

REVIEW

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MITOGENESIS, MITOPHAGY AND REGULATION OF MITOCHONDRIAL METABOLISM IN HEALTH AND DISEASE

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The state of mitochondrial homeostasis, comprising the processes of mitochondrial biogenesis, selective removal of damaged or dysfunctional mitochondria, mitochondrial dynamics (fusion and fission), as well as signaling systems of mitochondrial metabolism regulation are analyzed in this review. Particular attention is paid to how the bioenergetic demands of tissues are modulated in viral SARS-CoV, hepatitis B & C infections and asthma.

Keywords: mitochondrial homeostasis, mitogenesis, mitophagy, fusion and fission, metabolism, SARS-CoV-2, hepatitis.

Mitochondria are the primary bioenergetic organelles of cellular metabolism and their function underlies much of the metabolic activity throughout the organism. While their roles in oxidative phosphorylation (OXPHOS), the tricarboxylic acid (TCA) cycle, electron transport chain (ETC), production of reactive oxygen species (ROS) and oxidative or age-related damage are most widely understood, they also hold diverse roles as constituent components of the innate immune system. This review first approaches the role of mitochondrial homeostasis as a central feature of the physiologic mitochondrial compartment – the continuously fusing and fissioning mitochondrial component of the cell – before explaining mechanisms of mitochondrial biogenesis and autophagy. After detailing the regulatory mechanisms that control this process, these topics are explored in the context of specific diseases including SARS-CoV-2 infection, chronic viral hepatitis and asthmatic and obstructive patterns of pulmonary change.

The physiologic mitochondrion

Mitochondrial homeostasis and the mitochondrial compartment. The physiological state of the mitochondrial compartment of the cell is one of flux.

Mitochondrial morphology is heterogeneous and depends on the phenotype and function of the tissue, ranging from dense reticular networks in cells with high OXPHOS requirements to more discrete, small, separated organelles in tissues dependent on anaerobic glycolysis [1, 2]. It is a dynamic process whereby mitochondria continuously undergo fusion and fission, configuration being controlled by cellular and extracellular factors, and it is essential to the normal function of the cell [3].

Fission protein 1 (Fis1) acting in conjunction with dynamin related peptide 1 (Drp1) are the primary fission regulating peptides of the outer membrane. While Fis1 is an outer membrane protein, Drp1 is a cytosolic peptide recruited to the outer mitochondrial membrane [4-7]. Excessive Drp1 activation has been implicated in autosomal recessive juvenile Parkinsonism, which results from failure of mitochondrial fission processes and impaired mitophagy [8, 9]. Fusion is controlled mainly by GTPases mitofusin 1 and 2 (Mfn1, Mfn2) in the outer membrane and optic atrophy protein 1 (Opa1, also known as Mgm1) in the inner membrane. Their dysfunction has been implicated in diseases such as dominant optic atrophy [10] and Charcot-Marie-Tooth 2A [11].

Mitochondrial fusion and the prevention of excessive sized organelles is controlled by “flickering”, a momentary series of depolarisations of the mitochondrial membrane. Flickering activates Oma1, an inner membrane protease which deactivates Opa1. Flickering itself is regulated by superoxide dismutase 1 and cytochrome c oxidase, both of which are copper dependent and rely on Cu^{2+} and phosphate transporter Slc25a3 [12]. Morphologically, failure of fusion proteins results in fragmentation of the mitochondrial compartment and disorder of the cellular OXPHOS system [13-15]. Cells requiring a highly energy-dense profile display a rich, closely spaced reticular mitochondrial network that provides a key highway for metabolite and waste transport while allowing continued traffic of mitochondrial proteins that are encoded by nuclear genomes [16]. Mitochondrial homeostasis is ultimately controlled by two distinct and opposing processes – mitochondrial biogenesis (mitogenesis) and autophagy of defective mitochondria (mitophagy).

Mitogenesis. Mitochondrial biogenesis is a complex process requiring extensive crosstalk between nuclear and mitochondrial apparatus. The mitochondrial genome consists of around 16.5 thousand base pairs. 13 peptides are transcribed from mitochondrial DNA (mtDNA) and produced within the mitochondria: 7 of the 45 ETC complex I components, 1 component of the 11 comprising ETC complex III, 3 of the 13 comprising ETC complex

IV and 2 of the 18 required for ETC complex V. A further 22 tRNA and 2 mitochondrial ribosomal RNA genes are also present, without which mitochondrial protein transcription and translation could not take place [17]. The several thousand other components required to produce functioning mitochondria are derived from nuclear-encoded proteins which must be transcribed, translated, processed, and transported into the mitochondria.

mtDNA is housed within protein nucleoids consisting of high mobility group (HMG) proteins, particularly mitochondrial transcription factor A (TFAM). These proteins assist in structural stability, replication and transcription and are essential to mitochondrial biogenesis [18, 19]. This is conducted by a mtDNA replication apparatus which, while described in the literature, is nevertheless poorly understood. mtDNA polymerase (Poly) is a nuclear encoded protein composed of two subunits, encoded by genes POLG (held at locus 15q25) and POLG2 (held at locus 17q24.1). The process of mtDNA transcription is highly conserved in eukaryotes and is upregulated when cellular OXPHOS demands are increased. Pol γ acts with Twinkle (the mtDNA helicase) and mitochondrial single stranded DNA binding protein (mtSSB) to initiate mtDNA replication [20, 21]. Failure of Pol γ results in a variety of monogenic hereditary and sporadic disorders including microcerebrohepatopathy, Alpers-Huttenlocher syndrome (a triad of neurodevelopmental re-

List of Abbreviations: **ACBP** – Acyl-CoA binding protein; **AH** – Alcoholic hepatitis; **AMPK** – AMP-protein kinase; **ATG** – Autophagy-related; **BNip3** – Bcl-2 interacting protein 3; **CD36** – Cluster of differentiation 36 (also known as FAT/FATP – Fatty acid translocase/transport protein); **cGAS** – Cyclic GMP-AMP synthase; **COPD** – Chronic obstructive pulmonary disease; **DAMPs** – Damage associated molecular patterns; **Drp1** – Dynamin-related protein 1; **ETC** – Electron transport chain; **FAT/FATP** – Fatty acid translocase/transport protein (also known as CD36); **Fis1** – Fission protein 1; **FKBP8** – FK506 binding protein 8; **Glut4** – Glucose transporter 4; **GR** – Glucocorticoid receptor; **HCV** – Hepatitis C virus; **HIF-1 α** – Hypoxia inducible factor 1 alpha; **HMG** – High mobility group; **HBV** – Hepatitis B Virus; **IKK ϵ** – Inhibitor of NF κ B kinase epsilon; **IL** – Interleukin; **IRFs** – Interferon regulatory factors; **IRS** – Insulin receptor substrate; **Keap1** – Kelch-like ECH-associated protein 1; **LC3** – Microtubule-associated protein 1A/1B-light chain 3; **LPL** – Lipoprotein lipase; **MAVS** – Mitochondrial antiviral signalling protein; **MDA5** – Melanoma differentiation associated protein 5; **Mfn1/Mfn2** – Mitofusin 1/mitofusin 2; **mtDNA** – Mitochondrial DNA; **mtSSB** – Mitochondrial single-stranded DNA binding protein; **mTOR** – Mammalian target of rapamycin; **NF κ B** – Nuclear factor kappa-light-chain-enhancer of activated B cells; **NLRs** – Nucleotide-binding oligomerisation domain-like receptors; **NRF2** – Nuclear respiratory factor 2; **OXPHOS** – Oxidative phosphorylation; **PINK1** – PTEN Induced kinase 1; **PON2** – Paraoxonase-2; **PPAR** – Peroxisome proliferator-activated receptor; **PRRs** – Pattern recognition receptors; **RIG-I** – Retinoic acid inducible gene I; **ROS** – Reactive oxygen species; **RXR** – Retinoid X receptor; **SARS-CoV** – Severe acute respiratory syndrome coronavirus; **SNARE** – Soluble NSF attachment protein receptor; **SQSTM1** – Sequestrome-1 (also known as p62); **TBK1** – TANK-binding kinase 1; **TCA** – Tricarboxylic acid; **TFAM** – Mitochondrial transcription factor A; **TLR** – Toll-like receptor; **TOM** – Translocase of outer membrane; **TSC1/TSC2** – Tuberous sclerosis complex 1/tuberous sclerosis complex 2; **UCP** – Uncoupling protein; **UPR** – Unfolded protein response; **VDAC1** – Voltage dependent anion channel 1.

gression, seizures and liver failure) and progressive external ophthalmoplegia. Characteristic molecular features of these diseases include multiple mtDNA deletions, cytochrome c deficiency within muscle fibres and gross depletion of mtDNA throughout the body [22,23]. Germline failure of mtSSB is lethal in utero while localised inactivation in myocardial tissue results in cardiomyopathy in murine models [21].

Mitophagy. Mitophagy is the autophagic process by which mitochondria are degraded and recycled into their component parts. When mitochondria malfunction, damage associated molecular patterns (DAMPs) such as mtDNA and ROS are produced. Recognised by a host of pattern recognition receptors (PRRs), defective mitochondria are then selectively sequestered for disposal via lysosomal degradation [24].

Phosphatase and tensin homolog (PTEN) induced kinase 1 (PINK1) – Parkin interaction constitutes the classic mitophagy pathway. PINK1 is a serine/threonine kinase containing mitochondrial targeting sequence, bearing mitochondrial membrane side and a cytoplasmic facing kinase [25], and it is activated by depolarisation of the mitochondrial membrane [26, 27]. Parkin (so named for its aetiological role in the pathogenesis of several variants of autosomal recessive hereditary Parkinson disease [8, 9]) is a cytosolic E3 ubiquitin ligase which locates to the mitochondrial membrane when activated by PINK1. Activated Parkin chain-ubiquitylates N-terminally fused lysine residues on voltage dependent anion channel 1 (VDAC1) [25, 26], along with Mfn1 and Mfn2 [25, 28, 29], resulting in the recruitment

of autophagic adaptor protein p62 (also referred to as sequestome-1 or SQSTM1). p62 is the link between the ubiquitylation pathway proteins PINK1-Parkin and the autophagy related (ATG) proteins subsequently responsible for vesicle interactions and lysosomal envelopment of the organelle. p62 interacts with ATG8 homologues LC3 and B of the phagophore vesicle complex [30], allowing the defective organelle to be enveloped by the expanding phagophore membrane. At this point, activation of ATG9a allows fusion of the phagophore with the lysosome via SNARE-SNARE protein interaction [31], resulting in the introduction of proteolytic enzymes and organelle degradation within the autolysosome [32], as described in Fig. 1.

Parkin independent mitophagy is less well explored and appears to function via proteins involved in physiologic mitochondrial dynamics. Parkin knockout cells with defective mitochondria produce mitophagy by PINK1 interaction with Drp1, resulting in fracture of the outer mitochondrial membrane and chain-ubiquitylation of the inner membrane [33]. In Drp1 and Opa1 knockout (“mitochondrial stasis”) hepatocytes, p62 recruits cullin-RING scaffold protein associated ubiquitin ligases Keap1 and Rbx1, allowing an alternative PINK1-Parkin independent method of ubiquitylation [34]. An alternative method has been demonstrated in hypoxic cells. BNip3 and Nix (members of the Bcl-2 pro-apoptotic protein family [35]) prevent hypoxia inducible factor 1 α (HIF-1 α) stabilisation, resulting in the degradation of Mfn1, Mfn2 and translocase of outer membrane protein 20 (TOM20). This prevents fusion,

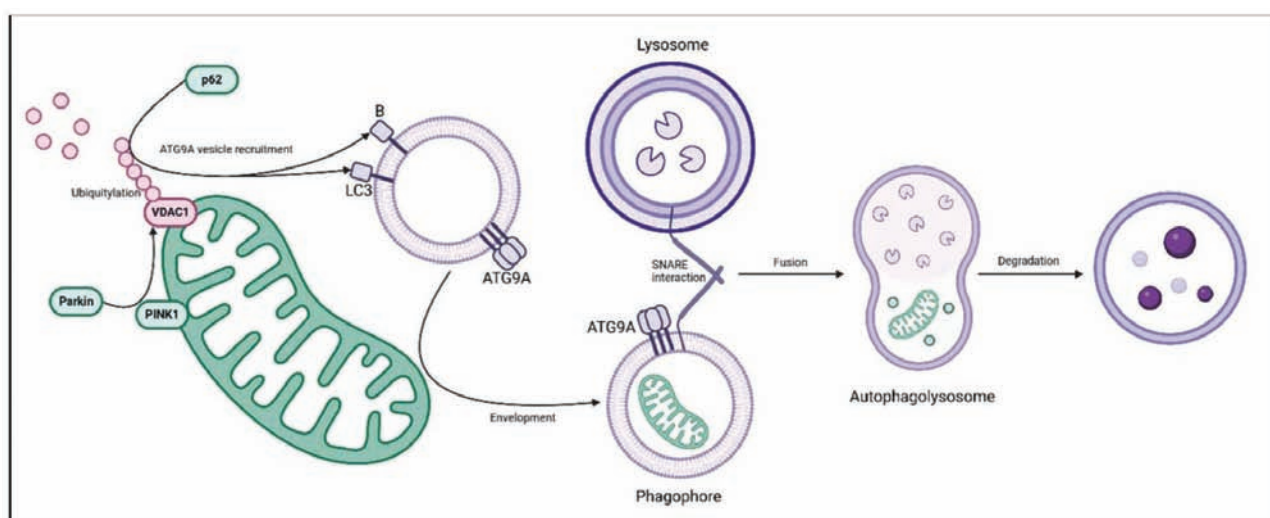


Fig. 1. The PINK1-Parkin Pathway (created in BioRender.com)

continued use of damaged organelle segments and failure of mitochondrial membrane integrity [36]. It remains to be seen whether Parkin independent mitophagy pathways occur concurrently to classic PINK1-Parkin autophagy or are truly independent of it and only occur when components are defective.

Cation signalling in mitochondrial homeostasis. Mitochondria are core components of cellular signalling apparatus and the biophysical properties of their membrane ion channels provides a key component of cellular homeostasis. A full review of calcium signalling within oxidative phosphorylation and mitochondrial homeostasis is beyond the scope of this article, yet research developments have shown that the cation signalling remains the ultimate means of fine control of energy production. Owing to the large free energy within cellular Ca^{2+} ion gradients, calcium concentration is a highly sensitive measure of the available free energy of the cell and calcium signalling allows for a precise and elegant means of controlling ATP production. The dominant method of calcium entry is via the mitochondrial calcium uniporter, a low affinity transporter situated in proximity to endoplasmic reticular networks allowing influx of ions to the organelle [37]. Calcium overload results in cessation of the electron transport chain, generation of ROS, depolarisation of the inner mitochondrial membrane and activation of apoptosis [38].

Ca^{2+} regulated mitochondrial carriers (CaMC) are the primary means of transduction for Ca^{2+} signalling transduction to mitochondria. These proteins are subdivided by the length of their N-terminal regulatory domain into long-CaMCs and short-CaMCs, and they control the entry of solutes that pass through the inner mitochondrial membrane in response to extracellular and cytosolic calcium signalling [39]. Within the mitochondrial compartment, calcium signalling controls every stage of oxidative phosphorylation. The production of acetyl-CoA from pyruvate is carried out by the pyruvate dehydrogenase complex. Calcium-dependent dephosphorylation of the complex by PDH phosphatase activates pyruvate dehydrogenase, resulting in conversion to acetyl-CoA. Within the TCA cycle, meanwhile, isocitrate dehydrogenase and α -ketoglutarate dehydrogenase have calcium sensitive motifs which, on binding, reduce the K_m of the enzyme complex for their substrates, increasing TCA flux under conditions of high calcium balance [40]. Studies have also found Complex III and V of the ETC are sensitive to Ca has signalling [41]. In this way, cellular stress in the form of increased calcium balance regulates the

entry of substrates to the TCA cycle, the throughput of TCA cycle metabolites and the output of ATP from the ETC.

A wide array of mitochondrial potassium channels have been discovered in every corner of eukaryotes, a number of which are tissue specific. Their primary function is the control of organelle membrane potential, and as such they are both calcium and voltage dependent. In essence, the low cellular energy levels result in reduced calcium effect on potassium channels, depolarisation of the organelle and initiation of apoptosis [37].

Regulation of Dynamics & Metabolism

The PPAR-PGC-1 axis. Nuclear transcription factors peroxisome proliferator-activated receptors (PPARs) hold a central role in determining the metabolic profile of cells and tissues. PPAR isoforms have heterogenous expression throughout the organism, their different localisation allowing fine control of the metabolic needs of the tissue [42]. Activated PPAR γ and PPAR β stimulate nuclear transcription of OXPHOS proteins and ETC subunits, along with stimulating mitochondrial transcription of mtDNA encoded genes [43]. Nuclear stimulators of PPAR γ include thyroid hormone T3 [44-46], prostaglandin J2 [42], long chain fatty acids [47] and thiazolidinedione pharmaceuticals such as rosiglitazone [48]. Within the nucleus PPARs exist as a heterodimer bound to retinoid X receptor which, on ligand activation, binds PPAR-responsive regulatory elements within the genome activating transcription [49]. With regards to PPAR γ (and to a certain extent PPAR α [50]), this includes fatty acid binding protein 2, acyl-CoA binding protein, lipoprotein lipase, fatty acid translocase/transport protein (also known as cluster of differentiation 36), acyl-CoA synthetase, glycerol kinase, insulin receptor substates 1 and 2 and glucose transporter 4. The net result of this is increased mobilisation of fats and fatty acids, their import to the cell, processing into usable metabolites and eventually, oxidative phosphorylation [42]. Acting via a similar mechanism, PPAR δ acts in skeletal muscle to upregulate cytochrome c, uncoupling proteins 2 and 3 (UCP2 and UCP3) [51] along with TCA cycle proteins succinate dehydrogenase and citrate synthase, resulting in a shift towards muscle fibres with higher OXPHOS potential [52].

PPAR isoforms act with PPAR γ coactivator 1 (PGC-1) to provide upregulation of diverse mitochondrial functions. In brown fat tissue, this is

most prominently the upregulation of uncoupling protein 1 (UCP1), essential for thermogenesis [53]. While PPARs act mainly to induce transcription of proteins responsible for lipid metabolism, the TCA cycle and OXPHOS components, PGC-1 is the primary nuclear stimulator of mitogenesis, ultimately marshalling over 1100 nuclear genes via several downstream transcription factors [54-56]. Well studied targets of the PPAR γ -PGC1 axis include nuclear respiratory factor 2, which activates TFAM to upregulate mtDNA replication and transcription [57], and UCP2 and paraoxonase-2, which allow enhanced action to mitigate the production of reactive oxygen species produced within mitochondria [56].

The role of AMPK, Sirtuins and mTOR. The major link element between lipid metabolism, TCA proteins, mitogenesis and mitophagy are NAD-dependent deacylase sirtuin proteins, themselves activated by AMP-protein kinase (AMPK) and mammalian target of rapamycin (mTOR). These pathways are highly conserved from single celled eukaryotes to mammals and have a complex role in the integration of nutrient sensing, metabolic demands and cell stress or damage, and their outcomes converge on mitophagy, mitogenesis and cell proliferative processes.

AMPK is activated when the AMP/ATP ratio increases within the cell, indicating low balance of ready-use energy. AMPK is a major stimulator of mitochondrial morphological change, mitophagy and mitogenesis and it is through this mechanism that cells with low energy balance, increased ROS and stress act to repair and replace defective components of the mitochondrial compartment [58].

Sirtuins are responsible for deacylation of histone proteins and are heavily linked to ageing processes. Of the seven sirtuin homologues known in mammalian cells, Sirt2 has been best studied for its role in longevity and is primarily localised within the nucleolus where it promotes genome stability in mitotically active cells [59, 60]. Genome sequencing of Sirt3, 4 and 5 appear to show mitochondrial targeting signals and confocal laser scanning microscopy of proteins tagged with MitoTracker red show localisation within the mitochondrial compartment [61, 62]. Sirt3 translocates to the mitochondrial compartment from the nucleus at times of cellular stress, such as when DNA damage occurs [63]. Deacylation targets of Sirt1, Sirt3 and Sirt5 include PGC-1 α in the nucleus [64] and BNip3 [65], Opa1 [66] and Parkin [67] in the mitochondria, while AMPK

also activates PINK1 and Fis1 [68]. PINK1 and the PINK1-Parkin pathway appear to play an important role in mediating mitochondrial flux – overexpression of PINK1 results in increased Drp1 activation and fragmentation of mitochondrial compartment while underexpression of PINK1 results in excessive fusion [69].

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase complex which in its active state stimulates ribosome biogenesis, protein synthesis and metabolism via the IRS-PI3K pathway, while inhibiting mitophagy. It is a major regulator of cellular growth and anabolism and, via interaction with a number of signalling pathways, responds to insulin stimulation and cellular energy levels [70]. mTOR signalling has been well documented owing to interaction with apoptotic apparatus via the PI3K/Akt/mTOR signalling cascade [71]. With regards to mitophagy, mTOR acts via the phosphorylation of tuberous sclerosis complex 2 (TSC2), maintained within endoplasmic reticular linkages to mitochondria, to negatively interact with FKBP8 binding protein 8 (FKBP8), which when active initiates LC3 vesicle-dependent autophagy [72]. In nutrient starvation, AMPK inactivates mTOR, allowing unopposed FKBP8 action, upregulating mitophagy [73]. Previously assumed to be separate processes, significant crosstalk exists between the PI3K/Akt/mTOR cascade and the unfolded protein response (UPR), which mediates metabolic and apoptotic response to endoplasmic reticular stress. Collectively, mTOR and the UPR provide the integration pathways to balance organismal metabolic requirements with nutrient availability. Unfavourable growth conditions or hypoxia produce UPR activation and mTOR inactivation, upregulating mitophagy, reducing the OXPHOS requirements of the cell, and balancing the metabolic requirements of the tissue with the nutrients available [74].

Direct action via mitochondrial receptors. Direct regulatory action on mitochondria is established in the literature, although poorly understood, and there remains much scope for future research. In macrophages, glucocorticoid action causes increased polarisation of the mitochondrial membrane, import of TCA cycle metabolites and upregulation of mitochondrial biogenesis [75]. Steroid and thyroid hormone receptors are found within the mitochondrial matrix, all nuclear encoded yet allowing for direct endocrine action within the mitochondria. Two major mitochondrial isoforms of the glucocorticoid

receptor (GR), GR α and GR β have been detected, two isoforms of the oestrogen receptor (ER), ER α and ER β along with two isoforms of the thyroid receptor c-erbA α and c-erbA β (Fig. 2) [76, 77].

New studies indicate that on ligand binding, cytoplasmic glucocorticoid receptors interact with pyruvate dehydrogenase complex proteins and translocate to within the mitochondrial compartment of the cell, where they upregulate TCA cycle activity [75]. It was noted in 1977 that isolated rat mitochondria respond to thyroid hormone T3 stimulation with increased OXPHOS activity [78] and the presence of matrix receptors for these hormones explains this finding. In addition to acting on nuclear transcription factors, T3 and steroid hormone administration results in increased mitochondrial genome expression by acting on c-erbA receptors to activate TFAM, increasing transcription of mitochondrial protein subunits [44].

Mitochondria – a component of the innate immune system

Inflammatory cytokine production. Dynamic morphological change of the mitochondrial compartment plays a key role in regulating inflammatory processes. Failure of the mitochondrial fusion-fission cycle results in depolarisation of the mitochondrial membrane, organelle swelling and the formation of “megamitochondria” [79-82]. ROS induced damage and mtDNA are recognised as DAMPs, and their resultant leak into the cytoplasm and extracellular environment causes activation of inflammatory processes. The most important PRRs in mitochondrial contexts are Toll-like receptors (TLRs), particularly TLR9. TLR9 is responsive to mtDNA and expressed both intracellularly in membranous vesicles and extracellularly on macrophages [83]. Of further note are retinoic acid inducible gene I (RIG-I), which binds non-cell double stranded DNA (dsDNA) [84], and melanoma differentiation associated protein 5 (MDA5), sensing non-cell RNA [85].

Secretion of pro-inflammatory IL-1 β and IL-18 by macrophages is dependent on activation of the “inflammasome”, a cytoplasmic protein-complex responsible for cleavage and activation of caspase-1. “Canonical” inflammasomes consist of pro-caspase 1, an aspartate specific cysteine protease (ASC) adaptor protein and a PRR – in this context, nucleotide-binding oligomerisation domain-like receptors (NOD-like receptors or NLRs) [86]. When the NLR is activated, pro-caspase 1 is converted to its active

form, allowing enzymatic cleavage of pro-IL-1 β and other cytokine progenitors to their active form [87]. “Non-canonical” inflammasomes do not depend on NLRs and result in gasdermin D cleavage by caspase-11, allowing IL-1 β secretion and pyroptosis [88, 89].

Mitochondrial antiviral signalling protein (MAVS) plays a key role as an intermediate between nuclear transcription factors NF κ B and interferon regulatory factors and the production of interferons during infection of the cell [84, 85]. In the resting state MAVS is bound to Mfn2 on the mitochondrial outer membrane. When the RIG-I and MDA5 complex responds to non-cell genetic material, they activate MAVS, which binds to TANK-binding kinase 1 (TBK1) and inhibitor of NF κ B kinase ϵ (IKK ϵ), translocating to the nucleus and activating IRFs to upregulate transcription of interferons. The cyclic GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway is a similar mechanism that responds to the presence of dsDNA converging directly on TBK1 and IKK ϵ [90, 91]. TLR9 activation by mtDNA acts via adaptor protein MyD88 and a series of IKK adaptors to converge on NF κ B, which when translocated to the nucleus upregulates transcription of pro-inflammatory cytokines TNF α , IL-1 and IL-6 [84].

While mitochondrial ROS have long been recognised as a potential trigger of NLRP inflammasomes, a constitutive level of ROS is also an essential component of the function of the innate immune system [83]. Transcription of MAVS is negatively regulated by ROS levels, and constitutive production of ROS by NADPH oxidase enzymes appears to be required for RIG-I mediated activation of IRF3 and production of proinflammatory cytokines [92].

SARS-CoV-2 infection and post-acute sequelae. The role of canonical and non-canonical inflammasome activation under viral infection is now well understood, and its core role in SARS-CoV-2 inflammation provides greater understanding of the pathogenesis of COVID-19 while also suggesting novel treatment options. SARS-CoV-2 open reading frames (ORFs) are translated from positive-strand RNA and interfere with autophagic processes, disrupting Parkin ubiquitylation and autophagolysosome fusion. This resultant metabolic derangement, along with suppression of the interferon production RIG-I/MAVS and cGAS-STING pathways, causes failure of innate immune antiviral processes [93-95].

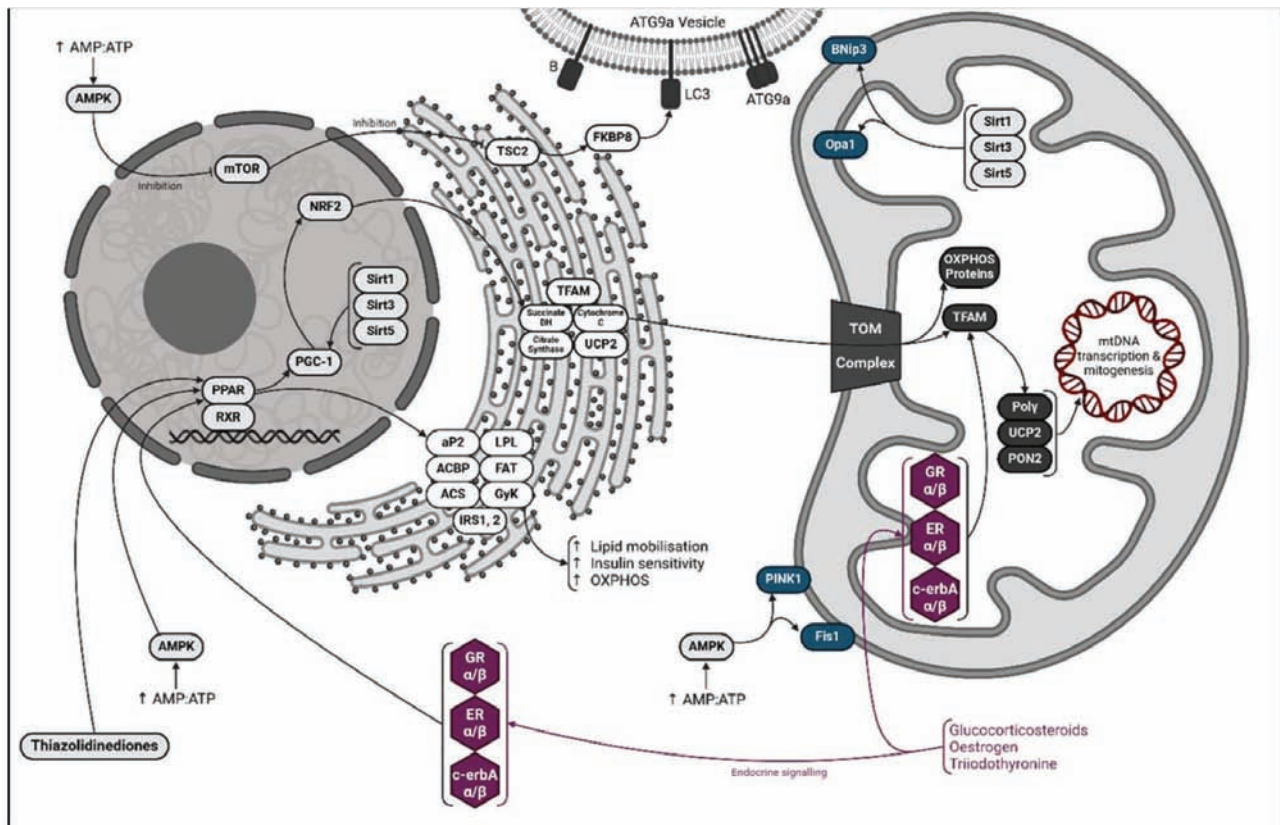


Fig. 2. Control of mitophagy, mitogenesis and metabolism Via AMPK and endocrine action on nuclear, reticular and mitochondrial structures (created in BioRender.com)

Of deeper interest are complex interactions between viral entities and mitochondrial structural and transport proteins. RNA-GPS studies early in the COVID-19 pandemic predicted interactions between viral polypeptides and subunits of ETC complexes I, III and IV [96, 97]. Fluorescence microscopy located SARS-CoV-2 genetic material within the mitochondrial matrix while indicating a consequent failure of mitophagy [98]. Viral accessory protein ORF3c has been demonstrated to utilise TOM20 to locate itself within the mitochondrial compartment of the cell where it too disrupts mitochondrial flux [94]. Pathological studies have also found that viral genetic material and polypeptide components of SARS-CoV-2 infection persist within post-mortem specimens [99, 100], at times for years [101]. The implication is that elements of the SARS-CoV-2 virus can sequester themselves within the mitochondrial component of the organism to evade immune surveillance and response. The inflammatory response to viral invasion, accumulation of defective components of the mitochondrial compartment and failure of tissue OXPHOS systems forms a putative theory for the

pathogenesis of post-acute sequelae in SARS-CoV-2 infection [96].

One of the more common manifestations of post-acute COVID-19 sequelae is encephalomyelitis/chronic fatigue syndrome-like symptoms of diminished muscle strength, pain, muscle cramping and fasciculations or muscle spasm correlated with limited exercise capacity and metabolic aberration in skeletal muscle tissue [102, 103]. Hypoxaemia, inflammatory responsive dysfunction in ETC complexes and direct and inflammatory action on microvasculature have been implicated [104], yet a number of studies indicate that dysregulation of ion transport and resultant sodium and calcium overload causes disturbance of microvascular structures and mitochondrial toxicity [105, 106]. Here, exercise-induced hypoperfusion induces anaerobic metabolism and increased proton production, which results in increased in sodium exchange via the sodium-proton exchanger, inhibition of Complex V and a rise in mitochondrial ROS production. This ultimately causes the sodium calcium exchanger to reverse flux, importing calcium to the skeletal muscle mi-

tochondrial compartment, causing calcium overload and resultant morphological defects throughout the tissue [107].

Disruption of mitochondrial innate immunity in hepatitis B & C infection. Hepatitis B (HBV) is an encapsulated DNA virus, while hepatitis C (HCV) is an RNA virus, yet both result in persistent and progressive liver damage, the outcome of which is hepatic fibrosis, cirrhosis and death. HBV and HCV gain access to the liver via an organ-specific multi-receptor complex, after which the viral particles are unencapsulated, the nucleocapsid is released into the cytoplasm and the viral DNA (HBV) or positive sense viral RNA (HCV) can act as material for translation of viral peptides [108].

HBV enhances its replicative ability by hijacking mitophagic processes, initially by stimulating excessive organelle fission by promoting Drp1, and ultimately by the upregulation of the PINK1-Parkin axis and degradation of Mfn2. The outcome of this process is persistence of the infected cell beyond usual viability, reducing ROS production and maintaining limited OXPHOS activity while using glycolysis metabolites to provide useful substrates for virion production [109,110]. In HCV, viral RNA is recognised by RIG-I and MDA5 PRRs, which trigger MAVS assisted IRF and NFκB based interferon response [111]. Viral non-structural (NS) proteins NS3 and NS4 are serine proteases that render MAVS ineffective by cleaving it from Mfn2, thus preventing RIG-I/MDA5 signalling [112], while also interfering with essential cofactors of TLR signalling [113]. Spread of the virus between hepatocytes results in a state of persistent inflammation in newly infected areas as pro-inflammatory pathways are activated, while chronically infected areas have interferon production suppressed by PRR interference [114].

HCV infection appears to increase mitophagy via an indirect route by suppression of mTOR, which when active suppresses mitophagy [115] or unfolded protein response [116] pathways, although whether this occurs in HCV infection to the same extent as in HBV is controversial within the literature [117,118]. The reverse is true in alcoholic hepatitis (AH), where hepatocytes from AH patients display reduced Drp1 and inactive mitochondrial fission. Electron micrograph studies show the accumulation of megamitochondria, while metabolomic studies show increased ROS, cell stress, cytosolic mtDNA and activation of cGAS-STING interferon signalling [119].

Aberrant hepatocyte calcium homeostasis provides another facet of chronic viral hepatitis. Both

HBV and HCV directly increase calcium uptake in hepatocyte mitochondria. HBV infection causes hepatocytes to upregulate mitochondrial Ca^{2+} uptake 1 channels and potentially VDAC3, although further work is required to elucidate the implications of viral interference with this structure [120]. HBV is also known to integrate its genetic material into the gene encoding Sarco/Endoplasmic Reticulum Calcium ATPase, the primary ER calcium pump [121]. One effect of cholestasis (the accumulation of bile acids within hepatic tissues) resulting from advanced viral hepatitis is impairment of intracellular calcium homeostasis within circulating T cells owing to the failure of mitochondrial calcium uptake, reduces the effective population of lymphocytes available to combat the infection [122]. HCV meanwhile, directly interacts with the mitochondrial calcium uniporter to cause calcium overload of the hepatic mitochondrial compartment, with resultant failure of ATP generation and apoptosis [120]. These advances have led to a number of trials targeting aberrant Ca^{2+} signalling in viral hepatitis, which may prove decisive in inhibiting HBV replication [123].

Nascent connections between mitophagy, asthma and COPD. Asthma as a disease is characterised by chronic airway inflammation, respiratory symptoms such as coughing and wheezing, varying in intensity over time [124]. Inappropriate mitophagy plays a role in the development of asthma in response to particulate matter. Tandem mass spectrometry in rat models shows marked upregulation of VDAC1 in lung tissue from asthmatic rats compared to controls [125]. Downstream, mitochondrial dysfunction results in altered calcium metabolism and concomitant increased smooth muscle contractility, causing the airway remodelling that is the morphological hallmark of this disease [126].

Genetic studies indicate that single nucleotide polymorphisms of ATG5 and SQSTM1 genes highly predispose to the development of asthma, while electron micrographs of bronchial biopsy material show increased autophagosome activity in patients with reduced lung function [127]. The mTOR pathway appears to play a role in the development of asthma, as evidenced by murine models where mTOR blockade through rapamycin alleviates symptoms of inflammation. Asthmatic mice produced by allergic sensitisation using cigarette smoke extract showed significantly decreased neutrophil count and markers of inflammation when treated with intraperitoneal infusions of rapamycin [128]. A similar study

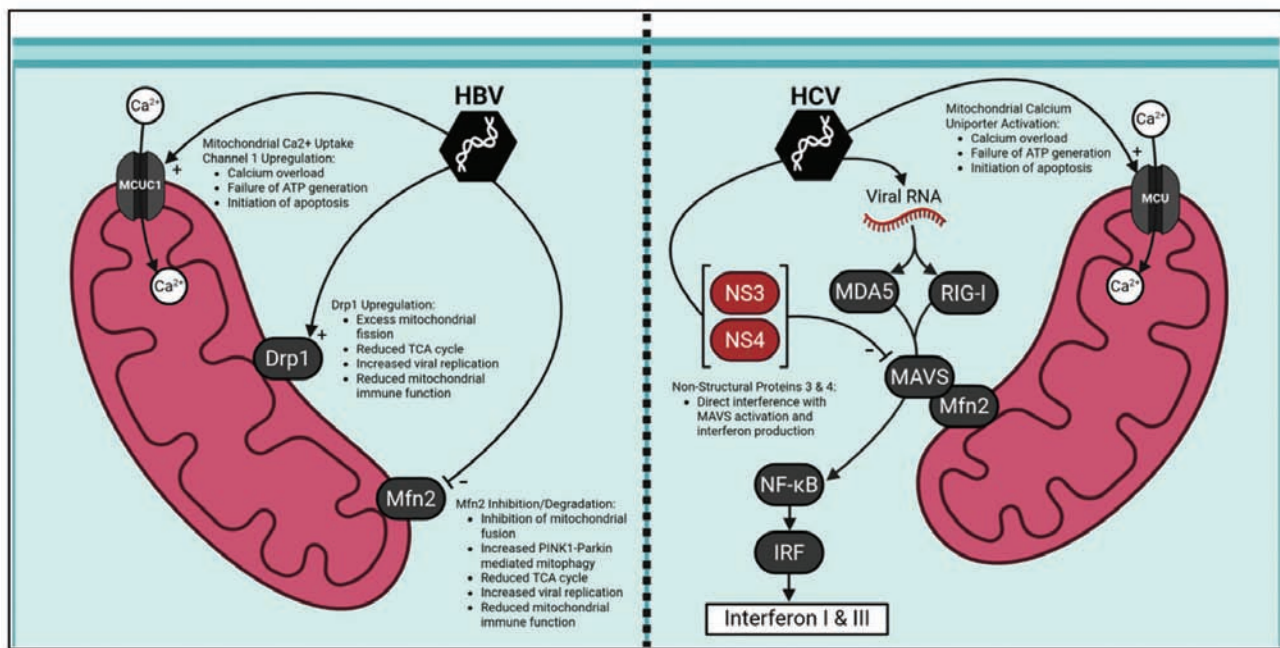


Fig. 3. The Effects of HBV (left) & HCV (right) on mitochondrial homeostasis (created in BioRender.com)

showed increased LC3 autophagosome formation in sensitised mice, with autophagy-related double-membrane vesicles more prominent in eosinophils from sensitised mice than in controls [129].

Histopathological examination of human large airway epithelial tissue demonstrates increased expression of ATG5 protein in severe cases of asthma with airway remodelling, the changes in correspondence to the severity of the remodelling process [130]. As the disease progresses, transforming growth factor β (TGF- β) signalling produces fibrosis while ultimately downregulating PINK1-Parkin autophagic processes, mitophagy and mitogenesis [131]. Immunohistochemical studies in asthmatic mice has demonstrated upregulated TFAM, NRF-1 and PGC-1 α in bronchial smooth muscle undergoing remodelling, which indicates attempted mitochondrial biogenesis in the face of increased metabolic demand [132].

Similar effects have been demonstrated in COPD, and rapamycin and mTOR blockade remain targets of interest in development of pharmaceutical treatments for pulmonary inflammatory disease [133]. The role of the PINK1-Parkin mitophagy pathway in pathogenesis was demonstrated by showing that PINK1 deficiency was protective against cell death and necroptosis in response to cigarette smoke in mouse models [133]. A similar study demonstrated the LC3 deficient mice had reduced airspace enlarge-

ment in response to cigarette smoke extract than control animals [134]. Another avenue of interest in COPD research involves altered lipid profile associated with pro-inflammatory states. Metabolomic studies of broncho-alveolar lavage fluid shows increased expression of pro-inflammatory cytokines IL-6 and IL-8 along with altered lipid surfactant profile [135]. Acyl-carnitines expression is also altered in COPD, which may provide another method of investigating mitochondrial disturbance owing to alterations in lipid metabolism and β -oxidation of long-chain fatty acids. Further high-quality multi-omic studies could do much to determine the metabolic underpinnings of airway remodelling and parenchymal change in COPD [136].

Conclusion. The mitochondrial compartment now finds a central role in our understanding of innate immunity. The metabolic and immune function of the mitochondrial compartment are complementary and essential to the other's proper function. The mitochondrial compartment itself exists within a dynamic and highly regulated continuum of biogenesis, autophagy and fusion-fission events, throughout which the bioenergetic and immune components of the cell can remain in balance with the demands of the organism. Morphological change in tissue is accompanied by change in the metabolic phenotype of component cells, underpinned by changes in the configuration of cellular mitochondria. The central

role of calcium signalling in mitochondrial function and the downstream effects of dysfunctional calcium homeostasis when the mitochondrial compartment fails provides a fascinating avenue for the development therapeutic interventions for a diverse array of diseases.

Via a complex, cascading network of extra- and intracellular signals the OXPHOS metabolic component of the cell is modulated in response to stress, starvation, pathogenic invasion, and other modalities of disease. Certain invaders such as SARS-CoV-2, HBV and HCV have evolved to take advantage of this apparatus. Our innate antiviral response to both acute and chronic SARS-CoV-2 infection can be characterised as a battle of control over E3 ubiquitin ligases, as viral material attempts to sequester itself within defective organelles that are resistant to proper mitochondrial homeostasis. In asthma, autophagic processes are upregulated and correspond to disease severity. Previous treatment methods have focused on targeting inflammatory pathways in the hopes that this would ameliorate the symptoms. While in mild to moderate cases this may prove effective, severe asthma has both a marked deleterious effect on the individual and high mortality.

Further metabolomic studies elucidating the role of mTOR signalling, PINK1-Parkin autophagy and downstream LC3 and ATG5 mediated autophagosome activity are warranted. Greater understanding of the pathophysiology of asthma enables the development of novel therapeutic interventions that should revolutionise the treatment of a widespread and severely debilitating illness. Similar patterns of expression in COPD enable comparisons and allows for further understanding of the metabolic apparatus that underpins disease progression, which in turn opens new fields for the development of therapeutics. Finally, the excellent advances in understanding both the variety, morphology and function of mitochondrial cation channels, along with their central role in cellular signalling apparatus, provides a promising field of research for future pharmacological development.

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МИТОГЕНЕЗ, МИТОФАГІЯ ТА РЕГУЛЯЦІЯ МИТОХОНДРІАЛЬНОГО МЕТАБОЛІЗМУ В НОРМІ ТА ПАТОЛОГІЇ

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У цьому огляді проаналізовано стан мітохондріального гомеостазу, який складається з процесів мітохондріального біогенезу, селективного виведення пошкоджених або дисфункціональних мітохондрій, мітохондріальної динаміки (злиття та поділ), а також сигнальних систем регуляції мітохондріального метаболізму. Особливу увагу приділено модуляції біоенергетичних потреб тканин за умов вірусних інфекцій SARS-CoV, гепатиту В і С, а також при бронхіальній астмі.

Ключові слова: мітохондріальний гомеостаз, мітогенез, мітофагія, злиття та поділ, метаболізм, SARS-CoV-2, гепатит.

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