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Review

Mitochondrial quality control and communications with the nucleus are important in maintaining mitochondrial function and cell health☆,☆☆

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ABSTRACT

Background: The maintenance of cell metabolism and homeostasis is a fundamental characteristic of living organisms. In eukaryotes, mitochondria are the cornerstone of these life supporting processes, playing leading roles in a host of core cellular functions, including energy transduction, metabolic and calcium signalling, and supporting roles in a number of biosynthetic pathways. The possession of a discrete mitochondrial genome dictates that the maintenance of mitochondrial 'fitness' requires quality control mechanisms which involve close communication with the nucleus.

Scope of review: This review explores the synergistic mechanisms that control mitochondrial quality and function and ensure cellular bioenergetic homeostasis. These include antioxidant defence mechanisms that protect against oxidative damage caused by reactive oxygen species, while regulating signals transduced through such free radicals. Protein homeostasis controls import, folding, and degradation of proteins underpinned by mechanisms that regulate bioenergetic capacity through the mitochondrial unfolded protein response. Autophagic machinery is recruited for mitochondrial turnover through the process of mitophagy. Mitochondria also communicate with the nucleus to exact specific transcriptional responses through retrograde signalling pathways.

Major conclusions: The outcome of mitochondrial quality control is not only reliant on the efficient operation of the core homeostatic mechanisms but also in the effective interaction of mitochondria with other cellular components, namely the nucleus.

General significance: Understanding mitochondrial quality control and the interactions between the organelle and the nucleus will be crucial in developing therapies for the plethora of diseases in which the pathophysiology is determined by mitochondrial dysfunction. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction — mitochondrial function and fitness are fundamental to cellular health

Mitochondria are critical cellular organelles best known for their role in providing efficient energetic support through the chemiosmotic process of oxidative phosphorylation (OXPHOS). Although mitochondria were first observed in the latter part of the 19th century, their role in aerobic energy transduction through the characteristic chemiosmotic mechanism of OXPHOS first began to be clarified in the 1960s [1]. Since then, mitochondria have also been shown to perform a variety of roles in processes such as the transduction of metabolic and stress signals [2,3], the production of free radicals such as reactive oxygen species (ROS) [4], and the induction of programmed cell death [3]. Central to cellular bioenergetic homeostasis is the requirement to sustain the mitochondrial population to ensure that cellular energy demands are met by energy supply. A variety of quality control (QC) mechanisms have evolved which ensure cellular bioenergetic homeostasis, managing mitochondrial components, products and by-products. Dysregulation of these pathways is emerging as a key theme in understanding many contemporary human diseases. Thus, it is increasingly clear that mitochondrial dysfunction and disordered regulation of mitochondrial homeostasis play integral roles in the pathophysiology of conditions such as cancer [5], neurodegeneration [6], as well as ageing [7]. In addition, dysfunction of mitochondria caused by mutations in genes coding for the organelle components typifies a distinctive class of conditions known as mitochondrial diseases [8].

Mitochondrial structure is characterised by two protein containing lipid bilayers. The main compartments of the organelle are the external outer mitochondrial membrane (OMM), the inter membrane space (IMS) and the matrix, which is enclosed by the inner mitochondrial membrane (IMM) that undergoes intense folding into cristae, which vastly expand the membrane surface area. The electron transport

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chain (ETC.) complexes work together through cellular respiration to generate the proton gradient across the IMM that delivers the crucial chemiosmotic force of the OXPHOS process. The biochemistry that underpins the OXPHOS process revolves around a variety of redox reactions, the transfer of electrons between protein complexes, and the eventual delivery of electrons to molecular oxygen (O_2). However, stray electrons can react prematurely and incompletely with O_2 in the local environment, especially if the respiratory chain is compromised, leading to the formation of free radicals known as reactive oxygen species (ROS) [4,9]. Primarily considered dangerous by-products that can impair the structure and activity of proteins and lipids, ROS also appear to be essential signalling components of cellular physiology [10,11]. Nevertheless, production of ROS can lead to the accumulation of damaged mitochondrial components. Primary cellular defences against this type of oxidative stress have been resourcefully adapted so as to detoxify the harmful effects of ROS while maintaining their signalling capacity.

Loss of activity, misfolding, and aggregation of protein components due to genetic mutations or environmental stress are important causes of mitochondrial dysfunction that lead to deterioration in cellular health [12–14]. The replenishment of mitochondrial proteins is a complex process, as it requires the coordinated expression of two genomes, the nuclear and mitochondrial. The human mitochondrial genome encodes only 13 proteins, all of which are critical components of the respiratory chain complexes, as well as two ribosomal subunits and all the tRNAs required for protein translation [15]. All other mitochondrial proteins are encoded by the nuclear genome. Formation of the functional OXPHOS complexes is heavily reliant on a strict stoichiometry of protein components in order to correctly assemble in the IMM [16]. Hence, the effective and measured transcription and translation of both genomes must be coordinated to avoid superfluous expression and accumulation of non-functional proteins within mitochondria. The nuclear genome also encodes for mitochondrial targeted proteins responsible for regulating mtDNA encoded gene expression and replication, thus playing a major part in regulating mitochondrial genome function and capacity [17]. This pathway is complemented by the emerging role of the converse regulation of nuclear gene expression in response to cues originating from the mitochondria, in a process termed retrograde signalling [18,19]. Hence, mechanisms of mitochondrial QC include the monitoring and control of components, function, and products, as well as the communication between mitochondria and other cellular components. During this review we aim to highlight current understanding of mitochondrial QC processes as they relate to different aspects of mitochondrial structure and function, as well as remarking on various associated systems that are essential for QC.

2. Antioxidant defences and the regulation of reactive oxygen species (ROS)

2.1. The multifaceted ROS — oxidative stress and physiological requirement for ROS

Oxidative stress is an environmental condition where ROS generated exceeds the capacity of antioxidant defences in neutralising free radicals, and thus results in damage caused by the aberrant reactivity of ROS with cellular components. Oxygen derived free radicals are an important by-product of the mitochondrial ETC., not only because of their potential to cause damage, but also because they are thought to play important signalling roles essential for physiological cellular function [9,11]. ROS are initially formed by the premature release of electrons from the ETC. and the reduction of molecular oxygen (O_2) to form the superoxide radical ($^{\bullet}O_2^-$) [4,9]. Superoxide is thought to be generated at seven different sites associated with proteins at the IMM, which mainly generate superoxide on the matrix side of the IMM. Of these sites, two also release O_2^- into the IMS [10]. Superoxide has a very short half-life and is highly reactive, causing damage to vital mitochondrial components such as mtDNA, lipid membranes and to respiratory complexes, all of which are located near the sites of superoxide production [9,10]. Superoxide can then be transformed into other free radical species via enzymatic catalysis mediated by superoxide dismutases that generate hydrogen peroxide (H_2O_2), by iron (Fe) mediated chemistry forming the highly reactive hydroxyl radical ($^{\bullet}OH^-$), and also reacting with nitric oxide ($^{\bullet}NO$) to form the highly reactive and very damaging peroxynitrite anion ($^{\bullet}ONOO^-$).

The presence of Fe in an environment in which H_2O_2 has been released can lead to the generation of $^{\bullet}OH^-$ on the basis of Fenton chemistry [20] (Fig. 1). The process is comprised of the oxidation of ferrous iron (Fe^{2+}) in the presence of H_2O_2 to form ferric iron (Fe^{3+}), which concomitantly releases a hydroxyl radical ($^{\bullet}OH^-$), followed by the reduction of the iron back to Fe^{2+} by the same H_2O_2 molecule that also releases a proton and a hydroperoxyl radical ($^{\bullet}OOH^-$) (i.e. a protonated form of $^{\bullet}O_2^-$). The following reaction describes the Fenton chemistry involved in $^{\bullet}OH^-$ production from H_2O_2 reacting with Fe^{2+}:

$$Fe^{2+} + H_2O_2 + H2 \rightarrow Fe^{3+} + {}^{\bullet}OH^- + H_2O$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + {}^{\bullet}OOH^- + H^+.$$

In order to prevent oxidative stress generated through Fenton chemistry, cells have evolved the capacity to regulate iron availability throughout the cell through specific storage components known as ferritins, which are able to regulate the release of iron within specific compartments such as the mitochondria [21]. Another protein linked with iron homeostasis in mitochondria is frataxin, which is primarily thought to be involved in facilitating iron–sulphur (Fe–S) cluster biogenesis. Mutations that lead to the reduced expression of frataxin are strongly linked with the neurodegenerative disease Friedreich's ataxia [22].

$^{\bullet}O_2^-$ also readily reacts with $^{\bullet}NO$ resulting in the formation of $^{\bullet}ONOO^-$, a free radical species which can have a major effect on cellular function and health [23]. $^{\bullet}ONOO^-$ and its products can potentially have a multitude of effects on protein, lipid, and DNA components, either through oxidation or nitration. For instance, the essential cofactor tetrahydrobiopterin (BH_4), of the endothelial nitric oxide synthase (eNOS), is highly sensitive to oxidation by $^{\bullet}ONOO^-$. Loss of BH_4 function through oxidative damage can lead the eNOS to generate $^{\bullet}O_2^-$ and contribute further to oxidative stress. This cycle of damage to eNOS by $^{\bullet}ONOO^-$ is thought to be an important pathophysiological factor in vascular disease [24]. The reaction of $^{\bullet}ONOO^-$ with other molecules can also lead to the formation of more damaging ROS. An example of this activity of $^{\bullet}ONOO^-$ is the reaction with CO_2 in the aqueous phase leading to the formation of carbonate ($^{\bullet}CO_3^-$) and nitrogen dioxide ($^{\bullet}NO_2$) [25]. Both $^{\bullet}CO_3^-$ and $^{\bullet}NO_2$ are potent one electron oxidants and are thought to readily cause damage to proteins, lipids, and DNA [23]. It is clear that the cellular elements exposed to superoxide in the immediate environment of its generation will determine the downstream consequences of ROS generation.

In contrast to the damaging effects of excessive ROS production, low levels of ROS produced by mitochondria appear to operate as important signals involved in maintaining cellular homeostasis and inducing stress responses [4]. As primary components involved in oxygen utilisation, mitochondria can also act as oxygen sensors and induce appropriate responses during hypoxic conditions. Interestingly, the mechanism that senses low levels of oxygen is thought to typically require the release of H_2O_2 by mitochondria in order to activate the transcriptional regulator known as hypoxia induced factor 1α (HIF-1) [11]. Although the HIF-1 subunit HIF-1α is constitutively expressed, it is hydroxylated by prolyl hydroxylase (PHD) on proline residues and marked for rapid degradation during normoxia. However, H_2O_2 appears to inhibit this activity of PHD and thus leads to stabilisation of HIF-1α, which activates the transcription of factors involved in hypoxic response [9]. Although the generation of ROS (which is highly reliant on oxygen availability) may seem paradoxical as a signal under hypoxic conditions, it may form