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Review

The Reactive Species Interactome - Mitochondria Axis

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Abstract : From oxidative eustress and distress, to bioenergetic metabolism, and cell death, the reactive species interactome (RSI) and mitochondria are two connected metabolisms that require further investigation improving redox medicine. The step before, finding new clues needs a comprehensive discussion of the two metabolisms, and their relationship. Here, the review focuses on the RSI-mitochondria axis, from mitochondrial roles to crosstalk between mitochondria and other organelles, and the major implication of the RSI in mitochondrial roles. Specifically, the review discussed the apoptosis-necroptosis-ferroptosis death traingle, mitochondrial protein quality control system, calcium homeostasis, and mitochondrial metabolome. Through mitochondrial diseases, and mitochondrial dysfunction associated with diseases, the RSI-mitochondria axis is proposed as a brand-new perspective, including with the involvement of bacterial microbiota, on redox signaling, and redox medicine.

Keywords: mitochondria; reactive species; eustress; distress; bioenergetic; microbiota

1. Introduction

The redox interactome, which combines redox catalysis, homeostasis, flux, landscape, homeorhesis and evolution, and mitochondria are two deeply connected metabolisms, which require further investigation appreciating their combined properties in redox medicine[1]. One key player linking both metabolisms is the Reactive Species Interactome (RSI)[2–4]. The RSI concept stands for the interactome of reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive sulfur species (RSS), reactive carbonyl species (RCS), and their downstream biological targets[2–4]. In addition to reactive species identification and interaction, their concentration is one of the most important parameters to consider, from oxidative eustress, the physiological exposure to reactive species, to oxidative distress, the supra-physiological exposure to reactive species[3,5].

In this review, first, mitochondrial key characteristics, and major roles are overviewed. Roles that require further investigations are discussed, namely apoptosis-necroptosis-ferroptosis death triangle, protein quality control system, calcium homeostasis, and metabolome. Intracellular interactions of mitochondria with other organelles that affect mitochondrial roles are discussed. Then, mitochondrial reactive species sources are questioned, and notable enzymes involved in both mitochondria and the RSI are highlighted. Finally, the RSI-mitochondria axis is proposed as a brand-new perspective to investigate, including considering bacterial microbiota as a key player in this axis.

2. Mitochondria: the characteristics

An outer membrane (OM), an intermembrane space (IMS), an inner membrane (IM), and a matrix constitute the semi-autonomous organelle mitochondria, which structural dynamics oscillate between fragmented and tubular networks, depending on metabolic status[6–8]. Mitochondria is an ancient bacterial symbiont, which matrix is organized with a characteristic shape of IM cristae maintained by MICOS, the mitochondrial contact site and cristae organizing system[7–9].

Importantly, mitochondria contain cardiolipin, which are mitochondria-specific phospholipids[10,11]. Cardiolipin are critical to better consider as these phospholipids

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constitute 25% of mitochondrial membrane lipids, and 65% are found in IM[11]. Cardiolipin are highly sensitive to peroxidation by ROS, and are involved in the programmed cell death apoptosis, through formation of mitochondrial membrane pores[10,11]. Cardiolipin are also biomarkers of damaged mitochondria when translocated to OM, and when interacting with autophagic marker LC3 (microtubule-associated protein 1A/1B-light chain 3), which is essential for autophagosome formation in mitophagy, a quality control mechanism to degrade damaged, and dysfunctional mitochondria[10,11]. In addition, cardiolipin are involved in the stabilization of OXPHOS (oxidative phosphorylation) complexes I, III, IV, and ATP synthase for mitochondrial ATP generation, and in mitochondrial fission through interaction with DRP1 (dynamin-related protein 1)[10,11].

Importantly too, mitochondria contain their own genome, namely mitochondrial DNA (mtDNA) in multiple copies packaged into nucleoids, which is essential for mitochondrial homeostasis and functions, and all machineries for mtDNA replication, mtDNA transcription, and mtRNAs translation[6,8,12,13]. Mitochondrial DNA mutations, replication, transcription, and regulation are critical to better consider in both physiology and pathology, as mtDNA alterations and disorders affect from cellular energy metabolism to cell death[12,13].

Mitochondrial matrix pH ranges from 7.8 to 8.1, while pH is 7.2 for cytosol, the Endoplasmic Reticulum (ER) and nucleus, 7 for peroxisomes, from 6.7 to 6 for the Golgi apparatus, and 4.7 for lysosomes[14]. In addition, in physiological condition, mitochondrial are fully functional at close to 50°C, meaning more than 10°C from cytosolic temperature[15].

Proteomic studies showed that mitochondria contain from ~1,000 to ~1,500 different proteins in yeast and human respectively, 99% being encoded by the nuclear genome, and 1% by the mitochondrial genome[6,7,16]. About 100 proteins are present in OM, ~60 proteins in IMS, more than 840 proteins in IM, and ~500 proteins in mitochondrial matrix[17]. Between 20 and 25% of the mitochondrial proteome regulates mtDNA, and ~15% of the mitochondrial proteome is involved in energy metabolism, including in OXPHOS[7]. Adaptation of the mitochondrial proteome to bioenergetic needs is the mitochondrial proteome plasticity[7]. Mitochondrial protein import, which includes OM translocases (TOM), IMS import and assembly machinery (MIA), and IM translocases (TIM) is therefore a vital pathway for mitochondrial stability and functions[6,7,16]. Impairment of TOM or TIM import activity induces mitochondrial stress response through mitochondrial protein quality control system activation[6,7]. This activation includes mitochondrial PINK1 (PTEN-induced putative kinase 1) and E3 ubiquitin ligase PARKIN (autosomal recessive Parkinson's disease 2), two key proteins involved in Alzheimer's disease, Parkinson's disease, and possibly in cancer development[6,7].

All the discussed characteristics of mitochondria are summarized in **Figure 1**.

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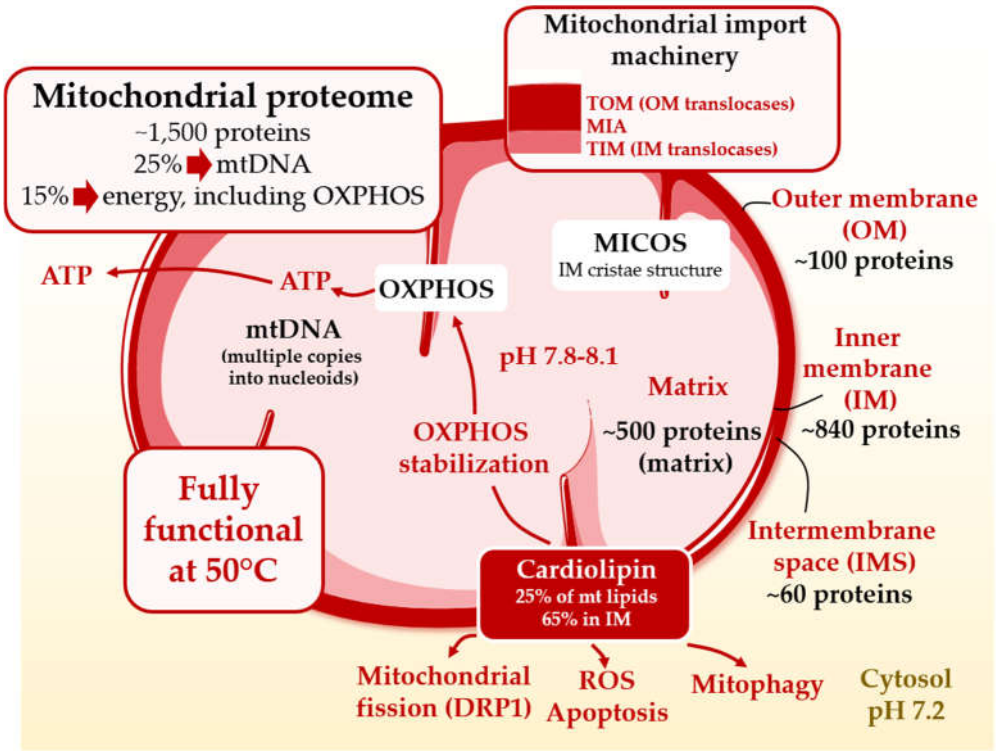

Figure 1. The key characteristics of mitochondria. OM, outer membrane; IMS intermembrane space; IM, inner membrane; DRP1, dynamin-related protein 1; MIA, IMS import and assembly machinery; MICOS, mitochondrial contact site and cristae organizing system; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; TIM, IM translocases ; TOM, OM translocases.

3. Mitochondria: major roles

Major mitochondrial roles are (1) bioenergetic metabolism through the Krebs cycle, and OXPHOS respiratory complexes for ATP generation, (2) programmed cell death apoptosis, (3) mitophagy, (4) biosynthesis of iron-sulfur (Fe-S) clusters and cofactors, (5) metabolism of amino acids, (6) metabolism of lipids, including β-oxidation of LCFAs (long chain fatty acids) and MCFAs (medium chain fatty acids) to generate acetyl-CoA for ATP synthesis, and (7) redox signaling[7] (**Figure 2**). In addition, mitochondria play a major role in cancer development by being transferred intercellularly from noncancer to cancer cells to maintain functional OXPHOS, which is essential for dihydroorotate dehydrogenase (DHODH)-dependent pyrimidine biosynthesis[18–20]. Finally, outside cells, intact mitochondria are circulating in the blood, although their functional role is still debated, with a possible role as extracellular signaling organelle[21,22].

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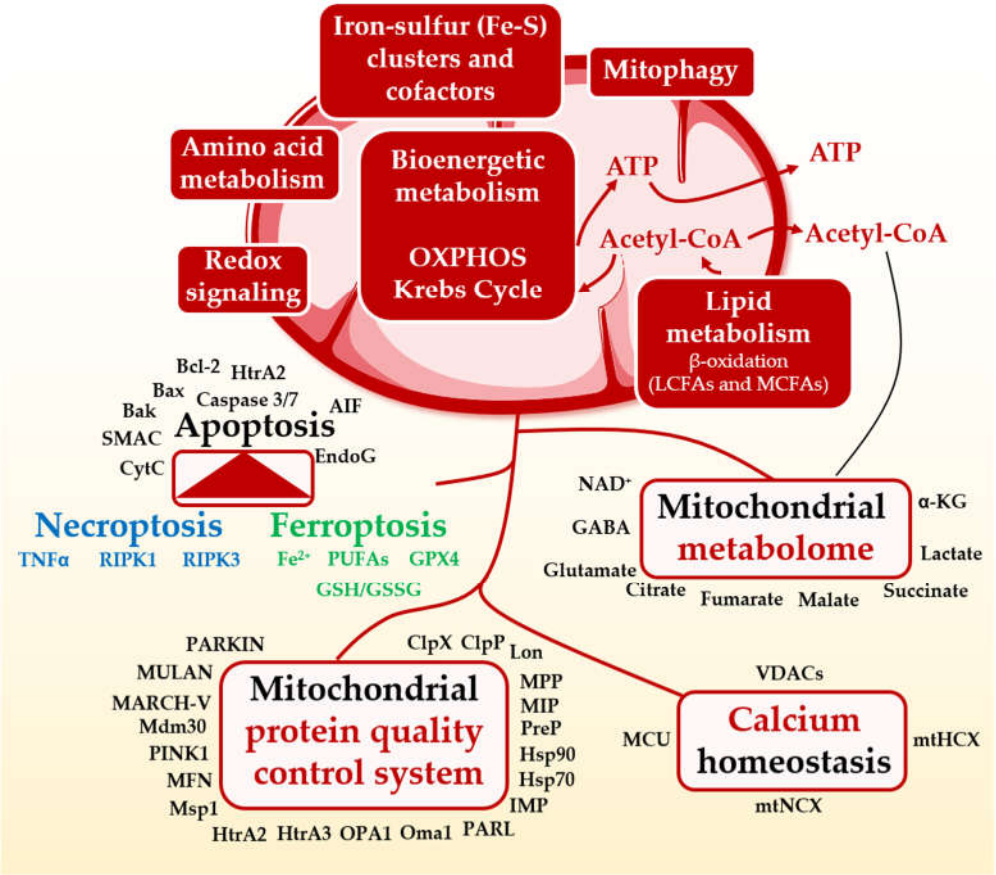

Figure 2. Major roles of mitochondria, and key roles to investigate. Major roles of mitochondria are summarized, as well key mitochondrial roles to further investigate improving the understanding of mitochondria functions, namely apoptosis-necroptosis-ferroptosis death triangle, mitochondrial protein quality control system, calcium homeostasis, and mitochondrial metabolome. AIF, apoptosis-inducing factor; Bcl-2, B-cell lymphoma 2; Bak, Bcl-2 antagonist/killer; Bax, Bcl-2 associated X; ClpP/X, caseinolytic mitochondrial matrix peptidase chaperone subunit P/X; CytC, cytochrome C; EndoG, endonuclease G; GABA, gamma aminobutyric acid; GPX4, glutathione peroxidase 4; Hsp70/90, heat shock protein 70/90; HtrA2/3, High temperature requirement A 2/3; IMP, inner membrane mitochondrial protease; MARCH-V, membrane-associated ring finger C3HC4; Mdm30, mitochondrial distribution and morphology 30; Lon, AAA+ serine protease; MCU, mitochondrial Ca^{2+} uniporter; MFN, mitofusin; MIP, mitochondrial intermediate peptidase; Msp1, mitochondrial sorting of proteins 1; MPP, mitochondrial processing peptidase; mtHCX, mitochondrial H^{+}/Ca^{2+} exchanger; mtNCX, mitochondrial Na^{+}/Ca^{2+} exchanger; MULAN, mitochondrial ubiquitin ligase activator of NFKB1; NAD, nicotinamide adenine dinucleotide; Oma1, i-AAA, inner membrane-embedded AAA protease, overlapping with mitochondrial AAA m-AAA protease; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PARKIN, autosomal recessive Parkinson's disease 2; PARL, presenilin-associated rhomboid-like serine protease; PINK1, PTEN-induced putative kinase 1; PreP, presequence metallopeptidase; PUFAs, polyunsaturated fatty acids; RIPK1/3, kinase receptor-interacting protein 1/3; SMAC, second mitochondria-derived activator of caspase; TNFα, tumor necrosis factor-α; VDACs, voltage-dependent anion-selective channel proteins; α-KG, α-ketoglutarate.

Following paragraphs focus on other mitochondrial roles, which require further investigation, including towards the redox interactome.

4. Mitochondria and Apoptosis-Necroptosis-Ferroptosis death triangle

Mitochondria are major regulators of apoptosis, including with cardiolipin, B-cell lymphoma 2 (Bcl-2) effector proteins Bax (Bcl-2 associated X) and Bak (Bcl-2 antagonist/killer) activation and oligomerisation, and the release of cytochrome c, SMAC (second mitochondria-derived activator of caspase), serine protease Omi/HtrA2 (high temperature requirement protein A2), AIF (apoptosis-inducing factor), and EndoG (endonuclease

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G) to form apoptosome, to activate caspases, including caspase 3 and 7, and to destroy the nuclear genome[10,11,23–27]. Although apoptosis is the most investigated cell death type regarding mitochondria, more than ten cell death types are described, including necroptosis, the regulated form of necrosis, and ferroptosis[28].

Necroptosis, which is initiated by TNFα (tumor necrosis factor-α), activated by kinase receptor-interacting proteins (RIPK), including RIPK1 and RIPK3, and characterized by necrosome formation, could be regulated by mitochondria[29–32]. Evidence for and against the role of mitochondria in necroptosis require further investigation, as mitochondrial calcium ions (Ca^{2+}) overload and ROS, including mitochondrial ROS O_2^- (superoxide anion) accumulation, induce necroptosis[29–32].

Ferroptosis could also be regulated by mitochondria. Ferroptosis is characterized by the accumulation of active iron Fe^{2+} and ROS H_2O_2 (hydrogen peroxide), and cytosolic and mitochondrial GPX4 (glutathione peroxidase 4) dysfunction, an antioxidant defense enzyme which regulates GSH/GSSG system to reduce polyunsaturated fatty acids (PUFAs) peroxidation[33–35]. Ultimately, PUFAs peroxidation and RCS accumulation, including malondialdehyde (MDA), lead to ferroptosis[33–35]. Mitochondrial ROS O_2^- and H_2O_2, and mitochondrial DHODH and GPX4, two enzymes which detoxify lipid peroxides, are involved in ferroptosis regulation[34,35].

Altogether, the most important investigation would be the essential role of mitochondria as a nexus linking apoptosis, necroptosis, and ferroptosis, through mitochondrial ROS, possibly other reactive species, and related notable antioxidant enzymes homeostasis, which will be further discussed (**Figure 2**).

5. Mitochondrial protein quality control system

Mitochondrial role in protein quality control system related to key chaperones and proteases require further investigation. Protein quality control system in mitochondria contributes to maintain healthy mitochondria with both a mitochondrial network of chaperones and proteases, and cytosolic proteolytic mechanisms, including UPS (ubiquitin-proteasome system), and heat shock proteins (Hsp), such as Hsp70 and Hsp90 [17].

Outer membrane proteins include several ubiquitin-ligases such as PARKIN, MULAN (mitochondrial ubiquitin ligase activator of NFKB1), MARCH-V (membrane-associated ring finger C3HC4 5) and Mdm30 (mitochondrial distribution and morphology 30), PINK1, MFN (mitofusin), and AAA+ (ATPases associated with various cellular activities) Msp1 (mitochondrial sorting of proteins 1)[17]. Intermembrane space proteins include HtrA2 serine protease, and two metalloproteases, Atp23 (ATP synthase 23) and Prd1 (proteinase yscD 1)[17]. Inner membrane proteins include GTPase OPA1 (optic atrophy 1), Oma1 ATP-independent metalloprotease (i-AAA, inner membrane-embedded AAA protease, overlapping with mitochondrial AAA m-AAA protease), PARL protease (presenilin-associated rhomboid-like serine protease), and IMP protease (inner membrane mitochondrial protease)[17]. Matrix proteins include chaperones such as Hsp10, Hsp60, Hsp78, mtHsp70 (mitochondrial Hsp70), PreP (presequence metallopeptidase) metalloprotease, MIP (mitochondrial intermediate peptidase), MPP (mitochondrial processing peptidase) protease, several ATP-dependent serine proteases such as Lon (AAA+ serine protease), ClpP (caseinolytic mitochondrial matrix peptidase chaperone subunit P), and ClpX (Clp subunit X)[17]. Matrix Lon and ClpX/P proteases are considered as protein quality safeguards, and exert critical role in regulating proteolysis for mitochondrial proteins involved in mtDNA maintenance and transcription, such as TFAM (Transcription Factor A, mitochondrial), and in OXPHOS maintenance[36].

One interesting example is the HtrA serine protease family, which includes Omi/HtrA2 and HtrA3[37–39]. As already mentioned, HtrA2 is involved in mitochondria homeostasis and apoptosis[37]. In addition, the HtrA3 serine protease, a cytosolic and mitochondrial protease, which is upregulated by nitroso-redox balance, regulates mitochondrial proteins, including POLG1 (DNA polymerase gamma 1), and OXPHOS activity, as

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it has been demonstrated in the progeroid Cockayne syndrome[38]. Replicative p21-dependent senescence associated with mitochondrial impairment is also regulated by HtrA3[39]. Thus, such a serine protease family requires further investigation improving the understanding of the mitochondrial protein quality control system.

Finally, mitochondrial-derived vesicles (MDVs) for mitochondrial proteins and lipids transport to other organelles, are involved in mitochondrial protein quality control system[17,40].

The mitochondrial protein quality control system contributes to mt UPR (mitochondrial unfolded protein response), a response to mitochondrial proteotoxic stress[41]. Regulation of mitochondrial protein import and folding, proteolysis of mitochondrial proteome, proteotoxic stress response, and OXPHOS maintenance make this system as a major one to further investigate[42]. Together, better consider mitochondrial protein quality control system would be an important step to improve the understanding of mitochondrial roles, including in bioenergetic metabolism and cell death types, in physiology and pathology (**Figure 2**).

6. Mitochondrial role in calcium homeostasis

Mitochondrial role in calcium storage and homeostasis needs further consideration. Mitochondria are important regulators of many calcium-dependent intracellular functions by sequestering and releasing calcium ions[43]. Mitochondrial Ca^{2+} concentration is 100-200nM as cytoplasm in resting conditions, while mitochondria can accumulate 10- to 20-fold more Ca^{2+} than cytoplasm during calcium stimulation[43]. Through VDACs (voltage-dependent anion-selective channel proteins) and MCU complex (mitochondrial Ca^{2+} uniporter), mitochondria capture calcium ions from cytosolic and the ER sources[43]. Mitochondrial activity, whichi is reflected by mitochondrial membrane potential, is an active force for Ca^{2+} uptake, while mtNCX (mitochondrial Na^{+}/Ca^{2+} exchanger) and mtHCX (mitochondrial H^{+}/Ca^{2+} exchanger) are mainly contributing to mitochondrial calcium ions efflux[43,44]. During oxidative distress, hypoxia, and inflammation, MCU complex are targeted by ROS, and pro-apoptotic Bcl2-family proteins interact with VDAC1 and VDAC3, thus linking mitochondrial calcium homeostasis with oxidative distress and apoptosis[43]. In addition, mitochondrial Ca^{2+} influx and efflux contribute to remodel intracellular Ca^{2+} dynamics and signaling, including in the major calcium ions storage site, the ER[43,44]. Importantly, what makes the story more attractive, is that calcium ions are involved in apoptosis, necroptosis, autophagy, insulin secretion, heart activity, inflammation, cancer, neuronal activity, stroke, neuromuscular disorders, and neurodegeneration[43–45]. Therefore, improving the understanding of mitochondrial Ca^{2+} homeostasis would be an important step for many calcium-dependent physiological and pathological pathways (**Figure 2**).

7. Mitochondrial metabolome

Mitochondrial metabolome needs further consideration. Mitochondrial metabolomics allow extraction, detection, and data analysis for many mitochondrial metabolites, and their involvement in metabolisms, including energy metabolism, lipid metabolism, amino acid metabolism, carbohydrate metabolism, and cofactor metabolism[46]. For example, in immortalized human embryonic kidney HEK293 cells, mitochondrial nucleotide NAD^{+} (nicotinamide adenine dinucleotide) was identified as important metabolite involved in mtDNA replication activation, and β-nicotinamide mononucleotide (β-NMN) metabolism was proposed to play a crucial role in maintaining mitochondrial nucleotide pool to support mtDNA replication[47].

Metabolomic analysis in the context of diabetic kidney disease also reveals that many metabolites, including uric acid, stearic acid, palmitic acid, aconitic acid, isocitric acid, 4-hydroxybutyrate, and glycolic acid, are involved in mitochondrial and fatty acid metabolism[48]. Metabolomic studies contribute to improve the understanding of mitochondrial dysfunction, including in mitochondrial diseases[49]. Specific metabolites, such as

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NAD^+/NADH, acetyl-CoA, succinate, citrate, lactate, pyruvate, fumarate, malate, and 2-ketoglutarate are identified as key metabolites to track, and to regulate in mitochondrial diseases, and related pathways, including energy metabolism and cell death[49].

In addition, mitochondrial glutamate metabolite related to glutamine metabolism and glutaminase activity, which generates glutamate from glutamine, is involved in OXPHOS activity, mitochondrial nucleotide pool maintenance with NAD^+/NADH and NADP+/NADPH (NAD phosphate), and antioxidant glutathione GSH/GSSG system regulation[50]. Reactive oxygen species are regulated by glutamine metabolism through GSH/GSSG system[50]. Glutamate affects other metabolites such as pyruvate, lactate, 2-ketoglutarate, and Krebs cycle intermediates, an exacerbated effect during hypoxia[50]. Moreover, from glutamine metabolism, several oncometabolites should be better considered, including α-ketoglutarate (α-KG), R-2-hydroxyglutarate (R-2-HG), succinate, and fumarate[50]. Metabolic reprogramming is induced by glutamine and derived metabolites, which makes this metabolism of interest to target in mitochondria, including in cancer[50]. Finally, glutamate transport into and out mitochondria is increasingly investigated, as glutamate is a powerful neurotransmitter as GABA neurotransmitter (gamma aminobutyric acid)[51]. Mitochondrial glutamate carriers include GC1/SLC2A22 (glutamate carrier 1) and GC2/SLC25A18 for the glutamate transport over mitochondrial IM, and mitochondrial aspartate-glutamate carriers include AGC1/Aralar/SLC25A12 (aspartate-glutamate carrier 1), AGC2/SLC25A13/Citrin[51]. Mitochondrial dysfunction, neuron activity disturbance, and myelin metabolism alteration are induced by GC and AGC dysregulation[51]. In GABAergic neurons, mitochondrial OXPHOS hyperactivity induces GABA neurotransmitter accumulation into mitochondria due to Aralar activity, which contributes to social behavioral deficits[52–54]. Altogether, linking metabolomics studies with mitochondrial function, and focusing on key metabolites, including Krebs cycle intermediates, should reveal new mitochondrial roles related to bioenergetic metabolism, cell death, protein quality control system, calcium homeostasis, and redox signaling (**Figure 2**).

From mitochondrial major roles to apoptosis-necroptosis-ferroptosis death triangle, protein quality control system, calcium homeostasis, and mitochondrial metabolites, another focus requires discussion, which is inter-organelle crosstalk including mitochondria.

8. Crosstalk between mitochondria and other organelles

Mitochondria interact with other organelles using membrane contact sites, vesicle transport, and molecules transduction for many functions, including bioenergetic metabolism, immune response, cell death, organelle biogenesis, lipid biosynthesis and exchange including PS (phosphatidylserine), cholesterol metabolism, and nuclear DNA function[20]. Non-exhaustively, several interactions are discussed to encourage further investigation related to mitochondrial roles, and redox signaling (**Figure 3**).

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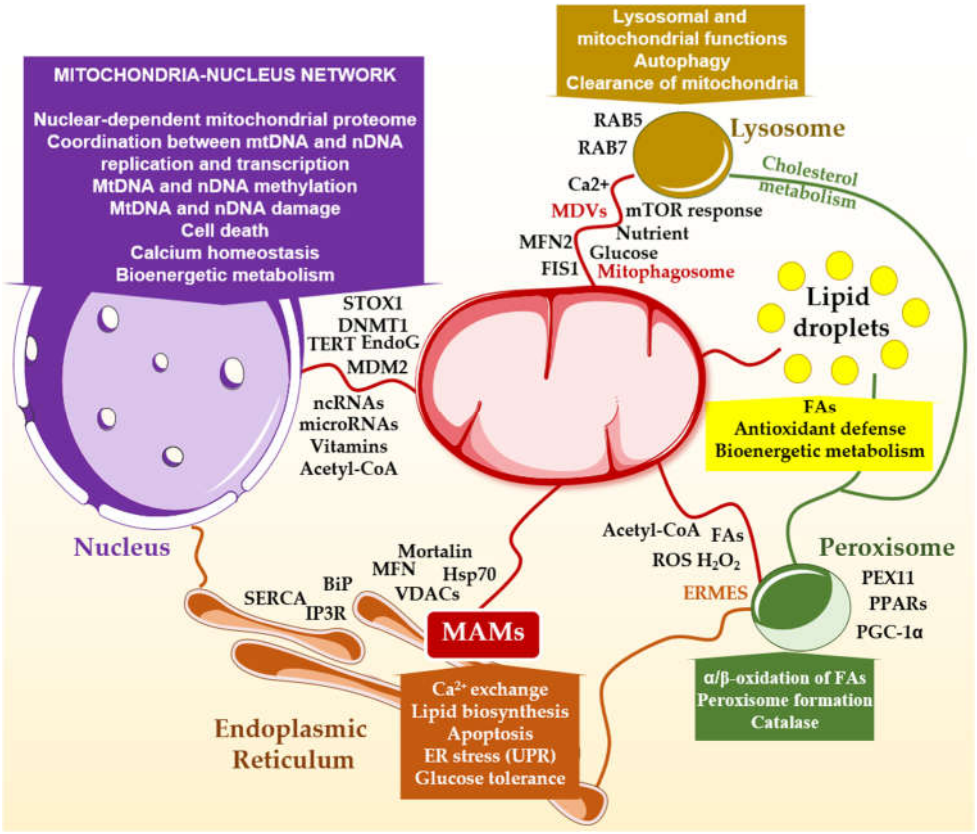

Figure 3. Crosstalk between mitochondria and key organelles. In a nonexhaustive manner, key interaction between mitochondria and other organelles are presented to encourage further investigation, including with key proteins and metabolites. BiP, Hsp70 member 5, GRP78; DNMT1, DNA methyltransferase 1; ER, Endoplasmic Reticulum; EndoG, endonuclease G; FAs, fatty acids; FIS1, mitochondrial fission 1; Hsp70, heat shock protein70; IP3R, inositol 1,4,5 triphosphate receptor; MDM2, mouse double minute 2; MDVs, mitochondrial-derived vesicles; MFN, mitofusin; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; ncRNAs, noncoding RNAs; nDNA, nuclear DNA; PEX11, peroxin-11; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PPARs, peroxisome proliferator-activated receptors; RAB5/7, ras-related protein 5/7; ROS, reactive oxygen species; SERCA, Sarcoplasmic/ER calcium ATPase; TERT, telomerase reverse transcriptase; UPR, unfolded protein response; VDACs, voltage-dependent anion-selective channel proteins.

9. Mitochondria and the Endoplasmic Reticulum

Mitochondria interact with the ER using stable close membrane contact sites called MAMs (mitochondria-associated ER membranes), a maintained interaction during ER movement along the cytoskeleton[20,55,56]. The MAMs are promoted by ERMES complex (ER-mitochondria encounter structure), and contain many proteins, including VDACs, MFN, IP3R (inositol 1,4,5 triphosphate receptor), Bcl-2 proteins, GRP-75/Mortalin/mtHsp70 (glucose-regulated protein 75), ER BiP (Hsp70 member 5, GRP78), and ER SERCA (Sarcoplasmic/ER calcium ATPase) [20,55–57]. Mitochondria-ER contact sites are involved in Ca^{2+} exchange, enzymes involved in lipid biosynthesis, including PS and PE (phosphatidylethanolamine), cholesterol transport, apoptosis control, including ER stress-mediated apoptosis, the ER stress response called UPR (unfolded protein response), insulin signaling, and glucose tolerance[20,55–57]. Mitochondria also communicate with the Golgi apparatus, in close contact with the ER, the precise communication being unclear, and possibly dependent on Ca^{2+} homeostasis[55].

10. Mitochondria and peroxisomes

Mitochondria interact with the single membrane-bound peroxisomes, which are involved in many pathways, including α- and β-oxidation of VLCFAs (very long chain fatty

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acids) to generate MCFAs, ROS H_2O_2 and acetyl-CoA, glyoxylate metabolism, amino acid regulation, and antioxidant defense through catalase[20,58]. Peroxisomal integrity maintenance through mitochondria close interaction is essential[20,58]. Mitochondria contribute to the formation of peroxisomes, including through PPARs (peroxisome proliferator-activated receptors), and the transcription factor PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1α), which modulates antioxidant enzymes, peroxisomal and mitochondrial biogenesis and functions[20]. As mitochondria, peroxisomes can fuse and divide, and are degraded in a lysosomal manner, called pexophagy[20]. Mitochondria-peroxisome interaction occurs using membrane contact sites, at ERMES complex and with peroxisomal proteins, including PEX11 (peroxin-11) that binds to mitochondrial Mdm34 protein and to ER membranes[20]. Mitochondria-peroxisomes interaction also occurs using vesicular transport, and diffusion of reactive species, including ROS, metabolites, including fatty acids and acetyl-coA[20]. Alteration of peroxisome functions impact on mitochondrial functions[20]. In addition, both peroxisomes and mitochondria interact with lipid droplet for fatty acids and antioxidant enzymes dynamics[58]. Mitochondria actively interact with lipid droplet for fatty acid biosynthesis, including TAG (triacylglycerol), and ATP generation[55]. This interaction, which is dependent on nutrient availability, impacts on fatty acid metabolism, mitochondrial dynamics, and bioenergetic metabolism[55].

11. Mitochondria and lysosomes

To degrade mitochondrial proteins and damaged mitochondria, lysosomes interact with MDVs, and mitophagosome respectively[55,59,60]. The mitochondria-lysosome crosstalk affects both mitochondrial and lysosomal functions, including through lysosomal small GTPase RAB5 and RAB7 (ras-related protein), mitochondrial FIS1 (mitochondrial fission 1) and MFN2, and calcium exchange[55,59,60]. This interaction, which could play a role in autophagy, is dependent on glucose, nutrient availability, and mTOR response (mammalian target of rapamycin)[55,59,60]. Interestingly, peroxisome also communicate with lysosome for cholesterol metabolism[58].

12. Mitochondria and the nucleus

Mitochondrial homeostasis and functions are dependent on the nucleus and nuclear genome. The mitochondrial genome is only coding for 13 proteins of OXPHOS, 2 ribosomal RNAs, and 22 transfer RNAs[12,20]. The nuclear dependence is essential for many proteins, including POLRMT (RNA polymerase mitochondrial), POLG1/2 mtDNA polymerase subunits, TFAM (transcription factor A, mitochondrial), PGC-1α, and the key antioxidant defense and OXPHOS modulator NRF2 transcription factor (nuclear factor, erythroid 2-related factor 2)[20]. Linked to a transitory giant mitochondrial tubular network for high ATP generation, mitochondrial DNA transcription and initiation of replication are prevalently coordinated with nuclear DNA synthesis phases, which includes a mtDNA replication and transcription pause during S-phase of the cell cycle[61]. Dysfunctional crosstalk between the nucleus and mitochondria induces bioenergetic metabolism alterations, oxidative distress with DNA damage in both organelles, calcium overload, and mTOR pathway disturbance[20,62]. Noncoding RNAs, including lncRNAs (long noncoding RNAs), produce both by the nuclear genome and mtDNA are part of the communication between the two organelles, for mitochondrial stability, apoptosis, and nuclear genome reprogramming[20]. In addition, it is important to note that nuclear-encoded microRNAs modulate mitochondrial respiration[20]. Moreover, colonization of nuclear genome by mitochondrial DNA fragments named NUMTs (nuclear DNA sequences of mitochondrial origin) provides key elements for DNA replication[63,64]. Nuclear DNA methylation by DNMTs (DNA methyltransferases), including DNMT1 and DNMT3, affects mitochondria through methylation of genes involved in mitochondria homeostasis, including PGC-1α, in mtDNA, including POLG1, and in OXPHOS, including NDUF genes (NADH:ubiquinone oxidoreductase subunit), UQCR2 (ubiquinol-cytochrome c reductase

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core protein 2) for complex III, and COX7B (cytochrome c oxidase subunit 7B) for complex IV[65]. Mitochondrial DNA is also methylated, including by the unique mitochondrial DNMT1, but the functional role remains unclear[65]. Mitochondrial-nuclear communication also occurs by dynamic mitochondrial metabolites, including B-vitamins B1 (thiamine) for the Krebs cycle, B2 (riboflavin) for FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) involved in many redox reactions such as antioxidant GSH/GSSG system, B3 (niacin) for NAD^+/NADH and $NADP^+$/NADPH, B5 (pantothenate) for coenzymeA, B6 (pyridoxal phosphate) for iron-sulfur biosynthesis, and B9/B11 for folate metabolism[66]. The hypoxia response HIF-1 transcription factor (Hypoxia-inducible factor 1), as well methylation and demethylation of DNA and histones are regulated by B-vitamins, including B2, B6 and B12 (cobalamin), by affecting HIF-1 stability, TET demethylase (ten-eleven translocation family of DNA demethylase) regulation, and KDM demethylase (histone lysine demethylase) regulation respectively[66]. Histone acylation is also modulated by HAT (histone acetyltransferase) and KAT (lysine acetyltransferase) fuelled by mitochondria-derived acetyl-coA, and by sirtuin deacetylases, which are dependent on B3 vitamin[66]. Modulation of mitochondrial respiration by B3 for OXPHOS complex I, and B2 for OXPHOS complex II, affects mitochondrial ROS generation, and oxidative distress that will affect nuclear DNA stability and function[66]. Moreover, during oxidative distress, accumulation of MDM2 (mouse double minute 2) into mitochondria, which is an oncoprotein that regulates nuclear transcription factors including tumor protein p53, reduces the generation of mtRNA ND6 (NADH-dehydrogenase 6), alters OXPHOS complex I function, and induces mitochondrial ROS generation[67]. In addition, storkhead box 1 (STOX1) winged-helix transcription factor, which accumulation causes human gestational disease pre-eclampsia characterized by hypertension, proteinuria, and cardiac hypertrophy, induces a switch of the nitrosoredox balance from ROS H_2O_2 to RNS $ONOO^-$, and promotes mitochondrial hyperactivity at 20% O_2 and in hypoxia in trophoblast cells[68]. Finally, mitochondrial dysfunctions alter telomere stability in the nuclear genome, and TERT (telomerase reverse transcriptase), which cycles between mitochondria and the nucleus, with a possible mitochondrial telomere-independent function of telomerase, positively regulates mitophagy through PINK1 modulation[69,70]. Upon oxidative distress in cancer cells, including ROS accumulation, over translocation of TERT into mitochondria could contribute to reduce mtROS generation, and prevent nuclear DNA damage and apoptosis[71]. Another example is the nuclear-encoded EndoG, which degrades nuclear DNA during apoptosis, that removes damage mtDNA, and that stimulates mtDNA replication initiation[72]. Altogether, many different ways for mitochondria-nucleus communication.

Interaction of mitochondria with the ER, peroxisomes, lipid droplet, lysosomes and the nucleus require further investigation improving the understanding of mitochondrial roles, which could correlate with apoptosis-necroptosis-ferroptosis death triangle, protein quality control system, calcium homeostasis, and mitochondrial metabolites. What makes this story more interesting is the involvement of ROS, and more largely, of reactive species, including mitochondrial reactive species, at all levels.

13. The Reactive Species Interactome

The concept of the Reactive Species Interactome is the interaction between ROS, RNS, RSS, RCS, and with downstream biological targets[2–4,73]. Originally defined as *a redox system*, the RSI could be at the heart of the redox interactome, and requires investigation to be fully demonstrated in physiology and pathology[1–4,73]. To overview, the ROS metabolism initiates from the precursor O_2 to form $O_2^{\cdot-}$-derived reactive species, including H_2O_2, and the notable enzymes are superoxide dismutase (SOD), catalase, xanthine oxidoreductase (XOR), and myeloperoxidase (MPO)[2,3,73]. The RNS metabolism generates nitric oxide (NO)-derived reactive species, including peroxynitrite, nitrite and nitrate, and the notable enzyme is nitric oxide synthase (NOS)[2,3,73]. The RSS metabolism, which is dependent on cysteine metabolism, generates hydrogen sulfide (H_2S)-derived reactive

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species, including H_2S_n, through many enzymes[2,3,73]. The RCS metabolism, including malondialdehyde (MDA), methylglyoxal (MGO) and 4-hydroxy-trans-2-nonenal (4-HNE), which connects ROS, RNS, and RSS, and whose notable enzyme is glutathione peroxidase (GPX), is a product of ROS metabolism and lipid peroxidation[3]. In addition, as recently reviewed, (1) ROS, and RSS are regulated by SOD, (2) ROS, RNS, and RSS are regulated by catalase, (3) ROS, and RNS are regulated by XOR, (4) ROS, RNS, RSS, and RCS are regulated by MPO, and (5) ROS, RNS, and RSS are regulated by NOS[3].

Reactive species are generated and diffused in the entire cytoplasm, including in mitochondria, and recent reviews already detailed the sources of the main endogenous reactive species, from their intra- and inter-species interactions to their downstream biological targets, different organelles, and enzymes involvement[2–4,73]. Therefore, next three sections will focus on mitochondrial reactive species sources, and, in a non-exhaustive manner, on notable enzymes linking the RSI and mitochondria, namely SOD, catalase, XOR, MPO, NOS, and GPX[3] (**Figure 4**).

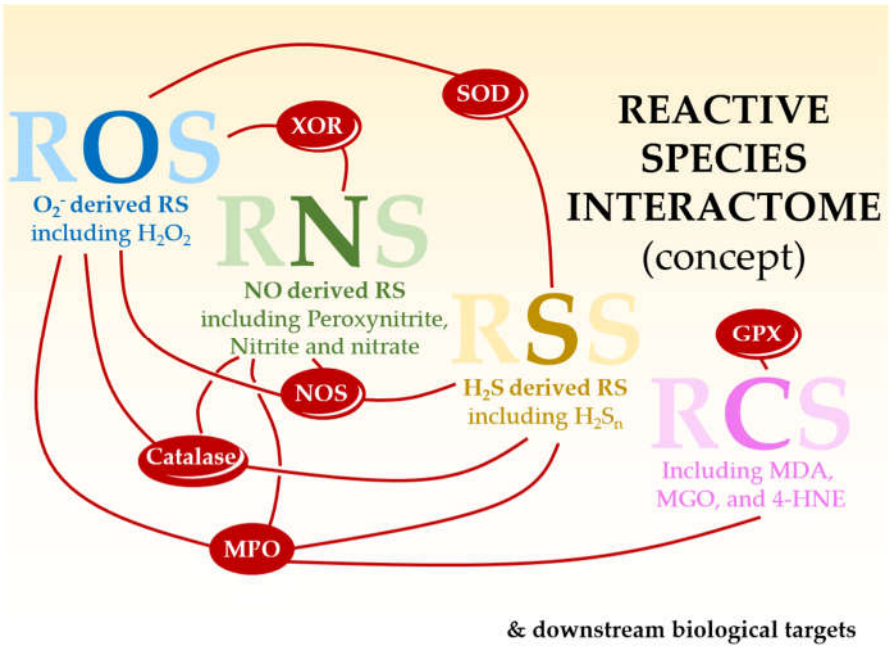

Figure 4. The concept of the Reactive Species Interactome (RSI). The RSI, which is the interaction between ROS, RNS, RSS, RCS, and with downstream biological targets, could be at the heart of the redox interactome, and requires investigation to be fully demonstrated in both physiology and pathology. GPX, glutathione peroxidase; MDA, malondialdehyde; MGO, methylglyoxal; MPO, myeloperoxidase; NOS, nitric oxide synthase; RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfur species; SOD, superoxide dismutase; XOR, xanthine oxidoreductase; 4-HNE, 4-hydroxy-trans-2-nonenal. .

14. Only ROS as mitochondrial reactive species?

It is regularly claimed that mitochondria are the major contributor to ROS generation, for a contribution of ~75-90%, although the ER is also claimed as another important contributor with nearly 25% of intracellular ROS[74,75]. Apart from this debate that still requires investigation improving the understanding of organelle contributions, in most studies and reviews, mitochondrial oxidative distress, which is the imbalance between ROS generation and antioxidant defense activity, is oversimplified to mitochondrial ROS (mtROS), mainly O_2^- and H_2O_2[74,76,77]. Only mtROS in mitochondria? (**Figure 5**)

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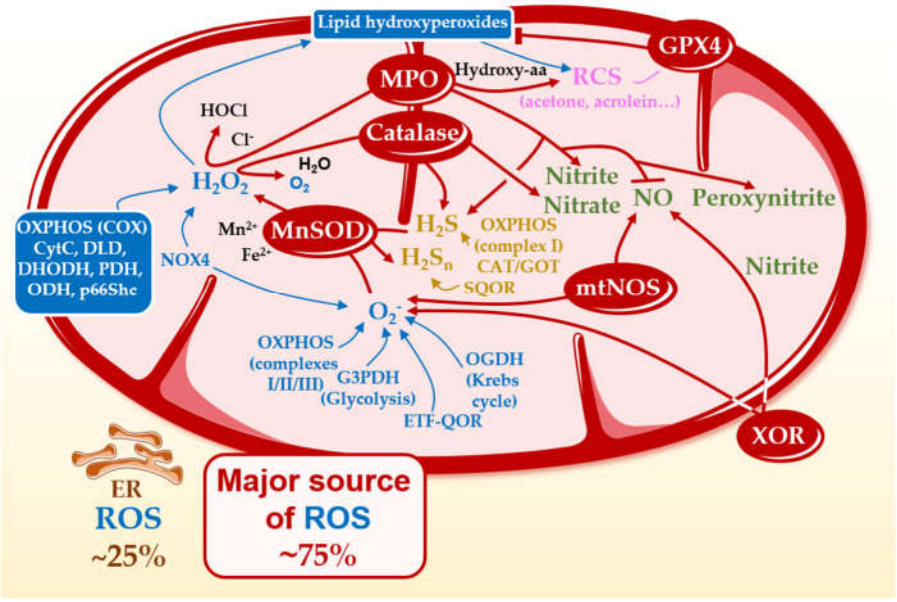

Figure 5. Only mtROS in mitochondria? In a nonexhaustive manner, the presence of ROS, RNS, RSS, RCS in mitochondria is highlighted, which includes notable enzymes involved in both RSI dynamics, and mitochondria homeostasis and function. CAT/GOT, cysteine aminotransferase/glutamate oxaloacetate transaminase; CytC, cytochrome c; COX, cytochrome c oxidase; DHODH, dihydroorotate dehydrogenase; DLD, dihydrolipoamide dehydrogenase; ER, Endoplasmic Reticulum; ETF-QOR, electron transfer flavoprotein-ubiquinone oxidoreductase; G3PDH, glycerol 3-phosphate dehydrogenase; GPX4, glutathione peroxidase 4; Hydroxy-aa, hydroxyl-amino acid; MnSOD, manganese superoxide dismutase; MPO, myeloperoxidase; mtNOS, mitochondrial nitric oxide synthase; NO, nitric oxide; NOX4, NADPH oxidase 4; ODH, 2-oxoglutarate dehydrogenase; OGDH, 2-oxoglutarate dehydrogenase; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfur species; SQOR, sulfide quinone oxidoreductase; XOR, xanthine oxidoreductase.

15. Mitochondrial ROS

Mitochondrial ROS O_2^- is generated by different mitochondrial proteins, including glycerol 3-phosphate dehydrogenase (G3PDH) during glycolysis, 2-oxoglutarate dehydrogenase (OGDH) in the tricarboxylic acid TCA/Krebs cycle, OXPHOS complexes I, and III[3,5,74,76–80]. Mitochondrial OXPHOS complex II, and electron transfer flavoprotein-ubiquinone oxidoreductase (ETF-QOR) also produce O_2^- at low level[74,81,82]. Mitochondrial NADPH oxidase 4 (NOX4) generates O_2^-, and preferentially H_2O_2[74,83].

Reduction of O_2^- to H_2O_2 is catalyzed by SOD, including in mitochondria with antioxidant superoxide dismutase manganese isoform MnSOD SOD2[3,74,84–86]. Interestingly, related to iron overload and manganese deficiency, a prooxidant alternative isoform also exists, namely peroxidase FeSOD2, which uses H_2O_2 to overoxidize many cellular components[74,84–86]. In addition, OXPHOS IV cytochrome c oxidase (COX), cytochrome c, dihydrolipoamide dehydrogenase (DLD), dihydroorotate dehydrogenase (DHODH), pyruvate dehydrogenase (PDH), 2-oxoglutarate dehydrogenase (ODH), and adaptor protein p66Shc also contribute to regulate ROS metabolism, mainly H_2O_2[2,3,74,79–82,87,88]. Finally, peroxisomal catalase, which is also found in mitochondria, dismutates H_2O_2 to O_2, and H_2O[3,74].

More than only ROS, several evidences encourage investigating the other reactive species in mitochondria.

16. Mitochondrial RNS, RSS, and RCS

As previously mentioned, (1) ROS, and RSS are regulated by SOD, (2) ROS, RNS, and RSS are regulated by catalase, (3) ROS, and RNS are regulated by XOR, (4) ROS, RNS, RSS, and RCS are regulated by MPO, and (5) ROS, RNS, and RSS are regulated by NOS[3].

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Considering that most the cited enzymes are located to mitochondria, mitochondrial reactive species are not only ROS (**Figure 5**).

Superoxide dismutase (SOD) regulates RSS by oxidizing H_2S into polysulfides H_2S_n[3,89]. Then, catalase is also able to produce nitrite NO_2^- and nitrate NO_3^-[3,90]. Catalase could also be a sulfide-sulfur oxidoreductase to metabolize H_2S as sulfide oxidase, to generate H_2S as sulfide reductase, and to eliminate H_2S_n[3,91]. Xanthine oxidoreductase (XOR), which is found in the cytosol and peroxisomes, is involved in purine catabolism to form uric acid[3,80,92,93]. Importantly, XOR also contributes to produce mitochondrial O_2^-, and to produce NO through nitrite and nitrate reduction[3,80,92,93]. Myeloperoxidase (MPO), which forms hypochlorous acid (HOCl) by oxidizing Cl^- with H_2O_2, namely the MPO-H_2O_2-chloride system, has been recently found in mitochondria in addition to the cytosol, vesicles and the nucleus[3,94–97]. Interestingly, MPO is also a major NO scavenger, and oxidizes nitrite to generate NO_2 or peroxynitrite ($ONOO^-$), which is the MPO-H_2O_2-nitrite system[3,98,99]. Furthermore, MPO also oxidizes H_2S, and generates different RCS, including acetone and acrolein, from hydroxy-amino acids[3,94–96]. Regarding NOS, mitochondria contain their own calcium-sensitive mitochondrial NOS (mtNOS)[100,101]. It is important to note that coupled NOS generate NO, while uncoupled NOS generate O_2^-, and that NO reacts with O_2^- to form $ONOO^-$, and with H_2S to form nitroxyl[3,80,102,103]. Finally, RCS, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), regulate XOR and GPX activities[3,104,105]. Glutathione peroxidase 4 (GPX4), which is localized to the nucleoplasm and mitochondria, neutralizes lipid hydroxyperoxides, which are the major source of RCS[3,104–107]. Altogether, it is proposed to carefully consider mtROS, mtRNS, mtRSS, mtRCS, and the notable enzymes Mn/FeSOD2, catalase, XOR, MPO, mtNOS, and GPX4 in the next studies.

To complete this proposal, other mitochondrial proteins are involved in the RSI dynamics, in particular through the RSS family. The accessory sulfurtransferase subunit, OXPHOS complex I is a source of H_2S[3,102]. The enzyme cysteine aminotransferase (CAT), which is involved in H_2S generation, is also a glutamate oxaloacetate transaminase (GOT) that metabolizes oxaloacetate to produce aspartate, α-ketoglutarate, and glutamate in mitochondria[108,109]. Finally, H_2S catabolism to form thiosulfate occurs, including in mitochondria, and mitochondrial sulfide quinone oxidoreductase (SQOR) generates persulfides H_2S_2[3,102,110,111].

Considering mitochondrial ROS, RNS, RSS, RCS, and notable enzymes involved in both the RSI and mitochondria, opens perspectives in mitochondrial homeostasis and roles, from interaction of mitochondria with redox-sensitive organelles, to redox-sensitive pathways, including mitochondrial bioenergetic, apoptosis-necroptosis-ferroptosis death triangle, protein quality control system, calcium homeostasis, and mitochondrial metabolites (**Figure 5**). This RSI-mitochondria axis could be a driving force for making new discoveries in physiology and pathology.

17. The RSI-Mitochondria axis in mitochondrial diseases and dysfunction

Here, the aim is not to compile all the diseases in which, together, reactive species and mitochondria are involved in. Rather several key mitochondrial diseases and mitochondrial dysfunction are discussed (**Figure 6**).

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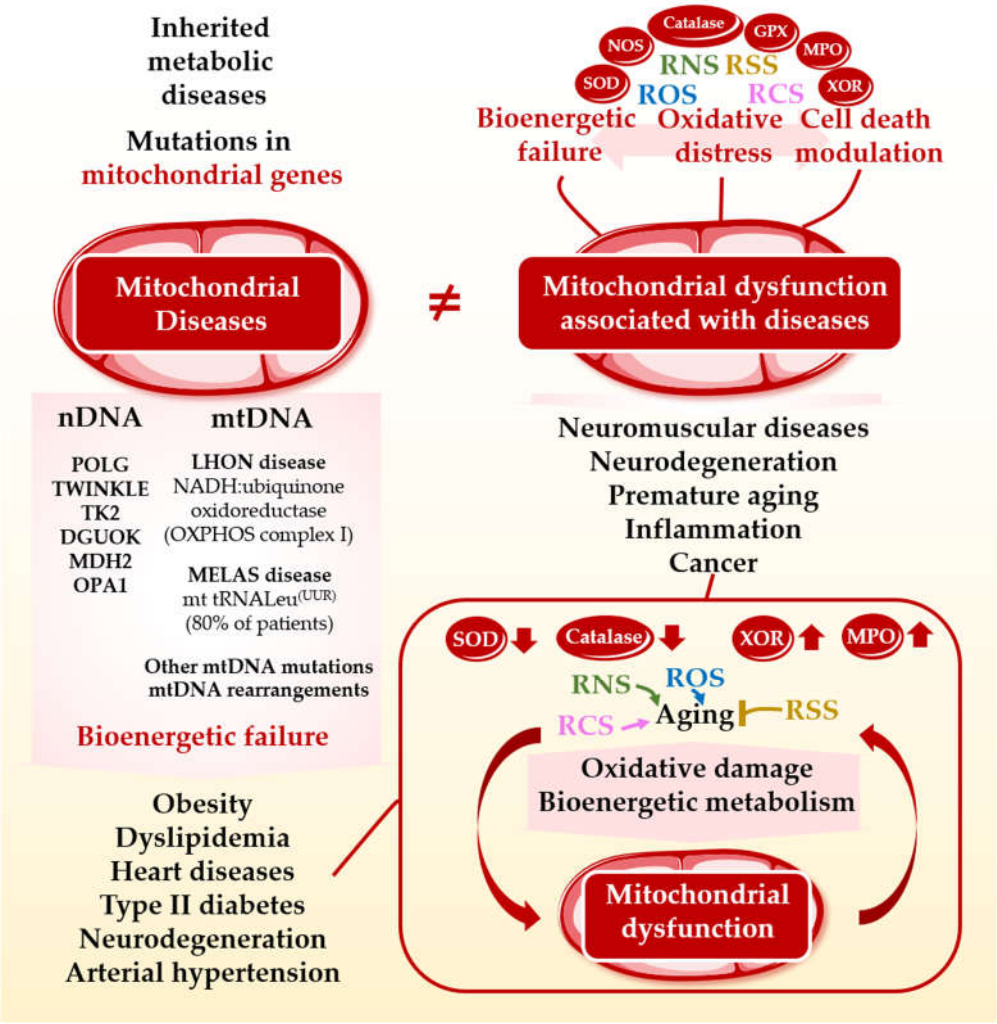

Figure 6. Mitochondrial diseases, mitochondrial dysfunction associated with diseases, and aging. Several examples of mitochondrial diseases are presented. Bioenergetic failure related to mitochondrial dysfunction, and oxidative distress related to reactive species and notable enzymes, should be more investigated in many diseases in which mitochondria are involved in, and in aging. DGUOK, deoxyguanosine kinase; LHON, Leber's hereditary optic neuropathy; MDH2, malade dehydrogenase 2; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MPO, myeloperoxidase; mt tRNA, mitochondrial transfer RNA; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; nDNA, nuclear DNA; OPA1, GTPase optic atrophy protein 1; OXPHOS, oxidative phosphorylation; POLG, DNA polymerase gamma; RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfur species; SOD, superoxide dismutase; TK2, thymidine kinase 2; XOR, xanthine oxidoreductase.

Mitochondrial diseases are different from mitochondrial dysfunction associated with diseases [112,113]. Mitochondrial diseases, which are common inherited metabolic diseases, are caused by mutations in mitochondrial genes in the nuclear DNA and mitochondrial DNA[112–114]. Mitochondrial diseases can affect any organ, including brain with neurodegeneration, strokes, ataxia, Parkinson's Disease and psychiatrics symptoms, liver, muscle, kidney, and the heart[114]. The LHON disease (Leber's hereditary optic neuropathy), caused by LHON-associated mtDNA mutations in a subunit of OXPHOS complex I NADH:ubiquinone oxidoreductase, and discovered by Douglas C. Wallace and colleagues in 1988, is the first example of mitochondrial disorder with bioenergetic failure[9,115–117]. The MELAS disease (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) is another well-known mitochondrial disease, which is a myopathy caused by mutations in the mitochondrial tRNALeu(UUR) gene in more than 80% of MELAS

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patients[112,116,118]. Mitochondrial DNA mutations are also associated with carotid intima-media thickness, atherosclerosis, and cardiovascular diseases[112,119]. In a non-exhaustive manner, mtDNA rearrangement mutations, mutations in mitochondrial DNA polymerase POLG, mtDNA maintenance protein twinkle, mitochondrial thymidine kinase 2 (TK2), mitochondrial deoxyguanosine kinase (DGUOK), mitochondrial malate dehydrogenase 2 (MDH2), and mitochondrial GTPase optic atrophy protein 1 (OPA1) lead to mtDNA deletion and depletion that affect muscle, pancreas with type II diabetes, the heart, and brain, including with neurodegeneration[9,114,116,120,121]. In addition, low mtDNA replication, and mitochondrial 7S DNA accumulation are associated with Parkinson's Disease[122]. Furthermore, alteration and aberrant function of mitochondrial kinase PINK1, which is involved in mitochondrial protein quality control and mitophagy, contribute to the pathophysiology of Parkinson's Disease[112,122,123]. Moreover, mitochondrial protein synthesis defects associated with mitochondrial tRNA mutations, and disruption of mitochondrial protein quality control, including with mAAA protease and chaperone complex, are other examples of mitochondrial diseases[114]. Finally, mitochondrial diseases are also associated with obesity, dyslipidemia, arterial hypertension, and it is important to note that mitochondrial DHODH is involved in cancer progression and recidive[9,19].

Then, mitochondrial dysfunction associated with many diseases, are dysfunction without mitochondrial genes and mtDNA mutation, and mainly related to bioenergetic failure, oxidative distress through ROS, and cell death types modulation, including apoptosis and ferroptosis[1–4,9,34,73–75,78,124]. Mitochondrial dysfunction contribute to inflammation, and many pathologies, including neuromuscular diseases, cancer, neurodegenerative disorders, and premature aging[19,38,112]. A good example is the case for the progeroid disorder Cockayne Syndrome, which is caused by DNA repair proteins CSA or CSB mutations, and characterized by accelerated aging, neurological and developmental abnormalities, and hypersensitivity to oxidative distress[38,125,126]. In the Cockayne Syndrome, caused by nitroso-redox imbalance, meaning reactive species dysregulation, the accumulation of HtrA3 serine protease (high temperature requirement A3) impairs mitochondrial bioenergetic metabolism, including by deregulating mitochondrial POLG catalytic subunit (POLG1), and leads to excessive replicative senescence[38,39]. This example is one example amongst more and more examples, with reactive species associated with mitochondrial diseases and mitochondrial dysfunction in diseases, including through OXPHOS alteration[114].

Another concern is aging, which is a physiological process associated with mitochondrial dysfunction, and many diseases. The link between mitochondria and aging is a long story, including through mtROS[3,9,124]. Originally, the *free radical theory of aging* was the concept of aging caused by ROS, and accumulation of oxidative damage[115,124]. Nowadays, improving knowledge of aging, many questions are still opened regarding ROS toxicity and roles, oxidative and other types of damage, mtDNA mutations, and nutrition related to mitochondrial bioenergetic metabolism[9,124]. Far from only ROS roles in aging, as recently reviewed, oxidative distress mediated by ROS, including $O_2^{\cdot-}$, H_2O_2 and through increased senescence, RNS, including NO, $ONOO^-$, and through nitrative damage, and RCS, including 4-HNE, MDA, and through lipid peroxidation, are pro-aging, while oxidative distress mediated by RSS, including H_2S, H_2S_n, and through inhibition of ROS and RNS generation, is anti-aging[3]. In addition, antioxidant defense decline, including SOD and catalase activity, and notable enzymes overactivation, including XOR and MPO, are pro-aging[3]. Thus, in aging, and premature aging, as previously discussed, mitochondrial ROS, RNS, RSS, RCS, and notable enzymes involved in both the RSI and mitochondria, should be further investigated.

In the RSI-Mitochondria axis, in physiology and pathology, one player may potentiate the effects, which is the bacterial microbiota.

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18. Bacterial microbiota as a key player in the RSI-Mitochondria axis ?

One of the most studied bacterial microbiota is the gut microbiota, which includes the most abundant phyla *Firmicutes* and *Bacteroidetes*[127].

The *microbiota-gut-brain axis*, which is defined as *a bidirectional communication system between the gut and the brain*, is related to metabolic pathways, through multiple bacterial metabolites, such as SCFAs, namely acetate, propionate, and butyrate[127,128]. In the gut, *Bacteroides*, *Bifidobacterium*, *Parabacteroides* and *Escherichia spp.* generate neurotransmitter GABA[129]. The gut bacterial microbiota in the microbiota-gut-brain axis could be a susceptibility factor for neurological diseases, including epilepsy, Huntington's disease, Parkinson's disease, autism spectrum disorder, and Alzheimer's disease[128,130]. The gut bacterial microbiota is also involved in neurodevelopment, including neurogenesis, myelination, and microglial activation, through SCFAs and other metabolites[128,130]. In Alzheimer's disease, gut dysbiosis leads to overgeneration of bacterial proinflammatory neurotoxins, and may promote neuroinflammation, amyloid-beta accumulation, increase in blood-brain-barrier permeability, insulin resistance, and oxidative distress[127–129]. The gut bacterial microbiota is suggested either to contribute to reactive species, including ROS, generation and/or to interfere with antioxidant defense[127,128]. In Parkinson's disease, gut bacterial microbiota dysbiosis, including with low abundance of bacterial SCFAs, and reduced plasma levels of NAD (nicotinamide adenine dinucleotide) and TUDCA (Tauroursodeoxycholic acid), could contribute to mitochondrial dysfunction[128,129,131]. Bacterial produced SCFA butyrate prevents mitochondrial bioenergetic failure by providing acetyl-CoA, bacterial produced TUDCA is an anti-apoptotic metabolites that upregulates mitophagy, and regulates OXPHOS complex I, and bacterial produced NAM (nicotinamide), the amide form of niacin, contributes to regulate the plasma level of NAD, which improves mitochondrial function, including energy generation[131].

The bacterial microbiota-mitochondria interaction could also be a crucial player in inflammatory diseases[132,133]. In Crohn's disease, which is a type of inflammatory bowel disease (IBD), alteration of the gut bacterial microbiota, including H_2S producer *Atopobium parvulum*, associated with decrease in butyrate content, impairs mitochondrial function, including mitochondrial OXPHOS, and mitochondrial proteins involved in H_2S regulation, such as sulfur dioxygenase (ETHE1), and thiosulfate sulfurtransferase (TST)[132,133]. Bacterial butyrate producer may cause mitochondrial dysfunction, and may contribute to overgenerate mtROS[127]. Mitochondrial ROS accumulation also affects the composition of the gut bacterial microbiota[132,133]. Then, in atherosclerosis, which is characterized by (1) fats and cholesterol deposition in the wall of the artery, (2) inflammation, and (3) increase in risk of myocardial dysfunction and stroke, bacterial metabolite trimethylamine N-oxide (TMAO) may deregulate lipid metabolism[133]. Increase in plasma TMAO is associated with increase in fats and cholesterol deposition in the wall of the artery[133]. In addition, mitochondrial dysfunction, through mtROS accumulation and associated with inflammation, is involved in the progression of atherosclerosis[133].

In addition, the gut bacterial microbiota-mitochondria axis is also involved in obesity and type 2 diabetes (T2D), through bacterial metabolites dysregulation, including SCFAs, and mitochondrial dysfunction at OXPHOS level due to mtROS, NO, and $ONOO^-$ accumulation [134]. Thus, gut bacterial microbiota dysbiosis is also a serious concern, including with low abundance of *Bacteriodetes* and *Akkermansia muciniphila* in obese and T2D patients, and a correlation between *Clostridium* and *Lactobacillus* species with insulin resistance[134]. In this line, genetic variants of the mtDNA affect mitochondrial bioenergetic function, and both the composition and the activity of the gut bacterial microbiota, including with different diet, and during exercise[135]. High protein consumption during resting days and training could negatively affect the gut bacterial microbiota composition and activity, including through overgeneration of H_2S, and so consequently possibly with mitochondrial dysfunction[135].

Moreover, during infection, including viral infection in COVID19 pathogenesis, it is suggested that mitochondrial dysfunction linked to oxidative distress mediated by

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mtROS, may contribute to bacterial microbiota dysbiosis, which will further contribute to coagulopathy, iron and ferroptosis dysregulation, and the vicious cycle of inflammation and oxidative distress in many organs[136].

Regarding aging, the diversity of the gut bacterial microbiota could be a hallmark of healthy aging[130]. Aging is associated with a reduction in diversity of the gut bacterial microbiota, a decrease in SCFA generation, including butyrate, and a colonization by different species, including streptococci, staphylococci, and enterococci[137]. In long living people, including centenarians, *Firmicutes* and *Bacteroidetes* are still dominants, and an enrichment has been reported in both facultative anaerobes from Proteobacteria phylum, and *Akkermansia*, *Lactobacillus*, and *Bifidobacterium*[137]. Furthermore, dysregulation of the gut bacterial microbiota affects oxidative distress and mitochondrial function in microglia from aged mice, through N^6-carboxymethyllysine metabolite, which is a member of RCS that contributes to modulate ROS generation[138].

In brain, in inflammation, in metabolic disorders, and in aging, the bacterial microbiota is linked to both mitochondria and reactive species, not only ROS[128,139]. The nexus between bacterial microbiota and mitochondria could be the RSI and notable enzymes. As already discussed, ROS are regulating, and are regulated by both bacterial microbiota and mitochondria[139]. For examples, *Lactobacillus* stimulate ROS production in gut stem cells, and gut bacterial dysbiosis is associated with decrease in colonic acid, SCFA acetate, propionate, butyrate, indole, phenolic acid, which together induce mitochondrial dysfunction, and mtROS generation[128,139]. Then, looking at RNS and RSS, in the gut, bacteria *Lactobacilli* and *Bifidobacterium* convert nitrite and nitrate into NO, *Streptococcus* generate NO, while *Salmonella* and *Escherichia coli* produce H_2S[129,140]. Commensal oral bacteria, including *Firmicutes Staphylococcus*, *Streptococcus*, *Veillonella*, and *Actinobacteria* play a crucial role in shaping the development of pulmonary hypertension, obesity, and cardiovascular diseases, through regulation of nitrate, nitrite, and NO synthesis and signaling, including with nitrite and nitrate reductase activities[141]. In Parkinson's disease, H_2S generated by gut bacterial microbiota, including by *Akkermansia muciniphila*, *Bilophila wadsworthia*, *Prevotella*, and *Porphyromonas*, may induce the disease, with an excess of H_2S that promotes mitochondrial dysfunction, increases iron content and ROS, and leads to alpha-synuclein aggregation[142]. In addition, during inflammation in the intestinal epithelium, H_2S is overgenerated by multiple bacteria, including *Fusobacterium*[143]. Moreover, colonic inflammation and colorectal cancer are associated with increase in RCS, including 4-HNE and MDA, which alter the gut bacterial microbiota by reducing the growth of beneficial anaerobic bacteria, and by increasing the growth of redox-resistant deleterious bacteria[144]. Moreover, the gut bacterial microbiota contributes to produce the aminated metabolite of epigallocatechin-3-gallate polyphenol, which scavenges RCS, including 4-HNE and MDA[145].

Focusing on notable enzymes involved in the RSI and mitochondria, during exercise, inflammation, and gut dysbiosis, the gut bacterial microbiota regulates SOD activity, although it requires further investigation improving the relationship between the gut bacterial microbiota, SOD, and the intestinal redox balance[135]. The colonic bacterial microbiota contributes to infectious colitis with *Citrobacter rodentium* that leads to increase in *Bacteroides*, and reduction in both antioxidant glutathione GSH, and mitochondrial MnSOD/SOD2[135,146]. To limit the immune response linked to mitochondrial dysfunction, several pathogenic bacteria tend to reduce mtROS generation through overactivating SOD activity, such as with *Mycobacterium tuberculosis*, and *Ehrlichia chaffeensis*[135,147,148]. The gut bacterial microbiota, including with *Bifidobacterium adolescentis*, also stimulates catalase activity to limit osteoporosis and neurodegeneration, and to improve healthspan and lifespan[149]. Bacterial microbiota-derived tryptophan indoles protect tissues during intestinal inflammation, by selectively inhibiting MPO[150]. Reduction in generation of hypochlorous acid by MPO through indoles, contributes to reduce intestinal damage, and inflammation[150]. The catecholate siderophore enterobactin produced by *Escherichia coli* is also an inhibitor of MPO, which contributes to gain a survival ad-

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vantage for *E.coli* during inflammatory gut diseases[128,151]. Together, the MPO inhibition links the bacterial microbiota, notable enzyme MPO within the RSI, and innate immune system[150,151]. Interestingly, brain damage due to extensive stroke lead to gut bacterial dysbiosis, which also affects immune system, thus contributing to pro-inflammation, and systemic oxidative distress[128,152]. In addition, regarding notable NOS enzyme, the gut bacterial microbiota is regulated by NO produced by NOS, while bacterial infection can lead to both upregulation of NOS and increase in NO content, which in turn stimule the immune response[153]. Furthermore, in mice, lactic acid bacteria, including *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, contribute to reduce uric acid in serum and urine, through reduction in XOR activity, by increasing SCFAs generation[154]. Finally, intestinal ischemia/reperfusion (I/R) alters gut microbiota, and induces ferroptosis[155]. Interestingly, in mice, gut bacterial microbiota capsiate metabolite reduces I/R-induced ferroptosis by enhancing glutathione peroxidase 4 (GPX4) expression[155].

Altogether, several points were discussed to encourage investigating the RSI-Mitochondria axis by including bacterial microbiota, when possible, as a new key player (**Figure 7**).

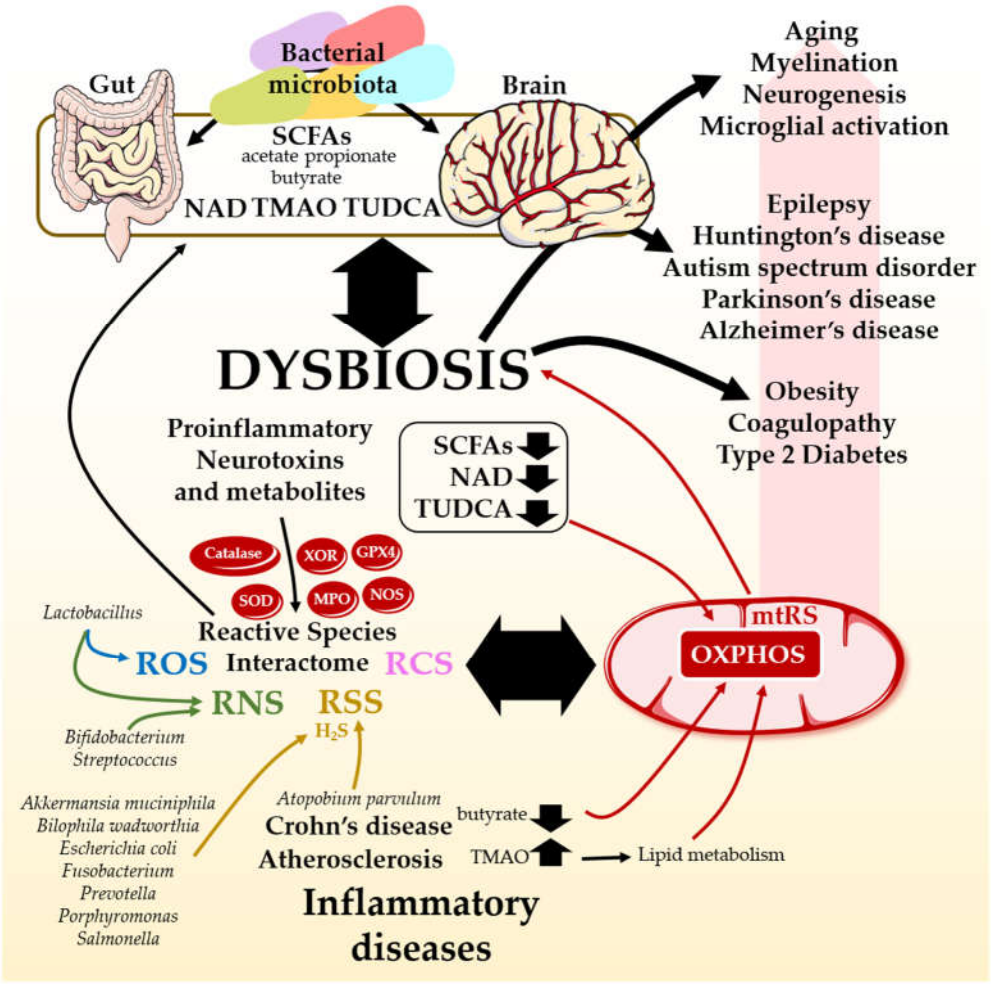

Figure 7. The gut bacterial microbiota and the RSI-mitochondria axis. Key links between the gut bacterial microbiota, and the RSI-mitochondria axis are presented to summarize the corresponding section. GPX4, glutathione peroxidase 4; MPO, myeloperoxidase; mtRS, mitochondrial reactive species; NAD, nicotinamide adenine dinucleotide; NOS, nitric oxide synthase; OXPHOS, oxidative phosphorylation; RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfur species; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; TMAO, trimethylamine N-oxide; TUDCA, Tauroursodeoxycholic acid; XOR, xanthine oxidoreductase.

19. Conclusion

This review is a new step, a new stone encouraging investigations on the RSI-mitochondria axis, from apoptosis-necroptosis-ferroptosis death triangle, protein quality control system, calcium homeostasis, and mitochondrial metabolites, to inter-organelle crosstalk including mitochondria, in physiology, mitochondrial diseases, and mitochondrial dysfunction associated with diseases. In addition, including bacterial microbiota in the RSI-mitochondria axis will strengthen the perspectives on redox signaling, redox physiology, and redox medicine.

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