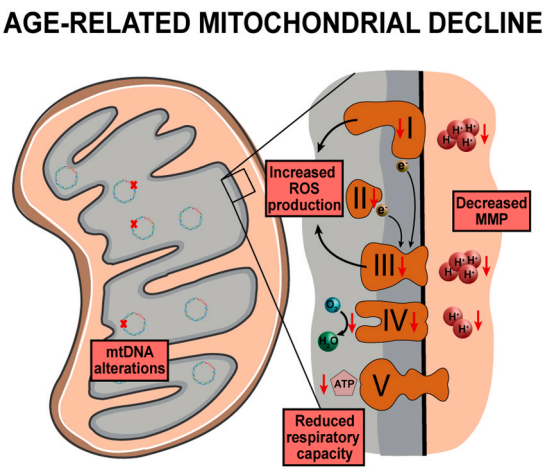

Fig. 1. Features of age-related mitochondrial decline. Mitochondrial dysfunction is characterized by accumulation of mitochondrial DNA (mtDNA) mutations, increased reactive oxygen species (ROS) production, decreased mitochondrial membrane potential (MMP) and reduced respiratory capacity.

importance of mitochondrial alteration not only in the biology of T cells but in the homeostasis of all the organism [11]. Considering the relevance of mitochondria in T cells, the disruption of mitochondrial function in T cells during aging has been associated with T cell functional decline [10,12]. Strikingly, the deletion of mitochondrial transcription factor A (Tfam) specifically in T cells not only mimics the age-associated mitochondrial dysfunction of T cells, but it also leads toward a whole-organism aging phenotype by inducing premature inflammaging in mice [13]. Furthermore, mitochondrial dysfunction in T cells has been linked to age-associated morbidities such as autoimmune diseases [14], cancer [15], metabolic diseases [16] or neurodegenerative disorders [11].

In this review, we will discuss the current knowledge of the different processes involved in the mitochondrial dysfunction during aging: mtDNA instability, alteration of metabolism, increased oxidative stress, disrupted mitochondrial dynamics, biogenesis, mitophagy, Ca2 + homeostasis and apoptosis, with special focus on their consequences in T cell function and deterioration.

2. Mitochondrial DNA instability during T cell aging

Mitochondria contain multiple copies of double-stranded, circular DNA molecules. Human mtDNA encodes for 13 proteins which are essential components of complexes I, III, IV and V of the respiratory chain [17]. Unlike nuclear DNA, mtDNA lacks certain DNA repair pathways (e.g. nucleotide base repair) although it possesses other DNA repair mechanisms that have been classically restricted to nuclear DNA (e.g. mismatch repair, base excision repair, single- and double-strand repair) [18]. Additionally, the absence of histone protection and its location in the mitochondrial matrix, an environment with high oxidative stress derived from the electron-transport chain (ETC) activity [19], make mtDNA more susceptible to damage and prone to the accumulation of mutations during aging, particularly deletions [20]. Loss of mtDNA integrity actively contributes to aging and age-associated diseases [4]. The accumulation of mtDNA mutations due to an altered mitochondrial polymerase gamma in a mouse model, known as mitochondrial DNA mutator, results in premature aging [21]. Consequently, such accumulation of mutations leads to alterations in ETC, OXPHOS disruption and increased ROS production. In addition, mtDNA encodes 10 microproteins, also known as mitochondrial-derived peptides (MDPs), such as humanin, MOTS-c or SHMOOSE whose alterations are associated with Alzheimer's disease and cognitive decline (SHMOOSE) or type II diabetes (MOTS-c) [22].

High mutation rates have been found in mtDNA of T cells isolated from patients with age-related diseases such as cancer [23] or autoimmune disorders [24]. Interestingly, human T cell populations increase their mtDNA copy number per cell during aging with the exception of the $CD8^+$ naïve pool, which is the population of T cells that suffers a higher age-related drop [25]. The deficient activity of the single- and double-strand break repair-involved nuclease MRE11A in $CD4^+$ T cells increases mtDNA oxidative stress causing OXPHOS disruption, mtDNA leakage to the cytosol, inflammasome assembly and autoimmunity [26]. Therefore, the accumulation of mtDNA instability in T cells contributes to the altered function of these organelle in aged T cells.

3. Mitochondrial metabolism during effector function of aged T cells

During their lifetime, T lymphocytes undergo different metabolic stages that are closely related to their function.

Naïve T cells have a quiescent metabolism that mainly relies on mitochondrial metabolic pathways such as OXPHOS and FAO as source of energy to sustain self-renewal via homeostatic proliferation [8,27]. This homeostatic proliferation slowly erodes naïve epigenetic and transcriptomic signature pushing naïve T cells toward a differentiated memory-like state. Indeed, human old naïve T cells lose their oxidative phosphorylation capacity due to a decrease in nuclear respiratory factor 1 (Nrf1) binding, which controls the transcription of many mitochondrial genes [28].

Upon activation, T cells clonally expand acquiring metabolic requirements of rapidly dividing cells. To fulfill this high energetic and anabolic demands, T cells engage in robust glycolysis and glutaminolysis, where glucose is fermented to lactate despite the presence of oxygen (Warburg effect), and the primary carbon flux into the tricarboxylic acid (TCA) cycle is switched from glucose to glutamine [27,29,30]. In addition, a myriad of pathways activated with the aerobic glycolysis quickly provide the biosynthetic building blocks needed during activation [31]. In fact, one of the pathways induced upon activation is the one-carbon metabolism that produces subunits for purine and thymidine synthesis, favoring mitochondrial biogenesis in activated T cells [32]. Therefore, different levels of reliance on mitochondrial metabolism have been denoted among the different populations of activated T cells [33]. Indeed, T cells with mitochondrial complex I, II or IV dysfunction present defects in proliferation [27]. The metabolic switch towards glycolysis promotes the disengagement of tumor necrosis factor (TNF), interferon gamma (IFN-γ) and interleukin(IL)-2 messenger RNA from metabolic enzymes, such as lactate dehydrogenase, favoring the production of these cytokines [34].

$CD4^+$ T cells are typically classified into conventional T helper (Th) cells and regulatory T (Treg) cells. Th cells acquire different functional phenotypes that are characterized by the expression of specific transcription factors and the release of distinct cytokines, resulting in the classification of Th1 cells (IFN-γ), which mainly support inflammatory and cytotoxic responses, Th2 (IL-4, IL-5 or IL-13), which primarily assist B cells in producing antibodies, Th17 (IL-17), Th22 (IL-22), Th9 (IL-9), and follicular helper T cells (IL-21).

Previous work of our group showed that mimicking age-associated mitochondrial dysfunction in mouse T cells by depleting Tfam specifically in these cells, forces a high glycolytic metabolism and a preferentially Th1 differentiation [35]. In the same line, *in vitro* inhibition of glutamine metabolism or deprivation of glutamine restrain the differentiation toward Th1, Th2 and Th17 proposing the glutamine metabolism as a remarkable pathway for these populations [36,37]. Differentiated Th17 cells also show increased mitochondrial respiration compared with naïve T cells [38,39]. Moreover, OXPHOS seems to be essential in Th17 differentiation since the *in vitro* blockade of complex I, III or V during Th17 differentiation led to Treg cell differentiation [40]. Therefore, the reduction of Th17/Treg ratio observed in old human peripheral blood mononuclear cells (PBMCs) upon *in vitro* stimulation

with phytohemagglutinin [41] may find a partial explanation in the difficulty of Th17 differentiation due to age-related mitochondrial dysfunction. However, absolute Th17 cell number is increased in the unchallenged PBMCs of old patients in comparison with young ones, leading to a higher susceptibility of Th17-linked inflammatory diseases such as multiple sclerosis or bowel inflammatory disease [41].

T regulatory cells are in charge of suppressing potentially deleterious activities of Th cells. In the last years, single cell RNA sequencing (scRNAseq) experiments revolutionized the means of detecting and defining cellular heterogeneity and are changing the Th/Treg dogma. By using such technique, the *in vivo* Th response appears to be difficult to classify into these discrete Th subsets, and it appears as a continuum of polarized phenotypes. Series of recent reports have demonstrated that $Foxp3^+$ Treg cells may differentiate into conventional effector Th cells, with or without concomitant downregulation of Foxp3 [42] suggesting that $Foxp3^+$ T cells may represent Th cells that are not fully differentiated.

Contrary to effector T cells, activated Tregs employ low rates of aerobic glycolysis and high rates of FAO [43]. This is supported by the fact that Treg-specific disruption of mitochondrial metabolism, by deleting mTOR or Tfam *in vivo*, abolishes their suppressive function, enhancing pro-inflammatory T cell activation and autoimmunity [44]. In addition, Treg-specific ablation of Tfam impairs Treg retention in non-lymphoid tissues through changes in the transcriptomic profile and the loss of Foxp3 expression, resulting in systemic hyperinflammation [45]. IL-15 supplementation restored mitochondrial fitness in Tregs from patients with HIV by upregulating Tfam and PGC-1α expression [46]. Furthermore, HIF1α-deficient mice, with higher reliance in OXPHOS, have enhanced Treg generation and the blockade of glycolysis inhibits Th17 differentiation [47,48].

Activated cytotoxic $CD8^+$ T cells have similar metabolic dependences to activated effector $CD4^+$ Th cells, with a great reliance on glycolysis and OXPHOS for TCR signaling transduction, proliferation and migration [49,50]. After long exposure to the stimulus, T cells stop proliferating and lose their effector capacity giving rise to dysfunctional exhausted T cells. Exhausted T cells are specially relevant in cancer [15] and chronic viral infections [51,52] but also accumulate during aging [53–55]. The co-inhibitory molecule programmed cell death protein 1 (PD1), a well-known inductor of exhaustion in $CD8^+$ T cells, attenuates glycolysis and affects mitochondrial cristae morphology, leading to mitochondrial dysfunction and inhibition of OXPHOS in human lymphocytes [56,57]. Improving mitochondrial metabolism by treating them with antioxidants, modulators of mitochondrial dynamics or IL-15 restores T cell antiviral function in HIV [52] and chronic hepatitis B infections in patients [51].

The metabolism of memory T cells also relies on FAO and OXPHOS, contrary to the glycolytic metabolism of their former differentiation states [58]. This metabolic switch is crucial for acquiring long-term survival in a similar metabolic strategy as that of naïve T cells [59]. However, memory $CD8^+$ T cells harbor higher mitochondrial mass and spare respiratory capacity (SRC) than both naïve and effector $CD8^+$ T cells [60] remarking an interesting difference between the quiescent mitochondrial state of naïve T cells and the metabolic state of memory T cells. In fact, mice lacking TNF receptor-associated factor 6 (TRAF6) are unable to develop memory $CD8^+$ T cells after infection due to altered expression of genes that regulate FAO [61]. In addition, pediatric patients with mitochondrial diseases, such as Pearson syndrome, Barth syndrome or Leigh syndrome, show reduced population of $CD45RO^+$ memory T cells [50]. Virtual memory T cells are antigen-inexperienced activated T cells that present high affinity for self-antigens and possess similar characteristics to conventional memory T cells [62]. These cells accumulate during aging forming a dysfunctional pool of memory T cells that has been related to the poorer response of T cells to vaccines observed in elderly populations [63].

Interestingly, the differentiation of effector T cells toward memory T cells goes hand in hand with the resolution of inflammation and it is closely regulated by several mitochondrial processes such as metabolic switch, mitochondrial dynamics or autophagy. Indeed, in a study that compares young (20–39 years-old) and old (beyond 70 years-old) participants, although the number of mitochondria of both naïve and memory $CD4^+$ T cells were similar, the mitochondria of old participants presented reduced autophagy efficiency, morphologically distorted mitochondria and mitochondrial dysfunction [64]. At the same time, the pathways related with OXPHOS and ETC were downregulated in old $CD4^+$ T cells and mitochondrial respiration was also impaired in the old samples [64]. Extracellular delivery of functional mitochondria from mouse embryonic fibroblast into old mouse $CD4^+$ T cells yields a better OXPHOS function, proliferation and switch to glycolysis upon activation, remarking importance of dysfunctional mitochondrial in the T cell dysfunction during aging [65].

Taking all together, T cells adapt their metabolism in a continuous process that allows the correct development of a successful biphasic immune response, with a resolution phase after the peak of inflammation. However, during aging, the age-related mitochondrial dysfunction disrupts this metabolic reprogramming disturbing the consequent functional changes in T cells, thus altering the correct resolution phase. This contributes to inflammaging by augmenting the number of inflammatory T cells and by hindering the differentiation and function of memory T cells and Tregs (Fig. 2) [13,64,66].

4. Mitochondrial oxidative stress during T cell aging

Mitochondria are the primary source of ROS in the cell as a side product of the normal respiratory chain function. Under homeostatic conditions, mitochondrial ROS are produced at low concentrations, and act as critical signalling molecules involved in a wide variety of cellular processes including cell cycle regulation, survival, and immune responses [67,68]. However, excessive production of ROS induces damage to cellular components, entailing loss of function and compromising cell survival. In addition, excessive ROS is closely linked with cellular senescence and aging [69]. Hence, mitochondrial oxidative stress has been classically considered a major driver of aging and age-related pathologies. Indeed, during aging, loss of fidelity in the assembly of the respiratory chain complexes results in an imbalanced redox homeostasis caused by the ineffective function of ETC, which in turn contributes to the alteration of the MMP [5]. Complexes I, II and III are the principal producers of ROS in the cell, and their stability has been shown to progressively be diminished with age [70,71]. Interestingly, the defects in the ETC during aging differ depending on the tissue: while complex II and III lose their activity with age in peripheral lymphocytes, complex III and IV are more sensitive to this loss in heart muscle and complex I appears to be more sensitive to age-associated loss of function in skeletal muscle, liver and brain [70,72,73].

Mild and low levels of ROS are essential for T cell activation, differentiation, proliferation and cytokine production. Upon TCR activation, there is an increased amount of ROS production via complex III and complex I of the ETC that leads to the activation of the nuclear factor of activated T-cells (NFAT) and subsequent IL-2 production [49]. ROS are also needed to stimulate other activation-related transcription factors of T cells such as NF-κB or AP-1 [74]. The increment of ROS also plays an important role in T cell metabolic reprograming through the induction of NFAT-dependent Myc expression [49,75].

Accumulation of mitochondrial ROS has been found in several age-associated T cell populations, which could exacerbate the activation of inflammatory pathways (Fig. 3). Human TEMRA (T effector memory cells that re-express CD45RA) harbour low numbers of mitochondria but high levels of ROS production [76]. Overproduction of ROS by the ETC complexes I and III can be reduced by its assembly into supercomplexes. Supercomplexes are associations between complexes I, III and IV that enhance complex I activity as well as the electron transfer efficiency, reducing the risk of electron leak and therefore lowering ROS production [77]. The decrease of the ETC supercomplexes stability during aging

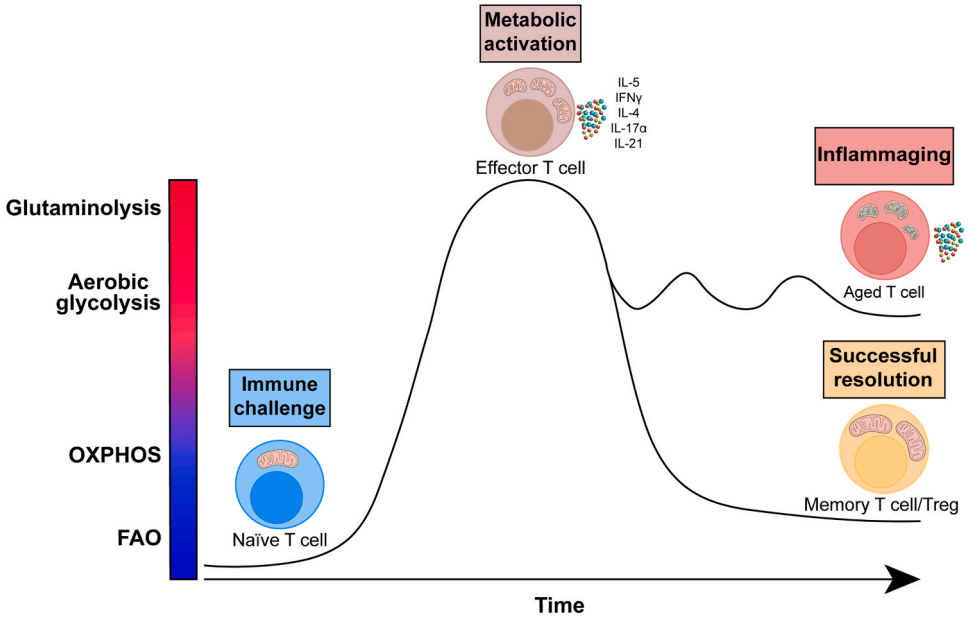

Fig. 2. Age-associated mitochondrial decline compromises the inflammatory response. Young T cells are able to reprogram their metabolism during the different phases of the immune response. However, mitochondrial alterations in aged T cells maintain T cells in an inflammatory phenotype, compromising the resolution phase and contributing to inflammaging. Abbreviations: OXPHOS, oxidative phosphorylation; FAO, fatty acids oxidation; Treg, regulatory T cell.

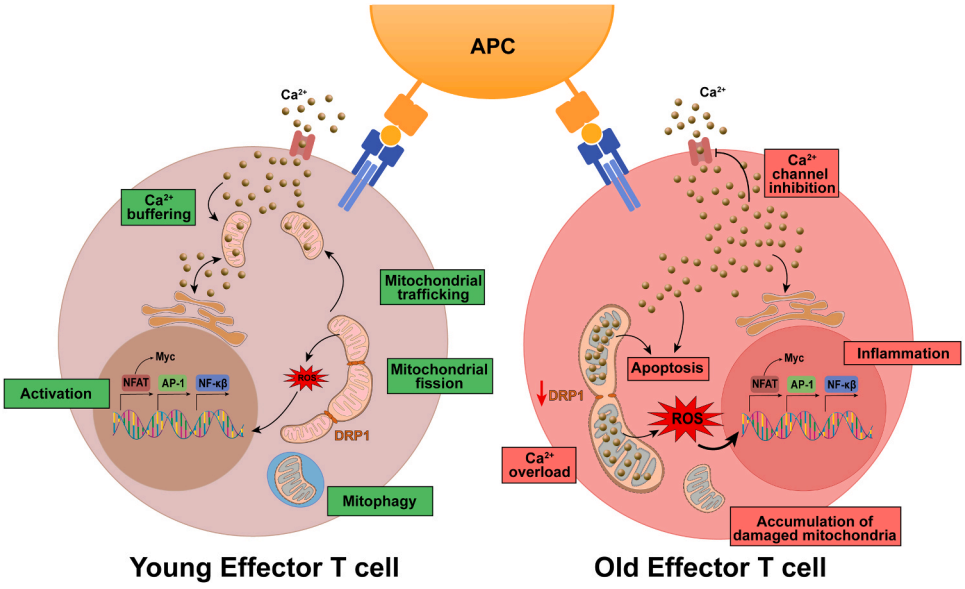

Fig. 3. Mitochondrial dysfunction consequences in old effector T cells. Mitochondria have important roles in the activation of effector T cells. Mitochondrial fission, mediated by dynamin related protein 1 (DRP1), contributes to the switch toward a glycolytic metabolism. Mitochondrial trafficking localizes mitochondria in the surroundings of the immune synapse, where it buffers the increment of calcium (Ca^{2+}) avoiding undesired consequences such as Ca^{2+} mediated apoptosis. In addition, damaged mitochondria produce reactive oxygen species (ROS) triggering inflammatory pathways, such as NK-κB. Damaged mitochondria are removed through mitophagy. In old T cells these processes are altered. There is an accumulation of damaged mitochondria leading to ROS overproduction and excessive inflammation. Additionally, DRP1 expression is reduced altering the mitochondrial fission. Ca^{2+} is not properly buffered and accumulates in bigger mitochondria, leading to apoptosis and inhibition of Ca^{2+} channels which impairs the T cell activation.

contributes to the overproduction of ROS and mitochondrial stress. In fact, methylation-controlled J protein (MCJ) knockout mouse model, which lacks a protein that dampers the assembly of supercomplexes, presents higher protection of $CD8^+$ memory T cells against viral infections [78]. Aged Tregs, which have defective proliferation and suppressive capacity, present increased levels of ROS [79]. Elevated levels of ROS, forced through an hypoxic environment, also promote exhaustion in $CD8^+$ T cells *in vitro* [80]. This exhaustion phenotype is defined by a deficiency of proliferation and cytokine production by T cells and it is proposed to be the consequence of continuously stimulated T cells. In addition, it might be partially explained due to an exacerbated activation of the integrated stress response (ISR) [81].

Mitochondrial dysfunction, together with amino acid deprivation and endoplasmic reticulum stress, is one of the stress conditions that activate the ISR, an evolutionarily conserved pathway to restore cellular homeostasis in response to different types of cellular stress [82]. ISR activates specific stress kinases (e.g. heme regulated inhibitor, HRI), which converge in the phosphorylation of the translation initiation factor 2 alpha (eIF2a), ultimately leading to the attenuation of protein synthesis and cellular proliferation [83]. Interestingly the mitochondrial modifications induced by hypoxia (e.g., increased fission-related axis OMA1-OPA1 [84]), promotes the production of ROS and the activation of ISR through DELE1 and HRI [85]. ISR is required for T cells to delay the production of cytokines until the activation of the second signal, which promotes the dephosphorylation of eIF2a and thus the cytokine synthesis [86]. However, the excess of ROS production during aging might disrupt the balance between eIF2a phosphorylation and dephosphorylation leading to altered cytokine production and proliferation in old T cells. Strikingly, an excess of ISR activation leads naïve T cells and tissue-resident memory T cells to apoptosis [87,88].

However, the idea of the negative contribution of ROS to aging has been challenged by the concept of mitohormesis, in which a mild and controlled mitochondrial stress is proposed to be beneficial for increasing longevity [89]. This concept is based on the idea that a sublethal exposure to mitochondrial stress contributes to lifespan extension by the activation of compensatory mechanisms that orchestrate an effective stress response which ultimately promotes cellular survival [90]. Indeed, a mild ETC perturbation has consequences not only in an autocrine manner but also in distal tissues, hence enhancing whole-organism health [91]. This process is mediated by soluble molecules secreted in response to mitochondrial stress collectively known as mitokines.

Mitokines are signaling molecules secreted in response to mitochondrial stress that enable mitochondrial and cellular communication [92]. Some mitokines act intracellularly while others are found in systemic circulation allowing the communication between distal tissues. These molecules include both nuclear-expressed proteins such as FGF21 or GDF15, and MDPs such as humanin. An increment in mitokines production occurs with age, and has been proposed as a mechanism of resistance to stress, being the chronic age-associated liberation of these molecules what becomes pathogenic [93].

Mitokines are involved in immune responses, and their role in T cell function has also been described in several works. The MDP MOTS-c is involved in inflammation and neuroprotection, and potentially contributes to healthy aging and regulation of inflammaging [94]. In addition, MOTS-c has been reported to prevent patients pancreatic β-islet destruction in autoimmune diabetes by reducing T cell activation and promoting Treg differentiation [95,96]. FGF21 is a metabolic regulator implicated in restoring the mitochondrial function and also has a protective role in age-associated thymic involution since its overexpression prevents thymus involution in mice, while its depletion induces the acceleration of thymus aging [97]. Another example of mitokines implicated in T cell activity is GDF15, a member of the TGF-β superfamily, which reduces T cell activation and expression of pro-inflammatory proteins in a mouse model of liver fibrosis [98]. The mitohormesis-promoting drug metformin increases lifespan [99,100] and reduces the production of Th17-profile cytokines ameliorating T cell inflammaging in patients through the improvement of mitochondrial bioenergetics [101]. However, the serum levels of GDF15 in prediabetic patients correlate with an increased production of pro-inflammatory cytokines by senescent $CD8^+$ T cells that contain higher concentration of ROS [102], suggesting that even the beneficial effects of mitohormesis may turn pathogenic when the mitochondrial oxidative stress is not mild and controlled.

5. Defective mitochondrial Ca^{2+} Homeostasis in old T cells

Ca^{2+} signaling modulates genes implicated in survival and proliferation of T cells upon TCR stimulation, making Ca^{2+} homeostasis crucial for T cell activation [27,103–105].

Intracellular Ca^{2+} is mainly stored in the endoplasmic reticulum (ER). Beside ER, mitochondria are important modulators of Ca^{2+} homeostasis [106]. A well-balanced concentration of mitochondrial Ca^{2+} is capital for the correct function of T cells [5]. During T cell activation, a constant flux of Ca^{2+} into de T cell is needed. When TCR simulation increases the influx of Ca^{2+}, mitochondria take the excess buffering its signal to avoid undesired consequences of high Ca^{2+} concentration such as Ca^{2+}-mediated apoptosis [107] or inhibition of Ca^{2+} channels (Fig. 3) [8]. In addition, mitochondrial Ca^{2+} activates mitochondrial enzymes that trigger TCA cycle [108] promoting the production of important intermediates for the ETC and therefore promoting ATP production [109].

Excess of Ca^{2+} uptake by mitochondria results in Ca^{2+}-induced nitric oxide production, Ca^{2+}-mediated cytochrome c (CytC) dissociation from the inner mitochondrial membrane (IMM) and opening of the mitochondrial permeability transition pore [5] resulting in increased ROS production, decreased MMP, apoptosis and mitochondrial dysfunction [110–112]. Nevertheless, aged mice T cells present reduced mitochondrial Ca^{2+} uptake [113,114]. The impairment of signaling and activation of naïve $CD4^+$ T cells from old mice has been related to mitochondrial dysfunction, which affects early activation signaling processes such as Ca^{2+} buffering [66,115]. All this suggests that defects in mitochondrial Ca^{2+} homeostasis might be both cause and consequence of T cells mitochondrial dysfunction during aging.

6. Mitochondrial dynamics alterations in old T cells

Mitochondria are dynamic structures that suffer processes of fusion and fission that modify their size, morphology and position within the cell according to its metabolic needs and function [116]. These processes, known as mitochondrial dynamics, are crucial for mitochondrial metabolism and for the mitochondrial quality control. Failures in mitochondrial dynamics during aging contribute to accumulation of unhealthy mitochondria [117,118].

Mitochondrial fission is orchestrated by fission 1 homolog protein (FIS1), mitochondrial fission factor (MFF), mitochondrial dynamics protein of 49 kDa (MID49) and mitochondrial dynamics protein of 51 kDa/mitochondrial elongation factor 1 (MID51/MIEF1) which recruit central fission protein dynamin related protein 1 (DRP1) to the fission site and constrict the mitochondria to mediate fission [119]. By segregating mitochondria, mitochondrial fission increases ROS production [120], accelerates cell proliferation [121] and mediates apoptosis [122]. It also promotes mitophagy by generating low MMP mitochondria, which are more easily degraded [123].

Mitochondrial fusion is first mediated by mitofusins 1 and 2 (MFN1 and MFN2), which catalyze the outer mitochondrial membrane fusion, and then by optic atrophy gene 1 (OPA1), which promotes the IMM fusion [124], generating bigger mitochondria. Inhibition of mitochondrial fusion in mammalian cells, through MFN2 ablation, yields in mitochondrial dysfunction with increase production of ROS, decreased OXPHOS and MMP [117]. Fused mitochondria buffer punctual mitochondrial damage and mutations in the mtDNA [125], maximize OXPHOS activity [126,127] and improve endoplasmic reticulum (ER) interactions [128]. Interestingly, mitochondrial fusion reduces Ca^{2+} transfer between ER and mitochondria, preventing Ca^{2+}-induced cell death [129]. Age-associated decrease of OPA1 contributes to age-related deterioration of several organs and tissues [130]. Mitochondrial fusion is also linked to MMP since dissipation of MMP induced the cleavage of OPA1 therefore hindering mitochondrial fusion [131].

Mitochondrial trafficking can be anterograde (away from the nucleus) or retrograde (toward the nucleus) and both processes decrease with age [125]. In non-lymphoid cells, mainly neurons and cardiac myoblast, mitochondrial trafficking regulation has also been related with MMP, ATP/ADP ratio, ROS production and Ca^{2+} concentration [132]. In neurons, MMP is a key regulator of mitochondrial transport leading depolarized mitochondria to move toward the nucleus and directing high MMP mitochondria away from the nucleus [133]. ATP/ADP ratio is also regulating mitochondrial trafficking due to the requirement of ATP for the active transport. High ROS accumulation reduces mitochondrial motility through p38α in T cells [134]. Finally, high Ca^{2+} concentration decreases mitochondrial motility in neurons, and has been proposed as a mechanism to localize mitochondria where Ca^{2+} buffering is needed [132]. Therefore, healthy mitochondria, with high MMP and proper ATP production, tend to have better trafficking than dysfunctional ones. As expected, MMP, ATP/ADP ratio, ROS production and Ca^{2+} are all altered in aging [125].

Mitochondrial trafficking is essential for polarization of T cells both during migration and during the formation of the immune synapse [27]. Upon antigen recognition, mitochondria move to the immune synapse in order to buffering Ca^{2+} signaling and provide ATP and ROS [103,135]. DRP1 coordinates mitochondrial interaction with the microtubule organization center to translocate the mitochondria into the immune

synapse upon TCR activation [136], underlying its important role in mitochondrial trafficking. During migration, ATP production, and therefore mitochondrial localization, is needed in the opposite site of the leading edge, also known as uropod [137,138]. Therefore, damaged mitochondrial dynamics may contribute to the deterioration of the immune synapse formation observed during aging [139].

During aging, there is a drastic mitochondrial morphology alteration in T cells (Fig. 3) [140]. Memory T cells, that rely in OXPHOS, possess fused mitochondrial networks, with tight cristae and closely associated ETC complexes. Accordingly, fusion protein OPA1 is essential for memory T cells generation [141]. In contrast, effector T cells, characterized by aerobic glycolytic metabolism, have smaller fragmented mitochondria with disorganized cristae [109,141]. Signaling through PD-1, a marker of exhausted T cells, prevents mitochondrial fragmentation after TCR stimulation by downregulating the fission protein DRP1 phosphorylation via ERK1/2 and mTOR pathways [142]. DRP1 expression decreases during aging [125]. In addition, *in vitro* knockout of DRP1 hinders the clonal expansion of effector T cells upon TCR activation, regulating effector T cell numbers *in vivo* [143]. All these data suggest that alterations on mitochondrial dynamics could contribute to age-associated T cell function decline.

7. Mitochondrial biogenesis and mitophagy in old T cells

In addition to dynamics, mitochondrial homeostasis is regulated by mitochondrial biogenesis and degradation (mitophagy) and both processes are also altered in old T cells.

Mitochondrial biogenesis is destined to produce more mitochondrial mass. This process is mainly regulated by the PPARγ coactivator 1 (PGC-1) family [144]. A member of this family, PGC-1α, has a master regulatory role by activating the Nrf1/2 and ERRα that further control Tfam, another important nuclear-encoded factor essential for the stabilization and replication of mtDNA and, therefore, capital for mitochondrial biogenesis [145,146].

During T cell activation and clonal expansion, there is an increase in mitochondrial mass and mtDNA levels [35,147]. Conversely, T cell exhaustion is characterized by metabolic alterations produced by the repression of PGC-1α expression after PD-1 ligation [148]. In fact, *in vivo* pharmacological strategies that enhance mitochondrial biogenesis such as IL-15 [46], IL-21 [149] or metformin [150] boost T cells response against different challenges. The induction of mitochondrial biogenesis through caloric restriction or enduring exercise rejuvenates mitochondrial function in mice [151,152]. Both caloric restriction and enduring exercise have a positive impact in aged T cells, maintaining a naïve T cell pool, enhancing the vaccine response and the T cell proliferative capacity [153,154].

The NAD^+-dependent deacetylases family known as sirtuins (SIRT) have also an important role in mitochondrial biogenesis. Among this family, SIRT3 is the main mitochondrial-located SIRT and its abrogation has been linked to age-related diseases [155] and to the induction of cellular mitochondrial dysfunctional-associated senescence (MiDAS) that presents a senescence associated secretory phenotype (SASP) that lacks the IL-1 arm [156]. There is an age-associated decline of the SIRT3-substrate NAD^+ due to an increased expression of the NADase CD38 in different tissues during aging that alters T cell polarization and survival [157]. Indeed, the CD38 knockout restores NAD^+ and mitochondrial function in old mice [157].

Mitophagy is a process that takes place in potentially cellular damage situations such as oxidative stress, hypoxia, MMP loss or accumulation of unfolded proteins, in order to remove damaged mitochondria through autophagosomes [158]. Mitophagy delays immune cell senescence by maintaining mitochondrial fitness [159]. Several stress-induced mitophagy pathways for each of the mentioned situations have been reviewed elsewhere [158]. Loss of MMP in damaged mitochondria leads to the stabilization of PTEN-induced putative kinase 1 (PINK1) on the outer mitochondrial membrane, allowing it to recruit the E3 ubiquitin ligase Parkin, which leads damaged mitochondria into autophagosomes for its consequently degradation. In addition, *in vitro* inhibition of MFN1 and MFN2 fission proteins inhibits Parkin-induced mitophagy supporting that mitochondrial fission is necessary for mitophagy [160].

The importance of mitophagy in homeostasis, activation, differentiation, metabolism and function of T cells is deeply reviewed elsewhere [161]. As expected, these processes are altered in aging leading to the accumulation of damaged mitochondria in T cells (Fig. 3) [4,64,162,163]. Depletion of autophagy-related genes (Atg), such as Atg5, in T cells results in impaired T cell survival, mitochondrial dysfunction and disrupted metabolic functions that have a negative impact on the responses to antigen and TCR-induced proliferation [164,165]. Alterations of mitophagy may be due to age-related signaling disturbances in T cells such as dysfunctional TCR activation [166], low production of IL-2 [167] or altered MAPK p38 signaling [76]. Mitochondria are the preferred content of autophagosomes in resting T cells whereas activated T cells tend to exclude them from the autophagosomes [164] suggesting a highly important role of mitophagy in regulating quiescent long-lived T cells. Congruently, senescent cells present increased mitochondrial mass resulting from a decrease in mitophagy, which has also thought to be a compensatory mechanism against the mitochondrial decline [5]. In addition, the mechanistic target of rapamycin (mTOR), which inhibits mitophagy [168], is upregulated both in aging [169] and in a T cell senescent induction mice model through the knockout of RIPK1 specifically in $CD4^+$ T cells [170].

Defective mitophagy and mitochondrial turnover contribute to the impairment of immune response and inflammaging in $CD4^+$ T cells of older individuals [64]. Compounds that promote mitophagy, such as spermidine, increase the lifespan of human PBMCs [171]. While the endogenous spermidine decreases in humans with age, its supplementation recovers autophagy in T cells, enhancing the vaccine response [172]. In addition, spermidine improves the mitochondrial function of aged $CD8^+$ T cells [173].

Altered mitophagy during aging deeply contributes to mitochondrial-mediated T cell dysfunction observed in aged T cells [174,175].

8. Mitochondrial dysfunction impact in regulated cell death of old T cells

One of the consequences of age-associated mitochondrial dysfunction is the alteration of regulated cell death (RCD) pathways such as apoptosis or pyroptosis, which will be comment in the following section. Following TCR stimulation, there is a massive clonal expansion that produces millions of T cells which are eliminated in the later resolution phase of the inflammatory process. This reduction to basal levels of T cells is mediated by cytokine withdrawal and CD95/Fas apoptotic pathway [176].

Lymphocytes from elderly subjects overexpress the CD95/Fas apoptotic molecules favoring an apparent mitochondrial independent apoptosis pathway [177]. However, CD95 ligation activates the Fas-associated protein with a death domain (FADD) that mediates the split of Bid, a Bcl-2 family member. Upon cleavage, Bid translocates into the mitochondria promoting the release of CytC to the cytosol [178]. Once in the cytosol CytC conforms the apoptosome by its association with Apaf-1 (apoptotic protease-activating factor 1), caspase 9 and ATP. This complex can proteolytically activate the caspase 9 leading to the activation of the caspase cascade, thus starting the degradation phase of apoptosis [179]. The changes and the impact of apoptosis during aging have been deeply reviewed elsewhere [180]. Regarding T cells, decreased MMP of $CD8^+$ T cells cultured with tumor cells induces the progressive destruction of both inner and outer mitochondrial membrane, leading to the release of CytC and promoting $CD8^+$ T cells apoptosis [174]. Another mitochondrial-released protein related to apoptosis is the apoptosis-inducing factor (AIF) which, upon apoptosis induction, translocates from the mitochondria into the nucleus

producing chromatin condensation and a dramatic DNA fragmentation [181]. The mitochondrial outer membrane permeabilization also allows the translocation of AIF to the cytosol, promoting apoptosis in T cells [182].

These data suggest that the mitochondria-mediated apoptosis pathways in T cells may be altered upon aged-related mitochondrial dysfunction, specially through the disruption of membrane permeability, promoting excessive apoptosis in T cells.

9. Causes of age-associated mitochondrial dysfunction in T cells

The origin of mitochondrial dysfunction is a combination of the accumulation of alterations in the mtDNA and the age-linked disruption of a proper mitochondrial turnover [4]. As mentioned, mtDNA is much more vulnerable to damage than nuclear DNA due to its high replicative index, the oxidative environment and lack of protective proteins like histones [20]. With aging, rounds of cellular division through homeostatic proliferation in naïve T cells and through clonal expansion in activated T cells, increase the incidence of mtDNA alterations consequently disrupting the function of mitochondrial membrane complexes, altering the NAD^+/NADH ratio, reducing the MMP, altering the respiratory capacity and augmenting the production of ROS [4,5].

In addition, during aging the mitochondrial turnover mechanisms, both mitochondrial biogenesis and mitophagy, are compromised [64], promoting the accumulation of damaged mitochondria that leads to mitochondrial stress and compromises T cell function, consequently leading to a vicious loop of inflammation. The accumulation of dysfunctional mitochondria allows the release of mitochondrial components to the T cell cytoplasm promoting inflammatory pathways such as cyclic GMP-AMP synthase - cGAMP interactor (cGAS-STING) or the inflammasome and altering others such as the NF-κB, contributing to inflammation and/or pyroptosis [183,184].

Although mtDNA damage and mitophagy deterioration are the most probable contributors to the origin of the mitochondrial dysfunction, is feasible to think that other age-linked events are contributing to this fact. A proper NAD^+/NADH ratio and NAD pool is required for the correct function of mitochondria. During aging, there is an increment in the expression and function of the NAD^+ degradative enzyme CD38 in several immune cells, including the myeloid and lymphoid pool. These augmented $CD38^+$ cells result in the disruption of the NAD^+/NADH ratio and the NAD^+ depletion contributing to mitochondrial dysfunction [157,185,186]. In addition, accumulation of genomic DNA alterations activates PARP1, an NAD^+-dependent enzyme, that contributes to NAD^+ consumption, misbalancing the optimal NAD^+/NADH ratio and NAD pool and contributing to mitochondrial dysfunction [5].

In addition to NAD^+/NADH misbalance, the aged environment in which T cells are embedded may also contribute to mitochondrial dysfunction. Although mitochondrial dysfunction has classically been proposed as cause of senescence [187], the plethora of molecules produced by senescent tissues included in the SASP, such as ROS, damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines might feedback the disruption of mitochondrial function in T cells. ROS and other DAMPs are well known activators of NF-κB [64]. This pro-inflammatory pathway promotes mitochondrial dysfunction in rat and human muscle and it is implicated in the regulation of mitochondrial function and mitochondrial dynamics [188,189]. Several inflammatory cytokines secreted by senescent cells as part of the SASP, such as IL-6 and IFN-γ, alter mitochondrial function in T cells. IL-6 contributes to $CD4^+$ T cell metabolic switch for their differentiation toward Th2 and Th17 [190]. In addition, IL-6 facilitates the formation of mitochondrial supercomplexes promoting mitochondrial membrane hyperpolarization and increasing the levels of mitochondrial Ca^{2+} while minimizing mitochondrial ROS production [191]. IFN-γ reduces mitochondrial respiration and dampers the maintenance of stem-like T cells [192].

Therefore, together with mtDNA damage and mitochondrial turnover alteration, the age-related unbalance of NAD^+/NADH ratio and the SASP-enriched environment potentially cause and accelerate mitochondrial dysfunction in old T cells.

10. Mitochondrial contribution to inflammaging

For many years, studies have shown that mitochondria are tightly associated to inflammation [184]. Due to its prokaryotic origin, mitochondria are one of the main sources of DAMPs [193]. The release of intra-mitochondrial components into the cytoplasm activates intracellular signalling receptors, leading to the activation of immune responses and to the consequent release of pro-inflammatory molecules such as IL-6, IL-1β or TNF [194]. Signalling by mitochondrial DAMPs (mtDAMPs) progressively increases with age, owing to the disruption of mitochondrial permeability associated to aging [93]. mtDAMPs include mitochondrial molecules such as cardiolipin, SMAC, N-formyl peptides, Tfam, ROS or mtDNA. The latter has been postulated as a major driver of inflammaging, since circulating mtDNA increases with age in humans and its plasma levels correlates with those of pro-inflammatory cytokines [195]. Indeed, the measurement of plasma mtDNA levels is considered an aging biomarker in HIV patients, since mtDNA plasma concentration is increased during aging in HIV patients and correlates with defective cognitive functions [196]. In the same line, mtDNA contributes to the progression of T-cell mediated autoimmune diseases [14]. High concentrations of mtDNA detected in sera of patients with psoriasis and in synovial liquid of patients with rheumatoid arthritis worsen disease prognosis [197].

mtDNA contributes to both the activation of cGAS-STING pathway and the assembly of the inflammasome, two independent signalling cascades through which mitochondrial dysfunction promotes acute inflammatory responses (Fig. 4). Release of mtDNA fragments into the cytosol triggers the activation of cGAS which binds to the adaptor protein STING and leads to the production of type I interferons, such as IFN-β1, and proinflammatory cytokines, such as TNF or IL-6 [198]. The activation of cGAS-STING pathway contributes to $CD8^+$ T cell activation [199] and Treg suppression function [200]. However, this pathway is a driver of inflammaging through a positive loop involving ROS production [201] and it negatively affects the function of T cells increasing cell death, reducing proliferation and increasing the type I interferon, TNF and IL-6 production [199,202,203]. Cytosolic mtDNA, specially the oxidized mtDNA, also activates NLRP3 promoting the assembly of the inflammasome, a structure that leads to the activation of caspase I and therefore leading to the release of active IL-18 and IL-1β by the pyroptotic cell death [204]. T cell pyroptosis has been described in HIV and RA patients, which share the common features of premature T cell aging [14]. The importance of cGAS-STING signalling versus the inflammasome assembly by mtDNA is influenced by cellular bioenergetics [184].

Besides mtDNA, other mtDAMPs contribute to inflammaging (Fig. 4). The IMM lipid cardiolipin, responsible for the curvature of the mitochondrial cristae, is important for the optimal NLRP3 signalling and inflammasome formation [205]. Importantly, its presence in the IMM is required for a proper $CD8^+$ T cell response against infections in mice [206], suggesting that delocalization of the IMM toward the cytosol due to mitochondrial dysfunction activates the inflammasome and is detrimental for T cell function. SMAC (second mitochondria-derived activator of caspase) is another mtDAMP that is translocated to the cytosol both in pro-apoptotic and pro-inflammatory contexts. It inhibits IAP (inhibitor of apoptosis protein) and switches NF-κB signalling from the canonical to the non-canonical pathway [207]. Interestingly, SMAC mimicking through pharmacological approaches has an immunomodulatory effect by reprogramming Th17 $CD4^+$ T cells towards Th2 $CD4^+$ T cells [208]. Finally, N-formyl peptides are potent neutrophil activators [193], although the contribution of aged T cells to this activation is not described yet.

These facts localize mtDAMPs as dual source of inflammaging, both T cell intrinsic and T cell extrinsic.

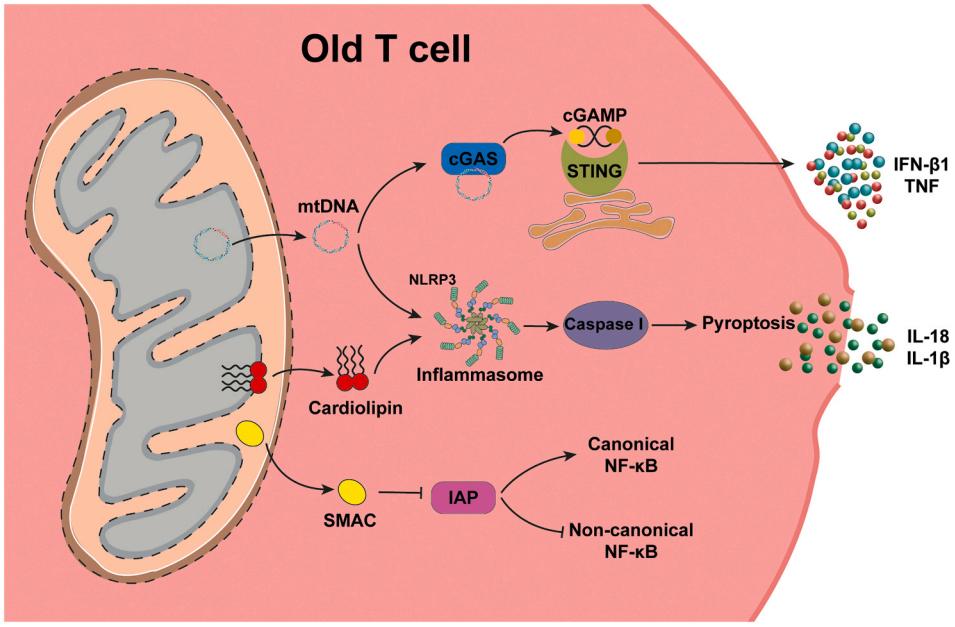

Fig. 4. Damaged mitochondria are a hub of inflammation in T cells. The alteration of membrane permeability in damaged mitochondria of old T cells facilitates the release of mitochondrial damaged-associated molecular patterns (mtDAMPs) such as mtDNA, cardiolipin or SMAC. mtDNA and cardiolipin activate inflammatory pathways such as cGAS-STING or promotes the assembly of the inflammasome, leading to the release of interferon type I molecules, TNF or IL-18 and IL-1β after pyroptosis. SMAC switches the non-canonical NF-κB to the canonical pathway. All these processes actively contribute to age-associated chronic inflammation.

11. Concluding remarks

In the last 30 years the key role of mitochondrial activity in the regulation of aging has been stablished in species ranging from yeast to mammals. Recent evidences started to identify tissues and organs whose mitochondrial activity is especially important to regulate aging and how different tissues and cells can communicate with each other. The accumulation of damaged mitochondria in old T cells alters the function of this important immune cell type resulting in increased vulnerability to infections, autoimmune diseases, cancer, reduced vaccination efficiency and contributing to inflammaging and age-related multimorbidity.

The most evident consequence of the age-associated mitochondrial dysfunction is the metabolic dysregulation that forces T cells to be more dependent on fermentation of pyruvate to lactate. This glycolytic shift of age-associated T cells impacts their stemness and effector function contributing to the accumulation of short-lived effector T cells. The increment of ROS production and oxidative stress by damaged mitochondria also contribute to T cell differentiation and activation. Alteration of mitochondrial dynamics restrains the metabolic switch needed for T cell activation and dampers the Ca^{2+} buffering by mitochondria, impairing the formation of the immune synapse and promoting undesired effects such as Ca^{2+} mediated apoptosis.

Functional deterioration of T cells during aging generates a myriad of T cell pools that are denominated as age-associated T cells (Taas). These Taas increase with aging and contribute to age-associated diseases either by an excessive inflammatory profile, promoting inflammaging and autoimmune diseases, or by an inefficient function, leading to infections, cancer progression or accumulation of senescent cells. Thanks to scRNAseq technology the transcriptomic differential features of Taas (e.g. natural killer-like $CD8^+$ T cells, cytotoxic $CD4^+$ T cells, exhausted T cells or activated Tregs) have been described allowing their identification and functional characterization [209]. However, whether age-related mitochondrial decline affects to all these subpopulations equally remains to be elucidated.

Along this work, the different mitochondrial dysfunction processes are presented separately. It is important to understand that all of them are interconnected increasing the complexity of understanding and potentially intervene in this important hallmark of aging. Further research is needed to go deeper on the knowledge of molecular mechanisms and functional consequences of age-associated mitochondrial decline, especially in T cells, with the final goal to design strategies to delay T cell dysfunction in old people and its wide consequences in immunity, cancer and age-related multimorbidity.

Acknowledgments

The authors thank M. M. Gómez de las Heras for his critical reading and helpful comments on the manuscript. This study was supported by the European Regional Development Fund (ERDF) and the European Commission through H2020-EU.1.1, European Research Council grant ERC-2021-CoG 101044248-Let T Be, and the Y2020/BIO-6350 NutriSION-CM synergy grant from Comunidad de Madrid (Spain). J.I.E.L. is supported by FPU grant (FPU20/04066) from Ministerio de Ciencia, Innovación y Universidades (Spain). S.D.P. is supported by the contract of the Y2020/Bio-6350 NutriSION-CM synergic grant from the Comunidad de Madrid (Spain).

Competing interests

The authors declare no competing interests.

References

[1] P. Andrieux, C. Chevillard, E. Cunha-Neto, J.P.S. Nunes, Mitochondria as a cellular hub in infection and inflammation, IJMS 22 (2021) 11338, https://doi.org/10.3390/ijms222111338.
[2] C. Franceschi, M. Bonafè, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, G. De Benedictis, Inflamm-aging. An evolutionary perspective on immunosenescence, Ann. N. Y Acad. Sci. 908 (2000) 244–254, https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.
[3] B.K. Kennedy, S.L. Berger, A. Brunet, J. Campisi, A.M. Cuervo, E.S. Epel, C. Franceschi, G.J. Lithgow, R.I. Morimoto, J.E. Pessin, T.A. Rando, A. Richardson, E.E. Schadt, T. Wyss-Coray, F. Sierra, Geroscience: linking aging to chronic disease, Cell 159 (2014) 709–713, https://doi.org/10.1016/j.cell.2014.10.039.
[4] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, Hallmarks of aging: an expanding universe, Cell 186 (2023) 243–278, https://doi.org/10.1016/j.cell.2022.11.001.
[5] S. Miwa, S. Kashyap, E. Chini, T. von Zglinicki, Mitochondrial dysfunction in cell senescence and aging, J. Clin. Invest 132 (2022), e158447, https://doi.org/10.1172/JCI158447.
[6] K.-A. Lee, R.R. Flores, I.H. Jang, A. Saathoff, P.D. Robbins, Immune senescence, immunosenescence and aging, Front. Aging 3 (2022), 900028, https://doi.org/10.3389/fragi.2022.900028.
[7] S. Han, P. Georgiev, A.E. Ringel, A.H. Sharpe, M.C. Haigis, Age-associated remodeling of T cell immunity and metabolism, Cell Metab. 35 (2023) 36–55, https://doi.org/10.1016/j.cmet.2022.11.005.

[8] N. Ron-Harel, A.H. Sharpe, M.C. Haigis, Mitochondrial metabolism in T cell activation and senescence: a Mini-Review, Gerontology 61 (2015) 131–138, https://doi.org/10.1159/000362502.
[9] L.A.J. O'Neill, R.J. Kishton, J. Rathmell, A guide to immunometabolism for immunologists, Nat. Rev. Immunol. 16 (2016) 553–565, https://doi.org/10.1038/nri.2016.70.
[10] M. Mittelbrunn, G. Kroemer, Hallmarks of T cell aging, Nat. Immunol. 22 (2021) 687–698, https://doi.org/10.1038/s41590-021-00927-z.
[11] K. Fan, Y. Li, H. Wang, X. Mao, J. Guo, F. Wang, L. Huang, Y. Li, X. Ma, Z. Gao, W. Chen, D. Qian, W. Xue, Q. Cao, L. Zhang, L. Shen, L. Zhang, C. Tong, J. Zhong, W. Lu, L. Lu, K. Ren, G. Zhong, Y. Wang, M. Tang, X.-H. Feng, R. Chai, J. Jin, Stress-induced metabolic disorder in peripheral CD4+ T cells leads to anxiety-like behavior, e19, Cell 179 (2019) 864–879, https://doi.org/10.1016/j.cell.2019.10.001.
[12] I. Buondonno, F. Sassi, F. Cattaneo, P. D'Amelio, Association between immunosenescence, mitochondrial dysfunction and frailty syndrome in older adults, Cells 12 (2022) 44, https://doi.org/10.3390/cells12010044.
[13] G. Desdín-Micó, G. Soto-Heredero, J.F. Aranda, J. Oller, E. Carrasco, E. Gabandé-Rodríguez, E.M. Blanco, A. Alfranca, L. Cussó, M. Desco, B. Ibañez, A.R. Gortazar, P. Fernández-Marcos, M.N. Navarro, B. Hernaez, A. Alcamí, F. Baixauli, M. Mittelbrunn, T cells with dysfunctional mitochondria induce multimorbidity and premature senescence, Science 368 (2020) 1371–1376, https://doi.org/10.1126/science.aax0860.
[14] T.V. Zhao, Y. Sato, J.J. Goronzy, C.M. Weyand, T-cell aging-associated phenotypes in autoimmune disease, Front Aging 3 (2022), 867950, https://doi.org/10.3389/fragi.2022.867950.
[15] L. Zhang, W. Zhang, Z. Li, S. Lin, T. Zheng, B. Hao, Y. Hou, Y. Zhang, K. Wang, C. Qin, L. Yue, J. Jin, M. Li, L. Fan, Mitochondria dysfunction in CD8+ T cells as an important contributing factor for cancer development and a potential target for cancer treatment: a review, J. Exp. Clin. Cancer Res 41 (2022) 227, https://doi.org/10.1186/s13046-022-02439-6.
[16] L.A. Callender, E.C. Carroll, C. Garrod-Ketchley, J. Schroth, J. Bystrom, V. Berryman, M. Pattrick, D. Campbell-Richards, G.A. Hood, G.A. Hitman, S. Finer, S.M. Henson, Altered nutrient uptake causes mitochondrial dysfunction in senescent CD8+ EMRA T cells during type 2 diabetes, Front. Aging 2 (2021), 681428, https://doi.org/10.3389/fragi.2021.681428.
[17] J.R. Friedman, J. Nunnari, Mitochondrial form and function, Nature 505 (2014) 335–343, https://doi.org/10.1038/nature12985.
[18] Z. Rong, P. Tu, P. Xu, Y. Sun, F. Yu, N. Tu, L. Guo, Y. Yang, The mitochondrial response to DNA damage, Front. Cell Dev. Biol. 9 (2021), 669379, https://doi.org/10.3389/fcell.2021.669379.
[19] I. Shokolenko, M. Alexeyev, Mitochondrial DNA: consensuses and controversies, DNA (Basel). 2 (2022) 131–148, https://doi.org/10.3390/dna2020010.
[20] T.E.S. Kauppila, J.H.K. Kauppila, N.-G. Larsson, Mammalian mitochondria and aging: an update, Cell Metab. 25 (2017) 57–71, https://doi.org/10.1016/j.cmet.2016.09.017.
[21] J. Geurts, S. Nasi, P. Distel, M. Müller-Gerbl, T.A. Prolla, G.C. Kujoth, U. A. Walker, T. Hügle, Prematurely aging mitochondrial DNA mutator mice display subchondral osteopenia and chondrocyte hypertrophy without further osteoarthritis features, Sci. Rep. 10 (2020) 1296, https://doi.org/10.1038/s41598-020-58385-w.
[22] H. Kumagai, B. Miller, S.-J. Kim, N. Leelaprachakul, N. Kikuchi, K. Yen, P. Cohen, Novel insights into mitochondrial DNA: mitochondrial microproteins and mtDNA variants modulate athletic performance and age-related diseases, Genes 14 (2023) 286, https://doi.org/10.3390/genes14020286.
[23] P.A. Bousquet, S. Meltzer, A.J. Fuglestad, T. Lüders, Y. Esbensen, H.V. Juul, C. Johansen, L.G. Lyckander, T. Bjørnetrø, E.M. Inderberg, C. Kersten, K. R. Redalen, A.H. Ree, The mitochondrial DNA constitution shaping T-cell immunity in patients with rectal cancer at high risk of metastatic progression, Clin. Transl. Oncol. 24 (2022) 1157–1167, https://doi.org/10.1007/s12094-021-02756-w.
[24] Y. Li, J.J. Goronzy, C.M. Weyand, DNA damage, metabolism and aging in pro-inflammatory T cells: rheumatoid arthritis as a model system, Exp. Gerontol. 105 (2018) 118–127, https://doi.org/10.1016/j.exger.2017.10.027.
[25] S. Rausser, C. Trumpff, M.A. McGill, A. Junker, W. Wang, S.-H. Ho, A. Mitchell, K. R. Karan, C. Monk, S.C. Segerstrom, R.G. Reed, M. Picard, Mitochondrial phenotypes in purified human immune cell subtypes and cell mixtures, ELife 10 (2021), e70899, https://doi.org/10.7554/eLife.70899.
[26] Y. Li, Y. Shen, K. Jin, Z. Wen, W. Cao, B. Wu, R. Wen, L. Tian, G.J. Berry, J. J. Goronzy, C.M. Weyand, The DNA repair nuclease MRE11A functions as a mitochondrial protector and prevents T cell pyroptosis and tissue inflammation, e6, Cell Metab. 30 (2019) 477–492, https://doi.org/10.1016/j.cmet.2019.06.016.
[27] G. Desdín-Micó, G. Soto-Heredero, M. Mittelbrunn, Mitochondrial activity in T cells, Mitochondrion 41 (2018) 51–57, https://doi.org/10.1016/j.mito.2017.10.006.
[28] D.M. Moskowitz, D.W. Zhang, B. Hu, S. Le Saux, R.E. Yanes, Z. Ye, J. D. Buenrostro, C.M. Weyand, W.J. Greenleaf, J.J. Goronzy, Epigenomics of human CD8 T cell differentiation and aging, Sci. Immunol. 2 (2017) eaag0192, https://doi.org/10.1126/sciimmunol.aag0192.
[29] C.-H. Chang, J.D. Curtis, L.B. Maggi, B. Faubert, A.V. Villarino, D. O'Sullivan, S. C.-C. Huang, G.J.W. van der Windt, J. Blagih, J. Qiu, J.D. Weber, E.J. Pearce, R. G. Jones, E.L. Pearce, Posttranscriptional control of T cell effector function by aerobic glycolysis, Cell 153 (2013) 1239–1251, https://doi.org/10.1016/j.cell.2013.05.016.
[30] G. Soto-Heredero, M.M. Gómez de las Heras, E. Gabandé-Rodríguez, J. Oller, M. Mittelbrunn, Glycolysis – a key player in the inflammatory response, FEBS J. 287 (2020) 3350–3369, https://doi.org/10.1111/febs.15327.
[31] A.A. Shestov, X. Liu, Z. Ser, A.A. Cluntun, Y.P. Hung, L. Huang, D. Kim, A. Le, G. Yellen, J.G. Albeck, J.W. Locasale, Quantitative determinants of aerobic glycolysis identify flux through the enzyme GAPDH as a limiting step, Elife 3 (2014), e03342, https://doi.org/10.7554/eLife.03342.
[32] N. Ron-Harel, D. Santos, J.M. Ghergurovich, P.T. Sage, A. Reddy, S.B. Lovitch, N. Dephoure, F.K. Satterstrom, M. Sheffer, J.B. Spinelli, S. Gygi, J.D. Rabinowitz, A.H. Sharpe, M.C. Haigis, Mitochondrial biogenesis and proteome remodeling promote one-carbon metabolism for T cell activation, Cell Metab. 24 (2016) 104–117, https://doi.org/10.1016/j.cmet.2016.06.007.
[33] E.L. Pearce, E.J. Pearce, Metabolic pathways in immune cell activation and quiescence, Immunity 38 (2013) 633–643, https://doi.org/10.1016/j.immuni.2013.04.005.
[34] M. Peng, N. Yin, S. Chhangawala, K. Xu, C.S. Leslie, M.O. Li, Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism, Science 354 (2016) 481–484, https://doi.org/10.1126/science.aaf6284.
[35] F. Baixauli, R. Acín-Pérez, C. Villarroya-Beltrí, C. Mazzeo, N. Nuñez-Andrade, E. Gabandé-Rodriguez, M.D. Ledesma, A. Blázquez, M.A. Martin, J.M. Falcón-Pérez, J.M. Redondo, J.A. Enríquez, M. Mittelbrunn, Mitochondrial respiration controls lysosomal function during inflammatory T cell responses, Cell Metab. 22 (2015) 485–498, https://doi.org/10.1016/j.cmet.2015.07.020.
[36] M. Kuwahara, M. Izumoto, H. Honda, K. Inoue, Y. Imai, J. Suzuki, S. Maruyama, M. Yasukawa, M. Yamashita, Glutamine metabolism regulates Th2 cell differentiation via the α-ketoglutalate-dependent demethylation of histone H3K27, Immunology (2017), https://doi.org/10.1101/184648.
[37] D. Klysz, X. Tai, P.A. Robert, M. Craveiro, G. Cretenet, L. Oburoglu, C. Mongellaz, S. Floess, V. Fritz, M.I. Matias, C. Yong, N. Surh, J.C. Marie, J. Huehn, V. Zimmermann, S. Kinet, V. Dardalhon, N. Taylor, Glutamine-dependent α-ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation, Sci. Signal 8 (2015) ra97, https://doi.org/10.1126/scisignal.aab2610.
[38] L. Franchi, I. Monteleone, L.-Y. Hao, M.A. Spahr, W. Zhao, X. Liu, K. Demock, A. Kulkarni, C.A. Lesch, B. Sanchez, L. Carter, I. Marafini, X. Hu, O. Mashadova, M. Yuan, J.M. Asara, H. Singh, C.A. Lyssiotis, G. Monteleone, A.W. Opipari, G. D. Glick, Inhibiting oxidative phosphorylation in vivo restrains Th17 effector responses and ameliorates murine colitis, J. Immunol. 198 (2017) 2735–2746, https://doi.org/10.4049/jimmunol.1600810.
[39] V.A. Gerriets, R.J. Kishton, A.G. Nichols, A.N. Macintyre, M. Inoue, O. Ilkayeva, P. S. Winter, X. Liu, B. Priyadharshini, M.E. Slawinska, L. Haeberli, C. Huck, L. A. Turka, K.C. Wood, L.P. Hale, P.A. Smith, M.A. Schneider, N.J. MacIver, J. W. Locasale, C.B. Newgard, M.L. Shinohara, J.C. Rathmell, Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation, J. Clin. Invest 125 (2015) 194–207, https://doi.org/10.1172/JCI76012.
[40] B. Shin, G.A. Benavides, J. Geng, S.B. Koralov, H. Hu, V.M. Darley-Usmar, L. E. Harrington, Mitochondrial oxidative phosphorylation regulates the fate decision between pathogenic Th17 and regulatory T cells, e4, Cell Rep. 30 (2020) 1898–1909, https://doi.org/10.1016/j.celrep.2020.01.022.
[41] V. Schmitt, L. Rink, P. Uciechowski, The Th17/Treg balance is disturbed during aging, Exp. Gerontol. 48 (2013) 1379–1386, https://doi.org/10.1016/j.exger.2013.09.003.
[42] N. Komatsu, K. Okamoto, S. Sawa, T. Nakashima, M. Oh-hora, T. Kodama, S. Tanaka, J.A. Bluestone, H. Takayanagi, Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis, Nat. Med. 20 (2014) 62–68, https://doi.org/10.1038/nm.3432.
[43] R.D. Michalek, V.A. Gerriets, S.R. Jacobs, A.N. Macintyre, N.J. MacIver, E. F. Mason, S.A. Sullivan, A.G. Nichols, J.C. Rathmell, Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets, J. Immunol. 186 (2011) 3299–3303, https://doi.org/10.4049/jimmunol.1003613.
[44] N.M. Chapman, H. Zeng, T.-L.M. Nguyen, Y. Wang, P. Vogel, Y. Dhungana, X. Liu, G. Neale, J.W. Locasale, H. Chi, mTOR coordinates transcriptional programs and mitochondrial metabolism of activated Treg subsets to protect tissue homeostasis, Nat. Commun. 9 (2018) 2095, https://doi.org/10.1038/s41467-018-04392-5.
[45] Z. Fu, J. Ye, J.W. Dean, J.W. Bostick, S.E. Weinberg, L. Xiong, K.N. Oliff, Z. E. Chen, D. Avram, N.S. Chandel, L. Zhou, Requirement of mitochondrial transcription factor A in tissue-resident regulatory T cell maintenance and function, e4, Cell Rep. 28 (2019) 159–171, https://doi.org/10.1016/j.celrep.2019.06.024.
[46] S.-A. Younes, A. Talla, S.P. Ribeiro, E.V. Saidakova, L.B. Korolevskaya, K. V. Shmagel, C.L. Shive, M.L. Freeman, S. Panigrahi, S. Zweig, R. Balderas, L. Margolis, D.C. Douek, D.D. Anthony, P. Pandiyan, M. Cameron, S.F. Sieg, L. H. Calabrese, B. Rodriguez, M.M. Lederman, Cycling CD4+ T cells in HIV-infected immune nonresponders have mitochondrial dysfunction, J. Clin. Investig. 128 (2018) 5083–5094, https://doi.org/10.1172/JCI120245.
[47] X. Liu, Z. Hu, H. Zhou, N-acetylcysteine improves inflammatory response in COPD patients by regulating Th17/treg balance through hypoxia inducible factor-1α pathway, Biomed. Res Int 2021 (2021), 6372128, https://doi.org/10.1155/2021/6372128.
[48] L.Z. Shi, R. Wang, G. Huang, P. Vogel, G. Neale, D.R. Green, H. Chi, HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells, J. Exp. Med 208 (2011) 1367–1376, https://doi.org/10.1084/jem.20110278.
[49] L.A. Sena, S. Li, A. Jairaman, M. Prakriya, T. Ezponda, D.A. Hildeman, C.-R. Wang, P.T. Schumacker, J.D. Licht, H. Perlman, P.J. Bryce, N.S. Chandel,

Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling, Immunity 38 (2013) 225–236, https://doi.org/10.1016/j.immuni.2012.10.020.
[50] T.N. Tarasenko, S.E. Pacheco, M.K. Koenig, J. Gomez-Rodriguez, S.M. Kapnick, F. Diaz, P.M. Zerfas, E. Barca, J. Sudderth, R.J. DeBerardinis, R. Covian, R. S. Balaban, S. DiMauro, P.J. McGuire, Cytochrome c oxidase activity is a metabolic checkpoint that regulates cell fate decisions during T cell activation and differentiation, e7, Cell Metab. 25 (2017) 1254–1268, https://doi.org/10.1016/j.cmet.2017.05.007.
[51] P. Fisicaro, V. Barili, B. Montanini, G. Acerbi, M. Ferracin, F. Guerrieri, D. Salerno, C. Boni, M. Massari, M.C. Cavallo, G. Grossi, T. Giuberti, P. Lampertico, G. Missale, M. Levrero, S. Ottonello, C. Ferrari, Targeting mitochondrial dysfunction can restore antiviral activity of exhausted HBV-specific CD8 T cells in chronic hepatitis B, Nat. Med 23 (2017) 327–336, https://doi.org/10.1038/nm.4275.
[52] A. Alrubayyi, E. Moreno-Cubero, D. Hameiri-Bowen, R. Matthews, S. Rowland-Jones, A. Schurich, D. Peppa, Functional restoration of exhausted CD8 T cells in chronic HIV-1 infection by targeting mitochondrial dysfunction, Front Immunol. 13 (2022), 908697, https://doi.org/10.3389/fimmu.2022.908697.
[53] Y. Elyahu, I. Hekselman, I. Eizenberg-Magar, O. Berner, I. Strominger, M. Schiller, K. Mittal, A. Nemirovsky, E. Eremenko, A. Vital, E. Simonovsky, V. Chalifa-Caspi, N. Friedman, E. Yeger-Lotem, A. Monsonego, Aging promotes reorganization of the CD4 T cell landscape toward extreme regulatory and effector phenotypes, Sci. Adv. 5 (2019) eaaw8330, https://doi.org/10.1126/sciadv.aaw8330.
[54] D.A. Mogilenko, I. Shchukina, M.N. Artyomov, Immune ageing at single-cell resolution, Nat. Rev. Immunol. (2021), https://doi.org/10.1038/s41577-021-00646-4.
[55] G. Soto-Heredero, G. Desdín-Micó, M. Mittelbrunn, Mitochondrial dysfunction defines T cell exhaustion, Cell Metab. 33 (2021) 470–472, https://doi.org/10.1016/j.cmet.2021.02.010.
[56] J. Ogando, M.E. Sáez, J. Santos, C. Nuevo-Tapioles, M. Gut, A. Esteve-Codina, S. Heath, A. González-Pérez, J.M. Cuezva, R.A. Lacalle, S. Mañes, PD-1 signaling affects cristae morphology and leads to mitochondrial dysfunction in human CD8 + T lymphocytes, J. Immunother. Cancer 7 (2019) 151, https://doi.org/10.1186/s40425-019-0628-7.
[57] N.E. Scharping, A.V. Menk, R.S. Moreci, R.D. Whetstone, R.E. Dadey, S. C. Watkins, R.L. Ferris, G.M. Delgoffe, The tumor microenvironment represses T Cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction, Immunity 45 (2016) 374–388, https://doi.org/10.1016/j.immuni.2016.07.009.
[58] E.L. Pearce, M.C. Poffenberger, C.-H. Chang, R.G. Jones, Fueling immunity: insights into metabolism and lymphocyte function, Science 342 (2013), 1242454, https://doi.org/10.1126/science.1242454.
[59] D. O'Sullivan, G.J.W. van der Windt, S.C.-C. Huang, J.D. Curtis, C.-H. Chang, M. D. Buck, J. Qiu, A.M. Smith, W.Y. Lam, L.M. DiPlato, F.-F. Hsu, M.J. Birnbaum, E. J. Pearce, E.L. Pearce, Memory CD8(+) T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development, Immunity 41 (2014) 75–88, https://doi.org/10.1016/j.immuni.2014.06.005.
[60] G.J.W. van der Windt, B. Everts, C.-H. Chang, J.D. Curtis, T.C. Freitas, E. Amiel, E. J. Pearce, E.L. Pearce, Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development, Immunity 36 (2012) 68–78, https://doi.org/10.1016/j.immuni.2011.12.007.
[61] E.L. Pearce, M.C. Walsh, P.J. Cejas, G.M. Harms, H. Shen, L.-S. Wang, R.G. Jones, Y. Choi, Enhancing CD8 T-cell memory by modulating fatty acid metabolism, Nature 460 (2009) 103–107, https://doi.org/10.1038/nature08097.
[62] K.M. Quinn, A. Fox, K.L. Harland, B.E. Russ, J. Li, T.H.O. Nguyen, L. Loh, M. Olshanksy, H. Naeem, K. Tsyganov, F. Wiede, R. Webster, C. Blyth, X.Y.X. Sng, T. Tiganis, D. Powell, P.C. Doherty, S.J. Turner, K. Kedzierska, N.L.La Gruta, Age-related decline in primary CD8+ T Cell responses is associated with the development of senescence in virtual memory CD8+ T cells, Cell Rep. 23 (2018) 3512–3524, https://doi.org/10.1016/j.celrep.2018.05.057.
[63] K.R. Renkema, G. Li, A. Wu, M.J. Smithey, J. Nikolich-Žugich, Two separate defects affecting true naive or virtual memory T cell precursors combine to reduce naive T cell responses with aging, J. Immunol. 192 (2014) 151–159, https://doi.org/10.4049/jimmunol.1301453.
[64] A. Bektas, S.H. Schurman, M. Gonzalez-Freire, C.A. Dunn, A.K. Singh, F. Macian, A.M. Cuervo, R. Sen, L. Ferrucci, Age-associated changes in human CD4+ T cells point to mitochondrial dysfunction consequent to impaired autophagy, Aging 11 (2019) 9234–9263, https://doi.org/10.18632/aging.102438.
[65] C.A. Headley, S. Gautam, A. Akhter, V. Dwivedi, R. Ault, J.B. Torrelles, J. Gelfond, J. Turner, Extracellular delivery of functional mitochondria reverses the dysfunction of CD4+ T cells in aging, Immunology (2021), https://doi.org/10.1101/2021.02.21.432151.
[66] P.J. McGuire, Mitochondrial dysfunction and the aging immune system, Biology 8 (2019) 26, https://doi.org/10.3390/biology8020026.
[67] P.D. Ray, B.-W. Huang, Y. Tsuji, Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling, Cell Signal 24 (2012) 981–990, https://doi.org/10.1016/j.cellsig.2012.01.008.
[68] Y. Yang, A.V. Bazhin, J. Werner, S. Karakhanova, Reactive oxygen species in the immune system, Int Rev. Immunol. 32 (2013) 249–270, https://doi.org/10.3109/08830185.2012.755176.
[69] T. Finkel, N.J. Holbrook, Oxidants, oxidative stress and the biology of ageing, Nature 408 (2000) 239–247, https://doi.org/10.1038/35041687.
[70] S. Miwa, H. Jow, K. Baty, A. Johnson, R. Czapiewski, G. Saretzki, A. Treumann, T. von Zglinicki, Low abundance of the matrix arm of complex I in mitochondria predicts longevity in mice, Nat. Commun. 5 (2014) 3837, https://doi.org/10.1038/ncomms4837.
[71] N.A. Dencher, M. Frenzel, N.H. Reifschneider, M. Sugawa, F. Krause, Proteome alterations in rat mitochondria caused by aging, Ann. N. Y Acad. Sci. 1100 (2007) 291–298, https://doi.org/10.1196/annals.1395.030.
[72] K. Boengler, M. Kosiol, M. Mayr, R. Schulz, S. Rohrbach, Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue, J. Cachex-.-. Sarcopenia Muscle 8 (2017) 349–369, https://doi.org/10.1002/jcsm.12178.
[73] M. Drouet, F. Lauthier, J.P. Charmes, P. Sauvage, M.H. Ratinaud, Age-associated changes in mitochondrial parameters on peripheral human lymphocytes, Exp. Gerontol. 34 (1999) 843–852, https://doi.org/10.1016/S0531-5565(99)00058-3.
[74] M.M. Kaminski, S.W. Sauer, C.-D. Klemke, D. Süss, J.G. Okun, P.H. Krammer, K. Gülow, Mitochondrial reactive oxygen species control T cell activation by regulating IL-2 and IL-4 expression: mechanism of ciprofloxacin-mediated immunosuppression, J. Immunol. 184 (2010) 4827–4841, https://doi.org/10.4049/jimmunol.0901662.
[75] R. Wang, C.P. Dillon, L.Z. Shi, S. Milasta, R. Carter, D. Finkelstein, L. L. McCormick, P. Fitzgerald, H. Chi, J. Munger, D.R. Green, The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation, Immunity 35 (2011) 871–882, https://doi.org/10.1016/j.immuni.2011.09.021.
[76] S.M. Henson, A. Lanna, N.E. Riddell, O. Franzese, R. Macaulay, S.J. Griffiths, D. J. Puleston, A.S. Watson, A.K. Simon, S.A. Tooze, A.N. Akbar, p38 signaling inhibits mTORC1-independent autophagy in senescent human $CD8^+$ T cells, J. Clin. Invest 124 (2014) 4004–4016, https://doi.org/10.1172/JCI75051.
[77] R. Acín-Pérez, P. Fernández-Silva, M.L. Peleato, A. Pérez-Martos, J.A. Enriquez, Respiratory active mitochondrial supercomplexes, Mol. Cell 32 (2008) 529–539, https://doi.org/10.1016/j.molcel.2008.10.021.
[78] D.P. Champagne, K.M. Hatle, K.A. Fortner, A. D'Alessandro, T.M. Thornton, R. Yang, D. Torralba, J. Tomás-Cortázar, Y.W. Jun, K.H. Ahn, K.C. Hansen, L. Haynes, J. Anguita, M. Rincon, Fine-tuning of CD8 + T cell mitochondrial metabolism by the respiratory chain repressor MCJ dictates protection to influenza virus, Immunity 44 (2016) 1299–1311, https://doi.org/10.1016/j.immuni.2016.02.018.
[79] Z. Guo, G. Wang, B. Wu, W.-C. Chou, L. Cheng, C. Zhou, J. Lou, D. Wu, L. Su, J. Zheng, J.P.-Y. Ting, Y.Y. Wan, DCAF1 regulates Treg senescence via the ROS axis during immunological aging, J. Clin. Investig. 130 (2020) 5893–5908, https://doi.org/10.1172/JCI136466.
[80] N.E. Scharping, D.B. Rivadeneira, A.V. Menk, P.D.A. Vignali, B.R. Ford, N. L. Rittenhouse, R. Peralta, Y. Wang, Y. Wang, K. DePeaux, A.C. Poholek, G. M. Delgoffe, Mitochondrial stress induced by continuous stimulation under hypoxia rapidly drives T cell exhaustion, Nat. Immunol. 22 (2021) 205–215, https://doi.org/10.1038/s41590-020-00834-9.
[81] L. Liu, D.R. Wise, J.A. Diehl, M.C. Simon, Hypoxic reactive oxygen species regulate the integrated stress response and cell survival, J. Biol. Chem. 283 (2008) 31153–31162, https://doi.org/10.1074/jbc.M805056200.
[82] M.J. Derisbourg, M.D. Hartman, M.S. Denzel, Modulating the integrated stress response to slow aging and ameliorate age-related pathology, Nat. Aging 1 (2021) 760–768, https://doi.org/10.1038/s43587-021-00112-9.
[83] E. Mick, D.V. Titov, O.S. Skinner, R. Sharma, A.A. Jourdain, V.K. Mootha, Distinct mitochondrial defects trigger the integrated stress response depending on the metabolic state of the cell, ELife 9 (2020), e49178, https://doi.org/10.7554/eLife.49178.
[84] Z. Wu, M. Zuo, L. Zeng, K. Cui, B. Liu, C. Yan, L. Chen, J. Dong, F. Shangguan, W. Hu, H. He, B. Lu, Z. Song, OMA1 reprograms metabolism under hypoxia to promote colorectal cancer development, EMBO Rep. 22 (2021), https://doi.org/10.15252/embr.202050827.
[85] X. Guo, G. Aviles, Y. Liu, R. Tian, B.A. Unger, Y.-H.T. Lin, A.P. Wiita, K. Xu, M. A. Correia, M. Kampmann, Mitochondrial stress is relayed to the cytosol by an OMA1–DELE1–HRI pathway, Nature 579 (2020) 427–432, https://doi.org/10.1038/s41586-020-2078-2.
[86] S. Scheu, D.B. Stetson, R.L. Reinhardt, J.H. Leber, M. Mohrs, R.M. Locksley, Activation of the integrated stress response during T helper cell differentiation, Nat. Immunol. 7 (2006) 644–651, https://doi.org/10.1038/ni1338.
[87] D. Kamimura, T. Atsumi, A. Stofkova, N. Nishikawa, T. Ohki, H. Suzuki, K. Katsunuma, J. Jiang, H. Bando, J. Meng, L. Sabharwal, H. Ogura, T. Hirano, Y. Arima, M. Murakami, Naïve T cell homeostasis regulated by stress responses and TCR signaling, Front. Immunol. 6 (2015), https://doi.org/10.3389/fimmu.2015.00638.
[88] S.L. Hayward, C.D. Scharer, E.K. Cartwright, S. Takamura, Z.-R.T. Li, J.M. Boss, J. E. Kohlmeier, Environmental cues regulate epigenetic reprogramming of airway-resident memory CD8+ T cells, Nat. Immunol. 21 (2020) 309–320, https://doi.org/10.1038/s41590-019-0584-x.
[89] P.C. Tapia, Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: "Mitohormesis" for health and vitality, Med Hypotheses 66 (2006) 832–843, https://doi.org/10.1016/j.mehy.2005.09.009.
[90] G. Rose, A. Santoro, S. Salvioli, Mitochondria and mitochondria-induced signalling molecules as longevity determinants, Mech. Ageing Dev. 165 (2017) 115–128, https://doi.org/10.1016/j.mad.2016.12.002.
[91] J. Durieux, S. Wolff, A. Dillin, The cell-non-autonomous nature of electron transport chain-mediated longevity, Cell 144 (2011) 79–91, https://doi.org/10.1016/j.cell.2010.12.016.

[92] J. Burtscher, A. Soltany, N.P. Visavadiya, M. Burtscher, G.P. Millet, K. Khoramipour, A.V. Khamoui, Mitochondrial stress and mitokines in aging, Aging Cell 22 (2023), https://doi.org/10.1111/acel.13770.
[93] M. Conte, M. Martucci, A. Chiariello, C. Franceschi, S. Salvioli, Mitochondria, immunosenescence and inflammaging: a role for mitokines, Semin Immunopathol. 42 (2020) 607–617, https://doi.org/10.1007/s00281-020-00813-0.
[94] W. Wan, L. Zhang, Y. Lin, X. Rao, X. Wang, F. Hua, J. Ying, Mitochondria-derived peptide MOTS-c: effects and mechanisms related to stress, metabolism and aging, J. Transl. Med 21 (2023) 36, https://doi.org/10.1186/s12967-023-03885-2.
[95] J.A. Bluestone, J.H. Buckner, M. Fitch, S.E. Gitelman, S. Gupta, M.K. Hellerstein, K.C. Herold, A. Lares, M.R. Lee, K. Li, W. Liu, S.A. Long, L.M. Masiello, V. Nguyen, A.L. Putnam, M. Rieck, P.H. Sayre, Q. Tang, Type 1 diabetes immunotherapy using polyclonal regulatory T cells, Sci. Transl. Med. 7 (2015), https://doi.org/10.1126/scitranslmed.aad4134.
[96] L.S.K. Walker, M. von Herrath, CD4 T cell differentiation in type 1 diabetes, Clin. Exp. Immunol. 183 (2015) 16–29, https://doi.org/10.1111/cei.12672.
[97] Y.-H. Youm, T.L. Horvath, D.J. Mangelsdorf, S.A. Kliewer, V.D. Dixit, Prolongevity hormone FGF21 protects against immune senescence by delaying age-related thymic involution, Proc. Natl. Acad. Sci. USA 113 (2016) 1026–1031, https://doi.org/10.1073/pnas.1514511113.
[98] H.K. Chung, J.T. Kim, H.-W. Kim, M. Kwon, S.Y. Kim, M. Shong, K.S. Kim, H.-S. Yi, GDF15 deficiency exacerbates chronic alcohol- and carbon tetrachloride-induced liver injury, Sci. Rep. 7 (2017) 17238, https://doi.org/10.1038/s41598-017-17574-w.
[99] W. De Haes, L. Frooninckx, R. Van Assche, A. Smolders, G. Depuydt, J. Billen, B. P. Braeckman, L. Schoofs, L. Temmerman, Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2, Proc. Natl. Acad. Sci. USA 111 (2014) E2501–E2509, https://doi.org/10.1073/pnas.1321776111.
[100] I. Mohammed, M.D. Hollenberg, H. Ding, C.R. Triggle, A critical review of the evidence that metformin is a putative anti-aging drug that enhances healthspan and extends lifespan, Front. Endocrinol. 12 (2021), 718942, https://doi.org/10.3389/fendo.2021.718942.
[101] L.P. Bharath, M. Agrawal, G. McCambridge, D.A. Nicholas, H. Hasturk, J. Liu, K. Jiang, R. Liu, Z. Guo, J. Deeney, C.M. Apovian, J. Snyder-Cappione, G.S. Hawk, R.M. Fleeman, R.M.F. Pihl, K. Thompson, A.C. Belkina, L. Cui, E.A. Proctor, P. A. Kern, B.S. Nikolajczyk, Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation, e6, Cell Metab. 32 (2020) 44–55, https://doi.org/10.1016/j.cmet.2020.04.015.
[102] H.-S. Yi, S.Y. Kim, J.T. Kim, Y.-S. Lee, J.S. Moon, M. Kim, Y.E. Kang, K.H. Joung, J.H. Lee, H.J. Kim, K. Chun, M. Shong, B.J. Ku, T-cell senescence contributes to abnormal glucose homeostasis in humans and mice, Cell Death Dis. 10 (2019) 249, https://doi.org/10.1038/s41419-019-1494-4.
[103] A. Quintana, C. Schwindling, A.S. Wenning, U. Becherer, J. Rettig, E.C. Schwarz, M. Hoth, T cell activation requires mitochondrial translocation to the immunological synapse, Proc. Natl. Acad. Sci. USA 104 (2007) 14418–14423, https://doi.org/10.1073/pnas.0703126104.
[104] I.M.A. Wolf, A.H. Guse, Ca2+ Microdomains in T-Lymphocytes, Front Oncol. 7 (2017) 73, https://doi.org/10.3389/fonc.2017.00073.
[105] S. Feske, J. Giltnane, R. Dolmetsch, L.M. Staudt, A. Rao, Gene regulation mediated by calcium signals in T lymphocytes, Nat. Immunol. 2 (2001) 316–324, https://doi.org/10.1038/86318.
[106] R. Bravo-Sagua, V. Parra, C. López-Crisosto, P. Díaz, A.F.G. Quest, S. Lavandero, Calcium transport and signaling in mitochondria, Compr. Physiol. 7 (2017) 623–634, https://doi.org/10.1002/cphy.c160013.
[107] R.M.L. La Rovere, G. Roest, G. Bultynck, J.B. Parys, Intracellular Ca(2+) signaling and Ca(2+) microdomains in the control of cell survival, apoptosis and autophagy, Cell Calcium 60 (2016) 74–87, https://doi.org/10.1016/j.ceca.2016.04.005.
[108] A.I. Tarasov, E.J. Griffiths, G.A. Rutter, Regulation of ATP production by mitochondrial Ca(2+), Cell Calcium 52 (2012) 28–35, https://doi.org/10.1016/j.ceca.2012.03.003.
[109] S. Han, P. Georgiev, A.E. Ringel, A.H. Sharpe, M.C. Haigis, Age-associated remodeling of T cell immunity and metabolism, Cell Metab. 35 (2023) 36–55, https://doi.org/10.1016/j.cmet.2022.11.005.
[110] T.-I. Peng, M.-J. Jou, Oxidative stress caused by mitochondrial calcium overload, Ann. N. Y Acad. Sci. 1201 (2010) 183–188, https://doi.org/10.1111/j.1749-6632.2010.05634.x.
[111] M.J. Hansson, R. Månsson, S. Morota, H. Uchino, T. Kallur, T. Sumi, N. Ishii, M. Shimazu, M.F. Keep, A. Jegorov, E. Elmér, Calcium-induced generation of reactive oxygen species in brain mitochondria is mediated by permeability transition, Free Radic. Biol. Med 45 (2008) 284–294, https://doi.org/10.1016/j.freeradbiomed.2008.04.021.
[112] Y. Liu, Y. Ma, J. Xu, G. Zhang, X. Zhao, Z. He, L. Wang, N. Yin, M. Peng, VMP1 prevents Ca2+ overload in endoplasmic reticulum and maintains naive T cell survival, J. Exp. Med. 220 (2023), e20221068, https://doi.org/10.1084/jem.20221068.
[113] C. Fernandez-Sanz, M. Ruiz-Meana, E. Miro-Casas, E. Nuñez, J. Castellano, M. Loureiro, I. Barba, M. Poncelas, A. Rodriguez-Sinovas, J. Vázquez, D. Garcia-Dorado, Defective sarcoplasmic reticulum-mitochondria calcium exchange in aged mouse myocardium, Cell Death Dis. 5 (2014), e1573, https://doi.org/10.1038/cddis.2014.526.
[114] M.W. Mather, H. Rottenberg, The inhibition of calcium signaling in T lymphocytes from old mice results from enhanced activation of the mitochondrial permeability transition pore, Mech. Ageing Dev. 123 (2002) 707–724, https://doi.org/10.1016/s0047-6374(01)00416-x.
[115] N. Ron-Harel, G. Notarangelo, J.M. Ghergurovich, J.A. Paulo, P.T. Sage, D. Santos, F.K. Satterstrom, S.P. Gygi, J.D. Rabinowitz, A.H. Sharpe, M.C. Haigis, Defective respiration and one-carbon metabolism contribute to impaired naïve T cell activation in aged mice, Proc. Natl. Acad. Sci. Usa. 115 (2018) 13347–13352, https://doi.org/10.1073/pnas.1804149115.
[116] A. Ferree, O. Shirihai, Mitochondrial dynamics: the intersection of form and function, Adv. Exp. Med Biol. 748 (2012) 13–40, https://doi.org/10.1007/978-1-4614-3573-0_2.
[117] D. Sebastián, M. Palacín, A. Zorzano, Mitochondrial dynamics: coupling mitochondrial fitness with healthy aging, Trends Mol. Med 23 (2017) 201–215, https://doi.org/10.1016/j.molmed.2017.01.003.
[118] Y.J. Liu, R.L. McIntyre, G.E. Janssens, R.H. Houtkooper, Mitochondrial fission and fusion: a dynamic role in aging and potential target for age-related disease, Mech. Ageing Dev. 186 (2020), 111212, https://doi.org/10.1016/j.mad.2020.111212.
[119] E. Smirnova, L. Griparic, D.L. Shurland, A.M. van der Bliek, Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells, Mol. Biol. Cell 12 (2001) 2245–2256, https://doi.org/10.1091/mbc.12.8.2245.
[120] T. Yu, J.L. Robotham, Y. Yoon, Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology, Proc. Natl. Acad. Sci. USA 103 (2006) 2653–2658, https://doi.org/10.1073/pnas.0511154103.
[121] N. Taguchi, N. Ishihara, A. Jofuku, T. Oka, K. Mihara, Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission, J. Biol. Chem. 282 (2007) 11521–11529, https://doi.org/10.1074/jbc.M607279200.
[122] R.J. Youle, M. Karbowski, Mitochondrial fission in apoptosis, Nat. Rev. Mol. Cell Biol. 6 (2005) 657–663, https://doi.org/10.1038/nrm1697.
[123] G. Twig, A. Elorza, A.J.A. Molina, H. Mohamed, J.D. Wikstrom, G. Walzer, L. Stiles, S.E. Haigh, S. Katz, G. Las, J. Alroy, M. Wu, B.F. Py, J. Yuan, J.T. Deeney, B.E. Corkey, O.S. Shirihai, Fission and selective fusion govern mitochondrial segregation and elimination by autophagy, EMBO J. 27 (2008) 433–446, https://doi.org/10.1038/sj.emboj.7601963.
[124] S. Cipolat, O. Martins de Brito, B. Dal Zilio, L. Scorrano, OPA1 requires mitofusin 1 to promote mitochondrial fusion, Proc. Natl. Acad. Sci. USA 101 (2004) 15927–15932, https://doi.org/10.1073/pnas.0407043101.
[125] A. Sharma, H.J. Smith, P. Yao, W.B. Mair, Causal roles of mitochondrial dynamics in longevity and healthy aging, EMBO Rep. 20 (2019), e48395, https://doi.org/10.15252/embr.201948395.
[126] S. Cogliati, C. Frezza, M.E. Soriano, T. Varanita, R. Quintana-Cabrera, M. Corrado, S. Cipolat, V. Costa, A. Casarin, L.C. Gomes, E. Perales-Clemente, L. Salviati, P. Fernandez-Silva, J.A. Enriquez, L. Scorrano, Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency, Cell 155 (2013) 160–171, https://doi.org/10.1016/j.cell.2013.08.032.
[127] P. Mishra, V. Carelli, G. Manfredi, D.C. Chan, Proteolytic cleavage of Opa1 stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation, Cell Metab. 19 (2014) 630–641, https://doi.org/10.1016/j.cmet.2014.03.011.
[128] O.M. de Brito, L. Scorrano, Mitofusin 2 tethers endoplasmic reticulum to mitochondria, Nature 456 (2008) 605–610, https://doi.org/10.1038/nature07534.
[129] G. Zhao, K. Cao, C. Xu, A. Sun, W. Lu, Y. Zheng, H. Li, G. Hong, B. Wu, Q. Qiu, Z. Lu, Crosstalk between mitochondrial fission and oxidative stress in paraquat-induced apoptosis in mouse alveolar type II cells, Int J. Biol. Sci. 13 (2017) 888–900, https://doi.org/10.7150/ijbs.18468.
[130] I. Erchova, S. Sun, M. Votruba, A perspective on accelerated aging caused by the genetic deficiency of the metabolic protein, OPA1, Front Neurol. 12 (2021), 641259, https://doi.org/10.3389/fneur.2021.641259.
[131] S. Duvezin-Caubet, R. Jagasia, J. Wagener, S. Hofmann, A. Trifunovic, A. Hansson, A. Chomyn, M.F. Bauer, G. Attardi, N.-G. Larsson, W. Neupert, A. S. Reichert, Proteolytic processing of OPA1 links mitochondrial dysfunction to alterations in mitochondrial morphology, J. Biol. Chem. 281 (2006) 37972–37979, https://doi.org/10.1074/jbc.M606059200.
[132] M. Yi, D. Weaver, G. Hajnóczky, Control of mitochondrial motility and distribution by the calcium signal: a homeostatic circuit, J. Cell Biol. 167 (2004) 661–672, https://doi.org/10.1083/jcb.200406038.
[133] K.E. Miller, M.P. Sheetz, Axonal mitochondrial transport and potential are correlated, J. Cell Sci. 117 (2004) 2791–2804, https://doi.org/10.1242/jcs.01130.
[134] V. Debattisti, A.A. Gerencser, M. Saotome, S. Das, G. Hajnóczky, ROS control mitochondrial motility through p38 and the motor adaptor miro/trak, Cell Rep. 21 (2017) 1667–1680, https://doi.org/10.1016/j.celrep.2017.10.060.
[135] C. Schwindling, A. Quintana, E. Krause, M. Hoth, Mitochondria positioning controls local calcium influx in T cells, J. Immunol. 184 (2010) 184–190, https://doi.org/10.4049/jimmunol.0902872.
[136] F. Baixauli, N.B. Martín-Cófreces, G. Morlino, Y.R. Carrasco, C. Calabia-Linares, E. Veiga, J.M. Serrador, F. Sánchez-Madrid, The mitochondrial fission factor dynamin-related protein 1 modulates T-cell receptor signalling at the immune synapse, EMBO J. 30 (2011) 1238–1250, https://doi.org/10.1038/emboj.2011.25.
[137] S. Campello, R.A. Lacalle, M. Bettella, S. Mañes, L. Scorrano, A. Viola, Orchestration of lymphocyte chemotaxis by mitochondrial dynamics, J. Exp. Med 203 (2006) 2879–2886, https://doi.org/10.1084/jem.20061877.
[138] S. Campello, L. Scorrano, Mitochondrial shape changes: orchestrating cell pathophysiology, EMBO Rep. 11 (2010) 678–684, https://doi.org/10.1038/embor.2010.115.
[139] M.G. Marko, T. Ahmed, S.C. Bunnell, D. Wu, H. Chung, B.T. Huber, S.N. Meydani, Age-associated decline in effective immune synapse formation of CD4(+) T cells is

reversed by vitamin E supplementation, J. Immunol. 178 (2007) 1443–1449, https://doi.org/10.4049/jimmunol.178.3.1443.
[140] E. Beregi, J. Biró, O. Regius, Age-related morphological changes in lymphocytes as a model of aging, Mech. Ageing Dev. 14 (1980) 173–180, https://doi.org/10.1016/0047-6374(80)90116-5.
[141] M.D. Buck, D. O'Sullivan, R.I. Klein Geltink, J.D. Curtis, C.-H. Chang, D.E. Sanin, J. Qiu, O. Kretz, D. Braas, G.J.W. van der Windt, Q. Chen, S.C.-C. Huang, C. M. O'Neill, B.T. Edelson, E.J. Pearce, H. Sesaki, T.B. Huber, A.S. Rambold, E. L. Pearce, Mitochondrial dynamics controls T cell fate through metabolic programming, Cell 166 (2016) 63–76, https://doi.org/10.1016/j.cell.2016.05.035.
[142] L. Simula, Y. Antonucci, G. Scarpelli, V. Cancila, A. Colamatteo, S. Manni, B. De Angelis, C. Quintarelli, C. Procaccini, G. Matarese, C. Tripodo, S. Campello, PD-1-induced T cell exhaustion is controlled by a Drp1-dependent mechanism, Mol. Oncol. 16 (2022) 188–205, https://doi.org/10.1002/1878-0261.13103.
[143] L. Simula, I. Pacella, A. Colamatteo, C. Procaccini, V. Cancila, M. Bordi, C. Tregnago, M. Corrado, M. Pigazzi, V. Barnaba, C. Tripodo, G. Matarese, S. Piconese, S. Campello, Drp1 controls effective T cell immune-surveillance by regulating T cell migration, proliferation, and cMyc-dependent metabolic reprogramming, e10, Cell Rep. 25 (2018) 3059–3073, https://doi.org/10.1016/j.celrep.2018.11.018.
[144] R.C. Scarpulla, Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network, Biochim Biophys. Acta 2011 (1813) 1269–1278, https://doi.org/10.1016/j.bbamcr.2010.09.019.
[145] A. Picca, A.M.S. Lezza, Regulation of mitochondrial biogenesis through TFAM-mitochondrial DNA interactions: useful insights from aging and calorie restriction studies, Mitochondrion 25 (2015) 67–75, https://doi.org/10.1016/j.mito.2015.10.001.
[146] G. López-Lluch, P.M. Irusta, P. Navas, R. de Cabo, Mitochondrial biogenesis and healthy aging, Exp. Gerontol. 43 (2008) 813–819, https://doi.org/10.1016/j.exger.2008.06.014.
[147] H. Tan, K. Yang, Y. Li, T.I. Shaw, Y. Wang, D.B. Blanco, X. Wang, J.-H. Cho, H. Wang, S. Rankin, C. Guy, J. Peng, H. Chi, Integrative proteomics and phosphoproteomics profiling reveals dynamic signaling networks and bioenergetics pathways underlying T cell activation, Immunity 46 (2017) 488–503, https://doi.org/10.1016/j.immuni.2017.02.010.
[148] B. Bengsch, A.L. Johnson, M. Kurachi, P.M. Odorizzi, K.E. Pauken, J. Attanasio, E. Stelekati, L.M. McLane, M.A. Paley, G.M. Delgoffe, E.J. Wherry, Bioenergetic insufficiencies due to metabolic alterations regulated by the inhibitory receptor PD-1 are an early driver of CD8(+) T cell exhaustion, Immunity 45 (2016) 358–373, https://doi.org/10.1016/j.immuni.2016.07.008.
[149] E.L. Bishop, N. Gudgeon, S. Dimeloe, Control of T cell metabolism by cytokines and hormones, Front. Immunol. 12 (2021), 653605, https://doi.org/10.3389/fimmu.2021.653605.
[150] J. Böhme, N. Martinez, S. Li, A. Lee, M. Marzuki, A.M. Tizazu, D. Ackart, J. H. Frenkel, A. Todd, E. Lachmandas, J. Lum, F. Shihui, T.P. Ng, B. Lee, A. Larbi, M.G. Netea, R. Basaraba, R. van Crevel, E. Newell, H. Kornfeld, A. Singhal, Metformin enhances anti-mycobacterial responses by educating CD8+ T-cell immunometabolic circuits, Nat. Commun. 11 (2020) 5225, https://doi.org/10.1038/s41467-020-19095-z.
[151] A. Safdar, J.M. Bourgeois, D.I. Ogborn, J.P. Little, B.P. Hettinga, M. Akhtar, J. E. Thompson, S. Melov, N.J. Mocellin, G.C. Kujoth, T.A. Prolla, M.A. Tarnopolsky, Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice, Proc. Natl. Acad. Sci. USA 108 (2011) 4135–4140, https://doi.org/10.1073/pnas.1019581108.
[152] A. Martin-Montalvo, R. de Cabo, Mitochondrial metabolic reprogramming induced by calorie restriction, Antioxid. Redox Signal 19 (2013) 310–320, https://doi.org/10.1089/ars.2012.4866.
[153] T. Asami, K. Endo, R. Matsui, T. Sawa, Y. Tanaka, T. Saiki, N. Tanba, H. Haga, S. Tanaka, Long-term caloric restriction ameliorates T cell immunosenescence in mice, Mech. Ageing Dev. 206 (2022), 111710, https://doi.org/10.1016/j.mad.2022.111710.
[154] R.J. Simpson, T.W. Lowder, G. Spielmann, A.B. Bigley, E.C. LaVoy, H. Kunz, Exercise and the aging immune system, Ageing Res Rev. 11 (2012) 404–420, https://doi.org/10.1016/j.arr.2012.03.003.
[155] E. McDonnell, B.S. Peterson, H.M. Bomze, M.D. Hirschey, SIRT3 regulates progression and development of diseases of aging, Trends Endocrinol. Metab. 26 (2015) 486–492, https://doi.org/10.1016/j.tem.2015.06.001.
[156] C.D. Wiley, M.C. Velarde, P. Lecot, S. Liu, E.A. Sarnoski, A. Freund, K. Shirakawa, H.W. Lim, S.S. Davis, A. Ramanathan, A.A. Gerencser, E. Verdin, J. Campisi, Mitochondrial dysfunction induces senescence with a distinct secretory phenotype, Cell Metab. 23 (2016) 303–314, https://doi.org/10.1016/j.cmet.2015.11.011.
[157] J. Camacho-Pereira, M.G. Tarragó, C.C.S. Chini, V. Nin, C. Escande, G.M. Warner, A.S. Puranik, R.A. Schoon, J.M. Reid, A. Galina, E.N. Chini, CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism, Cell Metab. 23 (2016) 1127–1139, https://doi.org/10.1016/j.cmet.2016.05.006.
[158] G. Chen, G. Kroemer, O. Kepp, Mitophagy: an emerging role in aging and age-associated diseases, Front Cell Dev. Biol. 8 (2020) 200, https://doi.org/10.3389/fcell.2020.00200.
[159] H. Zhang, D.J. Puleston, A.K. Simon, Autophagy and immune senescence, Trends Mol. Med. 22 (2016) 671–686, https://doi.org/10.1016/j.molmed.2016.06.001.
[160] A. Tanaka, M.M. Cleland, S. Xu, D.P. Narendra, D.-F. Suen, M. Karbowski, R. J. Youle, Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin, J. Cell Biol. 191 (2010) 1367–1380, https://doi.org/10.1083/jcb.201007013.
[161] F. Macian, Autophagy in T cell function and aging, Front Cell Dev. Biol. 7 (2019) 213, https://doi.org/10.3389/fcell.2019.00213.
[162] L.A. Callender, E.C. Carroll, E.A. Bober, A.N. Akbar, E. Solito, S.M. Henson, Mitochondrial mass governs the extent of human T cell senescence, Aging Cell 19 (2020), https://doi.org/10.1111/acel.13067.
[163] J. Jin, X. Li, B. Hu, C. Kim, W. Cao, H. Zhang, C.M. Weyand, J.J. Goronzy, FOXO1 deficiency impairs proteostasis in aged T cells, Sci. Adv. 6 (2020) eaba1808, https://doi.org/10.1126/sciadv.aba1808.
[164] V.M. Hubbard, R. Valdor, B. Patel, R. Singh, A.M. Cuervo, F. Macian, Macroautophagy regulates energy metabolism during effector T cell activation, J. Immunol. 185 (2010) 7349–7357, https://doi.org/10.4049/jimmunol.1000576.
[165] L.M. Stephenson, B.C. Miller, A. Ng, J. Eisenberg, Z. Zhao, K. Cadwell, D. B. Graham, N.N. Mizushima, R. Xavier, H.W. Virgin, W. Swat, Identification of *Atg5* -dependent transcriptional changes and increases in mitochondrial mass in *Atg5* -deficient T lymphocytes, Autophagy 5 (2009) 625–635, https://doi.org/10.4161/auto.5.5.8133.
[166] C.R. Arnold, T. Pritz, S. Brunner, C. Knabb, W. Salvenmoser, B. Holzwarth, K. Thedieck, B. Grubeck-Loebenstein, T cell receptor-mediated activation is a potent inducer of macroautophagy in human CD8(+)CD28(+) T cells but not in CD8(+)CD28(-) T cells, Exp. Gerontol. 54 (2014) 75–83, https://doi.org/10.1016/j.exger.2014.01.018.
[167] Y. Botbol, B. Patel, F. Macian, Common γ-chain cytokine signaling is required for macroautophagy induction during CD4+ T-cell activation, Autophagy 11 (2015) 1864–1877, https://doi.org/10.1080/15548627.2015.1089374.
[168] A. Bartolomé, A. García-Aguilar, S.-I. Asahara, Y. Kido, C. Guillén, U.B. Pajvani, M. Benito, MTORC1 regulates both general autophagy and mitophagy induction after oxidative phosphorylation uncoupling, e00441-17, Mol. Cell Biol. 37 (2017), https://doi.org/10.1128/MCB.00441-17.
[169] T. Weichhart, mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review, Gerontology 64 (2018) 127–134, https://doi.org/10.1159/000484629.
[170] T. Imanishi, M. Unno, N. Yoneda, Y. Motomura, M. Mochizuki, T. Sasaki, M. Pasparakis, T. Saito, RIPK1 blocks T cell senescence mediated by RIPK3 and caspase-8, Sci. Adv. 9 (2023) eadd6097, https://doi.org/10.1126/sciadv.add6097.
[171] T. Eisenberg, H. Knauer, A. Schauer, S. Büttner, C. Ruckenstuhl, D. Carmona-Gutierrez, J. Ring, S. Schroeder, C. Magnes, L. Antonacci, H. Fussi, L. Deszcz, R. Hartl, E. Schraml, A. Criollo, E. Megalou, D. Weiskopf, P. Laun, G. Heeren, M. Breitenbach, B. Grubeck-Loebenstein, E. Herker, B. Fahrenkrog, K.-U. Fröhlich, F. Sinner, N. Tavernarakis, N. Minois, G. Kroemer, F. Madeo, Induction of autophagy by spermidine promotes longevity, Nat. Cell Biol. 11 (2009) 1305–1314, https://doi.org/10.1038/ncb1975.
[172] G. Alsaleh, I. Panse, L. Swadling, H. Zhang, F.C. Richter, A. Meyer, J. Lord, E. Barnes, P. Klenerman, C. Green, A.K. Simon, Autophagy in T cells from aged donors is maintained by spermidine and correlates with function and vaccine responses, Elife 9 (2020), e57950, https://doi.org/10.7554/eLife.57950.
[173] M. Al-Habsi, K. Chamoto, K. Matsumoto, N. Nomura, B. Zhang, Y. Sugiura, K. Sonomura, A. Maharani, Y. Nakajima, Y. Wu, Y. Nomura, R. Menzies, M. Tajima, K. Kitaoka, Y. Haku, S. Delghandi, K. Yurimoto, F. Matsuda, S. Iwata, T. Ogura, S. Fagarasan, T. Honjo, Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice, Science 378 (2022) eabj3510, https://doi.org/10.1126/science.abj3510.
[174] Y.-R. Yu, H. Imrichova, H. Wang, T. Chao, Z. Xiao, M. Gao, M. Rincon-Restrepo, F. Franco, R. Genolet, W.-C. Cheng, C. Jandus, G. Coukos, Y.-F. Jiang, J. W. Locasale, A. Zippelius, P.-S. Liu, L. Tang, C. Bock, N. Vannini, P.-C. Ho, Disturbed mitochondrial dynamics in CD8+ TILs reinforce T cell exhaustion, Nat. Immunol. 21 (2020) 1540–1551, https://doi.org/10.1038/s41590-020-0793-3.
[175] S. Vaena, P. Chakraborty, H.G. Lee, A.H. Janneh, M.F. Kassir, G. Beeson, Z. Hedley, A. Yalcinkaya, M.H. Sofi, H. Li, M.L. Husby, R.V. Stahelin, X.-Z. Yu, S. Mehrotra, B. Ogretmen, Aging-dependent mitochondrial dysfunction mediated by ceramide signaling inhibits antitumor T cell response, Cell Rep. 35 (2021), 109076, https://doi.org/10.1016/j.celrep.2021.109076.
[176] A.N. Akbar, M. Salmon, Cellular environments and apoptosis: tissue microenvironments control activated T-cell death, Immunol. Today 18 (1997) 72–76, https://doi.org/10.1016/s0167-5699(97)01003-7.
[177] J.D. McLeod, Apoptotic capability in ageing T cells, Mech. Ageing Dev. 121 (2000) 151–159, https://doi.org/10.1016/s0047-6374(00)00206-2.
[178] H. Li, H. Zhu, C.J. Xu, J. Yuan, Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis, Cell 94 (1998) 491–501, https://doi.org/10.1016/s0092-8674(00)81590-1.
[179] D. Green, G. Kroemer, The central executioners of apoptosis: caspases or mitochondria, Trends Cell Biol. 8 (1998) 267–271, https://doi.org/10.1016/s0962-8924(98)01273-2.
[180] M. Pollack, C. Leeuwenburgh, Apoptosis and aging: role of the mitochondria, J. Gerontol. A Biol. Sci. Med Sci. 56 (2001) B475–B482, https://doi.org/10.1093/gerona/56.11.b475.
[181] E. Daugas, S.A. Susin, N. Zamzami, K.F. Ferri, T. Irinopoulou, N. Larochette, M. Prévost, B. Leber, D. Andrews, J. Penninger, G. Kroemer, Mitochondrio-nuclear translocation of AIF in apoptosis and necrosis, FASEB J. 14 (2000) 729–739, https://doi.org/10.1096/fasebj.14.5.729.
[182] S.B. Prabhu, J.K. Khalsa, H. Banerjee, A. Das, S. Srivastava, H.R. Mattoo, K. Thyagarajan, S. Tanwar, D.S. Das, S.S. Majumdar, A. George, V. Bal, J.

M. Durdik, S. Rath, Role of apoptosis-inducing factor (Aif) in the T cell lineage, Indian J. Med. Res. 138 (2013) 577.
[183] T.V. Zhao, Y. Sato, J.J. Goronzy, C.M. Weyand, T-cell aging-associated phenotypes in autoimmune disease, Front Aging 3 (2022), 867950, https://doi.org/10.3389/fragi.2022.867950.
[184] S. Marchi, E. Guilbaud, S.W.G. Tait, T. Yamazaki, L. Galluzzi, Mitochondrial control of inflammation, Nat. Rev. Immunol. 23 (2023) 159–173, https://doi.org/10.1038/s41577-022-00760-x.
[185] C.C.S. Chini, T.R. Peclat, G.M. Warner, S. Kashyap, J.M. Espindola-Netto, G.C. De Oliveira, L.S. Gomez, K.A. Hogan, M.G. Tarragó, A.S. Puranik, G. Agorrody, K. L. Thompson, K. Dang, S. Clarke, B.G. Childs, K.S. Kanamori, M.A. Witte, P. Vidal, A.L. Kirkland, M. De Cecco, K. Chellappa, M.R. McReynolds, C. Jankowski, T. Tchkonia, J.L. Kirkland, J.M. Sedivy, J.M. Van Deursen, D.J. Baker, W. Van Schooten, J.D. Rabinowitz, J.A. Baur, E.N. Chini, CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD+ and NMN levels, Nat. Metab. 2 (2020) 1284–1304, https://doi.org/10.1038/s42255-020-00298-z.
[186] A.J. Covarrubias, R. Perrone, A. Grozio, E. Verdin, NAD+ metabolism and its roles in cellular processes during ageing, Nat. Rev. Mol. Cell Biol. 22 (2021) 119–141, https://doi.org/10.1038/s41580-020-00313-x.
[187] E. Zlotorynski, Defective mitochondria ignite the SASP, 179–179, Nat. Rev. Mol. Cell Biol. 21 (2020), https://doi.org/10.1038/s41580-020-0228-x.
[188] R.B. Nisr, D.S. Shah, I.G. Ganley, H.S. Hundal, Proinflammatory NFkB signalling promotes mitochondrial dysfunction in skeletal muscle in response to cellular fuel overloading, Cell. Mol. Life Sci. 76 (2019) 4887–4904, https://doi.org/10.1007/s00018-019-03148-8.
[189] B.C. Albensi, What is nuclear factor Kappa B (NF-κB) doing in and to the mitochondrion, Front. Cell Dev. Biol. 7 (2019) 154, https://doi.org/10.3389/fcell.2019.00154.
[190] F. Valença-Pereira, Q. Fang, I.J. Marié, E.L. Giddings, K.A. Fortner, R. Yang, A. V. Villarino, Y.H. Huang, D.A. Frank, H. Wen, D.E. Levy, M. Rincon, IL-6 enhances CD4 cell motility by sustaining mitochondrial Ca $^{2+}$ through the noncanonical STAT3 pathway, Proc. Natl. Acad. Sci. U. S. A. 118 (2021), e2103444118, https://doi.org/10.1073/pnas.2103444118.
[191] R. Yang, D. Lirussi, T.M. Thornton, D.M. Jelley-Gibbs, S.A. Diehl, L.K. Case, M. Madesh, D.J. Taatjes, C. Teuscher, L. Haynes, M. Rincón, Mitochondrial Ca2+ and membrane potential, an alternative pathway for Interleukin 6 to regulate CD4 cell effector function, ELife 4 (2015), e06376, https://doi.org/10.7554/eLife.06376.
[192] J.M. Mazet, J.N. Mahale, O. Tong, R.A. Watson, A.V. Lechuga-Vieco, G. Pirgova, V.W.C. Lau, M. Attar, L.A. Koneva, S.N. Sansom, B.P. Fairfax, A. Gérard, IFNγ signaling in cytotoxic T cells restricts anti-tumor responses by inhibiting the maintenance and diversity of intra-tumoral stem-like T cells, Nat. Commun. 14 (2023) 321, https://doi.org/10.1038/s41467-023-35948-9.
[193] Q. Zhang, M. Raoof, Y. Chen, Y. Sumi, T. Sursal, W. Junger, K. Brohi, K. Itagaki, C. J. Hauser, Circulating mitochondrial DAMPs cause inflammatory responses to injury, Nature 464 (2010) 104–107, https://doi.org/10.1038/nature08780.
[194] C. Franceschi, P. Garagnani, G. Vitale, M. Capri, S. Salvioli, Inflammaging and 'Garb-aging,', Trends Endocrinol. Metab. 28 (2017) 199–212, https://doi.org/10.1016/j.tem.2016.09.005.
[195] M. Pinti, E. Cevenini, M. Nasi, S. De Biasi, S. Salvioli, D. Monti, S. Benatti, L. Gibellini, R. Cotichini, M.A. Stazi, T. Trenti, C. Franceschi, A. Cossarizza, Circulating mitochondrial DNA increases with age and is a familiar trait: implications for "inflamm-aging, Eur. J. Immunol. 44 (2014) 1552–1562, https://doi.org/10.1002/eji.201343921.
[196] C.D. Johnston, E.L. Siegler, M.C. Rice, H.M. Derry-Vick, K.C. Hootman, Y.-S. Zhu, C.O. Burchett, M.E. Choi, M.J. Glesby, Plasma cell-free mitochondrial DNA as a marker of geriatric syndromes in older adults with HIV, J. Acquir Immune Defic. Syndr. 90 (2022) 456–462, https://doi.org/10.1097/QAI.0000000000002993.
[197] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, A. Santoro, Inflammaging: a new immune-metabolic viewpoint for age-related diseases, Nat. Rev. Endocrinol. 14 (2018) 576–590, https://doi.org/10.1038/s41574-018-0059-4.
[198] Z. Sun, V. Hornung, cGAS–STING signaling, Curr. Biol. 32 (2022) R730–R734, https://doi.org/10.1016/j.cub.2022.05.027.
[199] W. Li, L. Lu, J. Lu, X. Wang, C. Yang, J. Jin, L. Wu, X. Hong, F. Li, D. Cao, Y. Yang, M. Wu, B. Su, J. Cheng, X. Yang, W. Di, L. Deng, cGAS-STING–mediated DNA sensing maintains CD8 $^{+}$ T cell stemness and promotes antitumor T cell therapy, Sci. Transl. Med. 12 (2020) eaay9013, https://doi.org/10.1126/scitranslmed.aay9013.
[200] C.S. Field, F. Baixauli, R.L. Kyle, D.J. Puleston, A.M. Cameron, D.E. Sanin, K. L. Hippen, M. Loschi, G. Thangavelu, M. Corrado, J. Edwards-Hicks, K.M. Grzes, E.J. Pearce, B.R. Blazar, E.L. Pearce, Mitochondrial Integrity Regulated by Lipid Metabolism Is a Cell-Intrinsic Checkpoint for Treg Suppressive Function, e5, Cell Metab. 31 (2020) 422–437, https://doi.org/10.1016/j.cmet.2019.11.021.
[201] B. Andrade, C. Jara-Gutiérrez, M. Paz-Araos, M.C. Vázquez, P. Díaz, P. Murgas, The relationship between reactive oxygen species and the cGAS/STING signaling pathway in the inflammaging process, IJMS 23 (2022) 15182, https://doi.org/10.3390/ijms232315182.
[202] N. Kuhl, A. Linder, N. Philipp, D. Nixdorf, H. Fischer, S. Veth, G. Kuut, T.T. Xu, S. Theurich, T. Carell, M. Subklewe, V. Hornung, STING agonism turns human T cells into interferon-producing cells but impedes their functionality, EMBO Rep. 24 (2023), https://doi.org/10.15252/embr.202255536.
[203] I. Benoit-Lizon, E. Jacquin, T. Rivera Vargas, C. Richard, A. Roussey, L. Dal Zuffo, T. Martin, A. Melis, D. Vinokurova, S.H. Shahoei, A. Baeza Garcia, C. Pignol, S. Giorgiutti, R. Carapito, R. Boidot, F. Végran, R.A. Flavell, B. Ryffel, E.R. Nelson, P. Soulas-Sprauel, T. Lawrence, L. Apetoh, CD4 T cell-intrinsic STING signaling controls the differentiation and effector functions of T $_{H}$ 1 and T $_{H}$ 9 cells, J. Immunother. Cancer 10 (2022), e003459, https://doi.org/10.1136/jitc-2021-003459.
[204] A. Linder, V. Hornung, Inflammasomes in T cells, J. Mol. Biol. 434 (2022), 167275, https://doi.org/10.1016/j.jmb.2021.167275.
[205] S.S. Iyer, Q. He, J.R. Janczy, E.I. Elliott, Z. Zhong, A.K. Olivier, J.J. Sadler, V. Knepper-Adrian, R. Han, L. Qiao, S.C. Eisenbarth, W.M. Nauseef, S.L. Cassel, F. S. Sutterwala, Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation, Immunity 39 (2013) 311–323, https://doi.org/10.1016/j.immuni.2013.08.001.
[206] M. Corrado, J. Edwards-Hicks, M. Villa, L.J. Flachsmann, D.E. Sanin, M. Jacobs, F. Baixauli, M. Stanczak, E. Anderson, M. Azuma, A. Quintana, J.D. Curtis, T. Clapes, K.M. Grzes, A.M. Kabat, R. Kyle, A.E. Patterson, R.K. Geltink, B. Amulic, C.G. Steward, D. Strathdee, E. Trompouki, D. O'Sullivan, E.J. Pearce, E.L. Pearce, Dynamic cardiolipin synthesis is required for CD8+ T cell immunity, e7, Cell Metab. 32 (2020) 981–995, https://doi.org/10.1016/j.cmet.2020.11.003.
[207] E. Varfolomeev, J.W. Blankenship, S.M. Wayson, A.V. Fedorova, N. Kayagaki, P. Garg, K. Zobel, J.N. Dynek, L.O. Elliott, H.J.A. Wallweber, J.A. Flygare, W. J. Fairbrother, K. Deshayes, V.M. Dixit, D. Vucic, IAP antagonists induce autoubiquitination of c-IAPs, NF-κB activation, and TNFα-dependent apoptosis, Cell 131 (2007) 669–681, https://doi.org/10.1016/j.cell.2007.10.030.
[208] J. Rizk, J. Kaplinsky, R. Agerholm, D. Kadekar, F. Ivars, W.W. Agace, W.W.-L. Wong, M.J. Szucs, S.A. Myers, S.A. Carr, A. Waisman, V. Bekiaris, SMAC mimetics promote NIK-dependent inhibition of CD4 $^{+}$ T $_{H}$ 17 cell differentiation, Sci. Signal. 12 (2019) eaaw3469, https://doi.org/10.1126/scisignal.aaw3469.
[209] G. Soto-Heredero, M.M. Gómez De Las Heras, J.I. Escrig-Larena, M. Mittelbrunn, Extremely differentiated T cell subsets contribute to tissue deterioration during aging, Annu. Rev. Immunol. 41 (2023) 181–205, https://doi.org/10.1146/annurev-immunol-101721-064501.