Nutrition Research Reviews (2020), 33, 90–101
doi:10.1017/S0954422419000210

Crosstalk between mitochondrial metabolism and oxidoreductive homeostasis: a new perspective for understanding the effects of bioactive dietary compounds

Mariangela Di Giacomo[1], Vincenzo Zara[1], Paolo Bergamo[2]† and Alessandra Ferramosca[1]*†
[1]*Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy*
[2]*Institute of Food Sciences, National Research Council (CNR-ISA), Avellino, Italy*

Abstract

Mitochondria play an important role in a number of fundamental cellular processes, including energy production, biosynthetic pathways and cellular oxidoreductive homeostasis (redox status), and their dysfunction can lead to numerous pathophysiological consequences. As the biochemical mechanisms orchestrating mitochondrial metabolism and redox homeostasis are functionally linked, mitochondria have been identified as a potential therapeutic target. Consequently, considerable effort has been made to evaluate the efficacy of natural compounds that modulate mitochondrial function. Molecules produced by plants (for example, polyphenols and isothiocyanates) have been shown to modulate mitochondrial metabolism/biogenesis and redox status; however, despite the existence of a functional link, few studies have considered the combined efficacy of these mitochondrial functions. The present review provides a complete overview of the molecular pathways involved in modulating mitochondrial metabolism/biogenesis and redox status. Crosstalk between these critical mechanisms is also discussed, whilst major data from the literature regarding their antioxidant abilities are described and critically analysed. We also provide a summary of recent evidence regarding the ability of several plant-derived compounds to target these mitochondrial functions. An in-depth understanding of the functional link between mitochondrial metabolism/biogenesis and redox status could facilitate the analysis of the biological effects of natural compounds as well as the development of new therapeutic approaches.

Key words: **Mitochondrial dysfunction: Bioactive molecules: Reactive oxygen species: Oxidative stress: Antioxidant mechanisms**

Introduction

Mitochondria play a critical role in the generation of metabolic energy in eukaryotic cells. These double membrane-enclosed organelles are characterised by the presence of enzymes that are involved in many distinct metabolic pathways (pyruvate and fatty acid oxidation and the Krebs cycle) and are responsible for producing the reducing equivalents (NADH and $FADH_2$) required to generate ATP via oxidative phosphorylation (OXPHOS)[1].

NADH and $FADH_2$ are used in the electron transport chain (ETC), which is composed of four distinct multi-subunit complexes (I, II, III and IV) and two electron shuttle molecules (ubiquinone or coenzyme Q (CoQ) and cytochrome *c*). The ETC is responsible for transporting reducing equivalents from electron donors to oxygen molecules, ultimately forming water. The energy released from these oxidation/reduction reactions is used to drive ATP synthesis. This sophisticated mechanism, which requires strict coupling between electron transfer through respiratory chain complexes and the phosphorylation of ADP to ATP, provides the majority (80–90 %) of all fatty acid-derived energy.

In addition to their basic role in ATP synthesis, mitochondria are a major source of reactive oxygen species (ROS), which are key mediators of cellular physiology and pathology[2–4]. Maintaining mitochondrial function is crucial, since perturbations can lead to negative consequences, such as impaired biomolecule synthesis, disrupted cellular osmolarity and cell death[5,6]; in fact, mitochondrial dysfunction has been associated with numerous human diseases, including metabolic, cardiovascular and neurodegenerative diseases, cancer, psychiatric disorders and ageing[7–13].

Some natural bioactive compounds offer attractive new therapeutic options, since they can target mitochondria. Thanks to their peculiar properties, these molecules are able to improve mitochondrial functionality and thus regulate the processes in which they are involved[14]. The present review

Abbreviations: $\Delta\Psi_m$, mitochondrial transmembrane potential; ΔpH, proton gradient; AMPK, AMP-activated protein kinase; CAT, catalase; CoQ, coenzyme Q; ETC, electron transport chain; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, glutathione disulfide; HO-1, haeme oxygenase; NRF, nuclear respiratory factor; Nrf2, nuclear factor erythroid-derived 2-like; OXPHOS, oxidative phosphorylation; PGC-1α, PPARγ coactivator-1α; ROS, reactive oxygen species; SOD2, superoxide dismutase 2; SIRT1, sirtuin 1; SIRT3, sirtuin 3; TCA, tricarboxylic acid; UCP, uncoupling protein.

* **Corresponding author:** Alessandra Ferramosca, fax +39 0832 298698, email alessandra.ferramosca@unisalento.it
† These authors contributed equally to the present review.

Table 1. Nutritional regulators of mitochondrial functions

Nutritional factors	Regulated process	Target
Macronutrients		
Low-protein diet	OXPHOS	↑ Complex III ↓ ATP synthase
	Redox homeostasis	↓ SIRT3, antioxidant enzymes
	Mitochondrial biogenesis	↓ SIRT 3
High-fat diet	ETC	$FADH_2$/NADH
	OXPHOS	↑ UCP2
High-carbohydrate diet	Fatty acid oxidation	↓ AMPK, ↓ ACC
Micronutrients		
Vitamins B_2 and B_3	ETC	↑ Complex I
Fe	ETC	↑ Complex I, ↑ complex II
Cu	ETC	↑ Complex IV
Mn	Redox homeostasis	↑ SOD2
Se	ETC	↑ Complex I, ↑ complex IV
Coenzyme Q_{10}	ETC	↑ Complex I, ↑ complex II

OXPHOS, oxidative phosphorylation; SIRT3, sirtuin 3; ETC, electron transport chain; UCP2, uncoupling protein 2; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; SOD2, superoxide dismutase 2.

summarises the most recent evidence regarding the ability of new bioactive compounds to target mitochondria and improve and/or restore their defective function, with a particular focus on their involvement in oxidative stress status. Since mitochondrial metabolic processes involve a number of proteins and protein complexes, the introductory paragraphs aim to provide the information necessary to understand the pathways via which these molecules elicit their biological effects, rather than a complete overview of the mechanisms that modulate mitochondrial function.

Nutritional regulation of mitochondrial function

Carbohydrates, lipids and proteins are not only substrates for metabolic bioenergetic pathways, but also modulate mitochondrial function. In fact, adequate nutrient levels are essential for mitochondrial function; an excessive supply (due to high-energy, high-carbohydrate or high-fat diets) or deficiency can be detrimental to mitochondria. Similarly, micronutrients such as vitamins and minerals are essential for mitochondrial function and biological activities, often affecting mitochondrial health as antioxidants, cofactors or coenzymes, or components of mitochondrial biogenesis and/or metabolic functions. A detailed description of how macro- or micronutrients modulate mitochondrial health and the molecular mechanisms involved is beyond the scope of this review because it has been recently and exhaustively analysed[15,16]. The modulation of mitochondrial function and redox homeostasis by nutritional components is summarised in Table 1. The molecular targets influenced by nutritional factors will be described in the following paragraphs.

Another interesting aspect of nutritional regulation is energy restriction, usually defined as a moderate (20–40 %) reduction in energy intake compared with *ad libitum* feeding, which can induce mitochondrial metabolic reprogramming by preserving oxidative capacity and decreasing oxidative damage[17]. Therefore, we will discuss mitochondrial mechanisms that benefit from energy restriction.

Key regulators of mitochondrial function

Mitochondria are responsible for converting food-derived chemical energy into energy that cells can use (ATP). Adequate nutrient levels are essential for mitochondrial function, with the fatty acid oxidation pathway playing a major role in this form of energy production. When fatty acids enter cells via specific cell surface transporters, fatty acyl-CoA synthase (FACS) adds CoA groups to give rise to acyl-CoA, which is then converted into a long-chain acyl-carnitine by carnitine palmitoyltransferase 1 (CPT1). This modification allows acyl groups to be transported across the inner mitochondrial membrane by carnitine translocase, where long-chain acyl-carnitine is converted back into long-chain acyl-CoA by carnitine palmitoyltransferase 2 (CPT2). In the mitochondrial matrix, fatty acids are broken down to acetyl-CoA molecules[18] which enter the Krebs cycle, also known as the tricarboxylic acid (TCA) cycle.

Malonyl-CoA is the product of the acetyl coenzyme A carboxylase (ACC) reaction in fatty acid synthesis and is an important regulator of fatty acid oxidation, with its concentration determining the switch between fatty acid synthesis and oxidation[19]. AMP-activated protein kinase (AMPK) appears to be extremely important for this process since it modulates cellular energy balance.

In response to an increased AMP:ATP ratio, AMPK phosphorylation inhibits fatty acid biosynthesis by inhibiting ACC activity[20], and thus reduces malonyl-CoA levels. As metabolic disorders can dysregulate fatty acid metabolism (elevated fatty acid synthesis or impaired fatty acid oxidation) and as AMPK plays a key role in regulating fatty acid synthesis and oxidation, this enzyme is considered an attractive target for managing metabolic disorders[21]. Moreover, AMPK is involved in sirtuin 1 (SIRT1) activation. Sirtuins are a family of NAD^+-dependent deacetylases involved in the regulation of many biological processes, including stress responses, metabolism, development and longevity. Like AMPK, SIRT1 is thought to regulate the physiological processes underlying energy restriction; Cohen *et al.*[22] demonstrated that energy restriction induces SIRT1 expression, suggesting that AMPK could be an important link between sensing and adapting to energy restriction[23]. In fact, AMPK can regulate NAD^+ levels to cause SIRT1 activation, which can alter the transcriptional activity of PPARγ coactivator-1α (PGC-1α).

PGC-1α belongs to a family of transcriptional coactivators that play a central role in regulating cellular metabolism[24], including maintaining glucose, lipid and energy homeostasis[25] and oxidative metabolism (respiration and mitochondrial biogenesis). PGC-1α levels are low under physiological conditions, but increase in response to increased bioenergetic demands or metabolic alterations. PGC-1α directly interacts with, and coactivates mitochondrial regulators, such as nuclear respiratory factors (NRF) NRF1 and NRF2, which are involved in the transcription of several mitochondrial genes encoding ETC subunits and the mitochondrial transcription factor A (TFAM or mtTFA)[26].

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

Several studies have shown that sirtuin 3 (SIRT3) also modulates energy homeostasis by regulating mitochondrial ETC activity via interactions with mitochondrial respiratory complexes[27].

In conclusion, the AMPK–SIRT1–PGC-1α axis is a major signalling pathway that orchestrates mitochondrial function and dynamics in mammalian cells; therefore, its deregulation is associated with the onset of several neurological diseases, and it has been suggested as a pharmacological target to prevent or treat such diseases[28].

Modulation of reactive oxygen species yield in mitochondria

In the ETC, electrons (transported from reduced to oxidised subunits according to their redox potential and then tetravalently added to oxygen) can spontaneously undergo side reactions with oxygen to give rise to superoxide and a variety of other downstream ROS. The mitochondrial ETC is a major site of cellular ROS production[27], which is considered an inevitable consequence of oxidative ATP production. Since mitochondrial dysfunction is involved in several metabolic disorders[29], ETC complexes I and III, which are the major sites of ROS production, could be considered therapeutic targets.

The ROS produced during cellular metabolism can be harmful or beneficial depending on the balance between their yield and the efficiency of antioxidant defences; thus, redox status is crucial for living organisms and has been preserved during evolution. The regulatory role of ROS in physiological processes has become apparent in the past two decades, with their production controlled by a complex network of intracellular signalling pathways and a complex defence system.

For example, various physiological stimuli can increase cellular PGC-1α levels alongside ROS yield, as PGC-1α can up-regulate mitochondrial biogenesis, respiratory capacity, OXPHOS and fatty acid β-oxidation. However, increasing evidence suggests that PGC-1α can also act as a powerful regulator of ROS removal by increasing the expression of the antioxidant enzymes, glutathione peroxidase (GPx) and SOD2 (also known as mitochondrial manganese-dependent superoxide dismutase or Mn-SOD)[30]. Conversely, decreased PGC-1α expression may reduce the expression of NRF-dependent metabolic and mitochondrial genes and contribute to ETC dysfunction and altered redox status.

Mitochondrial redox couples

In mitochondria, as in the cytosol, the redox state of the NADH/NAD^+ and NADPH/$NADP^+$ redox pairs are maintained independently as the nucleotides have different metabolic roles. Nicotinamide nucleotide transhydrogenase (NTT) is a mitochondrial NADP-reducing enzyme that catalyses the reduction of $NADP^+$ (at the expense of NADH) and is coupled to H^+ transport from the intermembrane space to the mitochondrial matrix. The NADH/NAD^+ pair supports electron transfer in the ETC (via respiratory complex I) and the antioxidant system. In mitochondria, high NADH concentrations provide electrons for OXPHOS[31], whilst high NAD^+ concentrations in the cytosol promote its role as a cofactor for oxidative reactions (i.e. the glyceraldehyde-3-phosphate dehydrogenase reaction in glycolysis). Notably, these molecules along with GSSG (glutathione disulfide)/GSH (reduced glutathione) and TrxSS (oxidised disulfide thioredoxin)/TrxSH2 (reduced thioredoxin) are the principal redox couples in redox signalling[32] and are interconnected. In particular, all components of the antioxidative defences, as well as GSSG and the GSH-dependent enzymes, glutathione reductase and GPx1 and GPx4 rely on NADPH as a common reductant for their oxidised forms. NNT maintains the NADPH pool by utilising TCA cycle-derived NADH to reduce $NADP^+$ to NADPH[33]. Other mitochondrial NADPH-regenerating enzymes are the $NADP^+$-dependent isocitrate dehydrogenase and malic enzyme[34,35]. NNT activity mainly depends on membrane potential and the activity of complexes I, III and IV, which control the level of mitochondrial NADH, the substrate for the transhydrogenase reaction. Moreover, GSH redox status is probably regulated by the availability of catabolites oxidised in the TCA cycle to generate NADH[36]. Mitochondrial matrix antioxidant defences are very effective at scavenging ROS species generated by the respiratory chain, particularly superoxide anions and H_2O_2[37,38]. Thus, it has been suggested that mitochondria are a sink rather than a source of cellular ROS under physiological conditions[39].

Key mitochondrial regulators of redox status

Mitochondrial respiratory chain

The inner mitochondrial membrane respiratory chain transfers electrons from reducing equivalents to oxygen to generate proton-motive forces that are the primary energy source for cellular ATP synthesis. Recent evidence suggests that the reversible redox modification of protein-thiols is an important response to changes in the cellular redox environment; conversely, ROS generation by respiratory chain complexes may affect the mitochondrial redox balance by reversibly or irreversibly thiol-modifying specific target proteins involved in redox signalling and pathophysiological processes. Moreover, the thiol-based modifications (for example, S-glutathionylation and S-nitrosylation) of mitochondrial respiratory chain complex subunits may regulate respiratory activity[40].

Uncoupling proteins

As mentioned above, the mitochondrial ETC is a major site of ROS production, with ROS yield depending on the redox state of its respiratory chain complexes. In particular, increased mitochondrial transmembrane potential ($\Delta\Psi_m$), which determines the proton-motive force along with the proton gradient (ΔpH), results in aberrant electron migration in the ETC and elevated ROS production. Under these conditions, the probability of electrons escaping the respiratory chain and forming superoxide anions increases[41]. The proton-motive force ($\Delta\Psi_m$ or ΔpH) and subsequent ROS production can be reduced either by decreasing substrate oxidation (electron influx) or increasing the consumption of proton-motive forces across the inner mitochondrial membrane.

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

In 1997, it was proposed that uncoupling proteins (UCP) can modulate the mitochondrial generation of superoxide anions via their uncoupling activity. The expression of UCP isoforms 1–3 may be stimulated by the increased generation of mitochondrial superoxide anions[42], causing protons to leak from the intermembrane space into the matrix (bypassing ATP synthase in OXPHOS) and decrease the $\Delta\Psi_m$. As a high $\Delta\Psi_m$ generates ROS[43], UCP-mediated proton gradient dissipation may greatly reduce ROS production in a feedback manner by lowering $\Delta\Psi_m$[44].

In conclusion, the correlation between $\Delta\Psi_m$ and ROS yield[43] may make uncoupling an acute (energetically costly) mechanism for modulating redox homeostasis by reducing ROS production[45].

AMP-activated protein kinase–sirtuin 1–PPARγ coactivator-1α axis

The transcriptional coactivator PGC-1α is known to regulate mitochondrial biogenesis[46], and can induce ROS removal by up-regulating UCP2 and UCP3 expression[47]. Moreover, its ability to regulate ROS homeostasis was confirmed by its role in activating antioxidant enzyme expression (namely GPx1 and SOD2)[48]. Furthermore, PGC-1α activation may up-regulate antioxidant enzyme expression (catalase (CAT) or SOD) by non-canonically activating AMPK via mitochondrial ROS[49].

A substantial body of evidence has suggested that SIRT1, like AMPK, responds to variations in nutrient availability, and its regulation has been attributed to changes in NAD^+ abundance (the NAD^+:NADH ratio). It has been shown that the SIRT1 protein is involved in mitochondrial adaptation to redox alterations[50]. The cytoprotective activity of SIRT3 could underlie its increased expression in tissues with high metabolism, which are, consequently, more exposed to the potentially damaging effects of mitochondrial ROS[51]. Both SIRT1 and SIRT3 were found to regulate PGC-1α; SIRT1 deacetylates and increases the transcriptional activity of PGC-1α[52,53], whilst SIRT3 is an important regulator of mitochondrial metabolism that plays a role in adaptation to metabolic stress (for example, fasting or energy restriction). In fact, SIRT3 activation by energy restriction has been shown to reduce ROS levels by activating mitochondrial SOD2[54,55] or deacetylating or activating mitochondrial isocitrate dehydrogenase 2 (IDH2), which catalyses the conversion of $NADP^+$ to NADPH and increases the mitochondrial GSH:GSSG ratio[56]. Thus, sirtuins are classified as vitagenes, a group of genes that preserve cellular homeostasis under stressful conditions[57].

Nuclear factor erythroid-derived 2-like

The activation of nuclear factor erythroid-derived 2-like (Nrf2) signalling plays a pivotal role in cellular protection and adaptation to external stressors, as well as a number of cytoprotective molecules produced by plants to protect themselves from microbial infection and other environmental conditions. The transcription of some vitagenes, such as haeme oxygenase (HO-1) and thioredoxin reductase (TrxR), is activated via the Nrf2 pathway. Under basal conditions, Kelch-like ECH-associated protein 1 (Keap1) prevents Nrf2 from binding to the antioxidant responsive element (ARE), thereby preventing its nuclear translocation and facilitating the degradation of Nrf2-Keap1 by the proteasome. The cysteine residues of Keap1 are susceptible to oxidative modification; thus, it can act as a redox sensor[58]. Nrf2 inducers can therefore improve the activity of cellular antioxidant/detoxifying defences via their mild pro-oxidant activity (eustress). In fact, when ROS levels are low (physiological conditions), they can activate 'oxidative eustress'[59] which underlies their function as second messengers in several biological and physiological processes[60]. This process is distinct from excessive ROS load ('oxidative stress'), which can damage cells and organs[61]. Under mild stress conditions, ROS can oxidise the cysteine residues of Keap1, thereby allowing Nrf2 to translocate into the nucleus where it activates the transcription of antioxidant/detoxifying enzymes (for example, GSR, GPx, CAT, HO-1 and TrxR; phase II enzymes) that protect cells against cytotoxic and oxidative damage[62].

The ability of a molecule to induce opposite biological effects depending on its dose (beneficial at low doses and toxic at high doses) is named hormesis[63]. The activation of the Nrf2 pathway plays a key role in protecting cells from external stressors and its physiologically relevant hormetic (dose-dependent) effects may prevent or mitigate chronic diseases by activating adaptive stress response signalling pathways[64]. Moreover, Nrf2 also modulates the expression of enzymes responsible for NADPH synthesis (i.e. malic enzyme 1 (ME1), isocitrate dehydrogenase 1 (IDH1), glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD))[65], which are involved in the biosynthesis and maintenance of the main intracellular antioxidant, GSH.

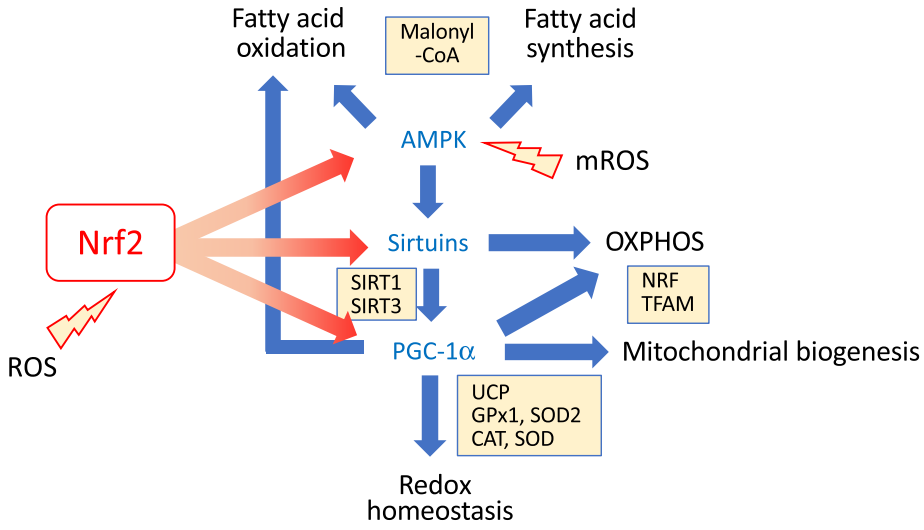
Functional link between Nrf2 and mitochondrial physiology

In addition to its key role in redox homeostasis, the Nrf2 pathway is linked to the AMPK–SIRT1–PGC-1α axis. Moreover, Nrf2 activation can sustain mitochondrial membrane potential (NADPH, NADH and $FADH_2$ regeneration) and biogenesis (PGC-1α)[66]. HO-1, an important enzyme in antioxidant defence and cellular metabolism[67], is also regulated by Nrf2 activation and can produce carbon monoxide (CO) during the metabolic conversion of haem to biliverdin[68] to stimulate mitochondrial biogenesis[66,67]. Furthermore, a study demonstrating that Nrf2 acetylation promotes its binding to antioxidant responsive element (ARE)[69] paved the way for studies supporting the involvement of Nrf2 in the antioxidant activity of SIRT3 and SIRT6[70–75].

Crosstalk between Nrf2 and mitochondrial homeostasis has been indicated by studies showing that the antidiabetic drug metformin can activate Nrf2 in an AMPK-dependent manner[76] and that SRT1720, a synthetic SIRT1 agonist, can elicit antioxidant/anti-inflammatory effects via the AMPK/Nrf2 pathway *in vivo*[77]. Additionally, under oxidative stress conditions the Nrf2 pathway can up-regulate UCP3 to counteract superoxide production by increasing proton conduction across the inner mitochondrial membrane[78].

Thus, it can be concluded that Nrf2 activity is linked with many aspects of mitochondrial physiology (mitochondrial biogenesis, fatty acid oxidation, respiration and ATP production;

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press



Player	Molecular function	Regulated process	Location
AMPK	Kinase activity	Fatty acid synthesis Fatty acid oxidation	Cytosol Mitochondria
CAT	Detoxification of ROS	Redox homeostasis	Cell
GPx1	Glutathione peroxidase	Redox homeostasis	Cell
Malonyl-CoA	Intermediate of fatty acid synthesis	Fatty acid synthesis Fatty acid oxidation	Cytosol Mitochondria
NRF	Transcription activator	OXPHOS/mitochondrial biogenesis	Mitochondria
Nrf2	Transcription activator	OXPHOS/mitochondrial biogenesis Fatty acid oxidation Redox homeostasis	Mitochondria Mitochondria Cell
PGC-1α	Transcription activator	OXPHOS/mitochondrial biogenesis Redox homeostasis	Mitochondria Cell
Sirtuins	NAD-dependent deacetylase	OXPHOS/mitochondrial biogenesis Redox homeostasis	Mitochondria Cell
SOD	Detoxification of ROS	Redox homeostasis	Cell
SOD2	Detoxification of ROS	OXPHOS Redox homeostasis	Mitochondria Cell
TFAM	Mitochondrial transcription factor	OXPHOS/mitochondrial biogenesis	Mitochondria
UCP	Mitochondrial ion channel	OXPHOS Redox homeostasis	Mitochondria Cell

Fig. 1. Pivotal role of nuclear factor erythroid-derived 2-like (Nrf2) in the regulation of mitochondrial pathways. In addition to its well-known role in redox homeostasis, Nrf2 is involved in the regulation of many aspects of mitochondrial metabolism, such as biogenesis, fatty acid oxidation, oxidative phosphorylation (OXPHOS) and redox homeostasis. The table describes the major players and their cellular location during these processes. AMPK, AMP-activated protein kinase; CAT, catalase; GPx, glutathione peroxidase; mROS, mitochondrial reactive oxygen species; NRF, nuclear respiratory factor; PGC-1α, PPARγ coactivator-1α; ROS, reactive oxygen species; SIRT1, sirtuin 1; SIRT3, sirtuin 3; SOD, superoxide dismutase; SOD2, superoxide dismutase 2; TFAM, mitochondrial transcription factor A; UCP, uncoupling proteins. For a colour figure, see the online version of the paper.

Fig. 1) in addition to its recognised role in redox homeostasis, as detailed in a recent review[65].

Mechanisms underlying the ability of polyphenols to modulate redox status

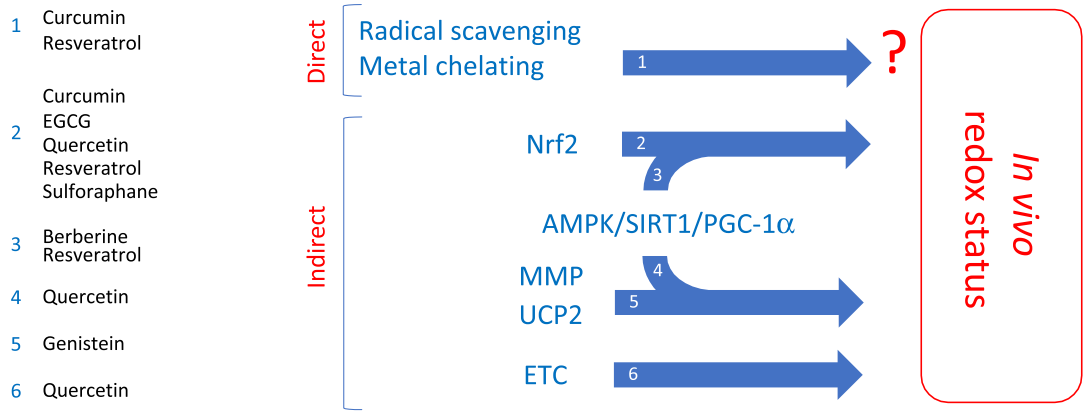
ROS function as 'redox messengers' under physiological conditions; however, excess ROS can trigger cell injury and oxidative stress, which can damage cellular structures (protein, lipid and DNA) and has been associated with the pathogenesis of human diseases[1] and ageing[79]. Due to the noxious effects of oxidative stress, cells possess a complex mechanism that fine tunes oxido-reductive homeostasis (redox status) and mitochondrial metabolism to prevent oxidative injury, which could disrupt mitochondrial integrity, impair the ETC and cause mitochondrial DNA damage.

As mentioned above, mitochondria have been identified as the main site of cellular superoxide anion radical production and are the major target of oxidative stress. Therefore, it has been suggested that the dietary consumption of some secondary metabolites could modulate redox status. Among the plethora of bioactive compounds, polyphenols are known to exert intracellular antioxidant effects via both direct and indirect mechanisms (Fig. 2).

Direct antioxidant activity of polyphenols

Reactive oxygen species scavenging. The direct antioxidant activity of polyphenols involves their ability to scavenge

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press



Bioactive compunds	Source	Effects
Berberine	European barberry, goldenseal, goldthread, Oregon grape, phellodendron, tree tumeric	↑ Fatty acid oxidation ↑ Mitochondrial biogenesis ↑ OXPHOS
Curcumin	Rhizome of *Curcuma longa*	↑ Fatty acid oxidation ↑ Mitochondrial biogenesis ↑ OXPHOS
EGCG	Green tea *(Camellia sinensis* L.*)*	↑ Fatty acid oxidation ↑ Mitochondrial biogenesis ↑ OXPHOS
Genistein	Soyabeans and other legumes, such as chickpeas	↑ OXPHOS
Quercetin	Plant foods, including leafy greens, tomatoes, berries, broccoli	↑ Mitochondrial biogenesis ↑ OXPHOS
Resveratrol	Various food stuffs, such as grapes, berries, red wine, nuts	↑ Fatty acid oxidation ↑ Mitochondrial biogenesis ↑ OXPHOS
Sulforaphane	Cruciferous vegetables such as broccoli, Brussels sprouts, cabbages	↑ Mitochondrial biogenesis ↑ OXPHOS

Fig. 2. Ability of bioactive compounds to modulate redox status. Several polyphenolic molecules, such as resveratrol, curcumin, quercetin and genistein, can affect redox homeostasis by directly and indirectly exerting antioxidant effects. The direct mechanisms consist of reactive oxygen species scavenging and metal chelation, whilst the indirect mechanisms include activating nuclear factor erythroid-derived 2-like (Nrf2) signalling, regulating inner mitochondrial membrane potential via uncoupling effects (up-regulating uncoupling protein 2 (UCP2) expression), and modulating radical species production via electron transport chain (ETC) complexes. The table describes the different bioactive compounds, where they originate, and their effects on mitochondrial metabolism. AMPK, AMP-activated protein kinase; EGCG, epigallocatechin gallate; MMP, matrix metalloproteinase; OXPHOS, oxidative phosphorylation; PGC-1α, PPARγ coactivator-1α; SIRT1, sirtuin 1. For a colour figure, see the online version of the paper.

mitochondrial ROS or chelate transition metals (for example, Cu and Fe) involved in the formation of free radicals (i.e. superoxide and hydroxyl) via the Fenton reaction.

Research into the bioactivity of quercetin has shown that the phytochemical can affect mitochondrial redox parameters by acting upon mitochondria directly or indirectly. These effects have been attributed to its chemical structure; however, its ability to control mitochondrial respiratory chain function is still under investigation. Some have reported that the enolic 3-OH group in quercetin (C-ring) is responsible for enhancing its antioxidant activity. Additionally, this 3-OH group seems to exhibit the ability to chelate Fe^{2+}, reducing its availability to react with H_2O_2 via the Fenton reaction. Moreover, it has been reported that quercetin can prevent methylmercury (MeHg) or mercuric chloride ($HgCl_2$) from decreasing reduced GSH levels in mitochondria. Interestingly, quercetin exhibits a more pronounced effect than CAT on decreased hydroperoxide formation levels in mitochondria exposed to MeHg or $HgCl_2$[80]. Thus, quercetin can protect mitochondria against mercurials via a mechanism that involves antioxidant effects against H_2O_2, since CAT, a H_2O_2-consuming enzyme, is similarly effective at protecting mitochondria from such agents.

Others have investigated an alternative mechanism via which quercetin directly exerts antioxidant effects on mitochondria[81], demonstrating that quercetin dose-dependently (1–10 μM) inhibits H_2O_2 generation in intact mitochondria isolated from rat brains and hearts without interfering with O_2 consumption. H_2O_2 is produced in mitochondria by SOD2, which is located in the mitochondrial matrix and converts superoxide anions into H_2O_2. SOD2 is a crucial determinant of energy homeostasis in mitochondria that acts not only as an antioxidant enzyme but more importantly as a central hub of redox signalling via H_2O_2 production[82]. Interestingly, SOD2 overexpression adversely affects mitochondrial oxidative metabolism and greatly stimulates glycolysis[13].

Metal chelation. As mentioned previously, hydroxyl radicals can also be generated via reactions catalysed by redox-active transition metals, such as Cu and Fe. In mitochondria, free Fe can occur under conditions that increase superoxide production

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

and affect the [4Fe–4S] cluster of aconitase and NADH-ubiquinone dehydrogenase. Some polyphenols (flavonoids such as baicalein, quercetin and myricetin, and non-flavonoids such as gallic, 2,3-dihydroxybenzoic and protocatechuic acids) have been shown to chelate Fe and Cu ions particularly well, rendering them unable to participate in reactions that generate free radicals[83]. Metal chelation may reduce the pro-oxidant capacity of metal ions; however, polyphenols can also act as pro-oxidants by chelating metals in a way that maintains or increases their catalytic activity[84]. These radicals are stabilised by the delocalisation of unpaired electrons around aromatic rings, enabling them to display pro-oxidant activities[85].

Nevertheless, the ROS-scavenging and metal-chelating abilities of polyphenols have only been demonstrated *in silico* or *in vitro*[86]; therefore, these results may not necessarily translate to *in vivo* systems, particularly since these biological effects are highly dependent on the dose reaching the target cell/tissue. Due to the low intrinsic activity of polyphenols (poor absorption, high metabolism or rapid elimination)[87,88], their concentration *in vivo* is low compared with that of endogenous antioxidants (for example, GSH). In addition, data have indicated that gut microflora may play a major role in their biotransformation from native phytochemicals into more bioavailable/active metabolites[89,90], further reducing the reliability of extrapolating their biological activity from *in vitro* to *in vivo* models.

Indirect antioxidant activity of polyphenols implies crosstalk with mitochondrial metabolism

The second mechanism of polyphenol antioxidant activity involves inhibiting ROS yield and stimulating ROS-removing enzymes. The link between mitochondrial metabolism and redox homeostasis is based on the activity of redox pairs (for example, NAD^+/NADH, $NADP^+$/NADPH), mitochondrial respiratory chain enzymes/proteins (for example, complex I and III, UCP and sirtuins), and transcriptional regulators such as Nrf2 and PGC-1α, which form a complex network that modulates crucial physiological functions.

The link between redox homeostasis and mitochondrial metabolism is further supported by the metabolic profiling data of healthy human subjects, showing that receiving dietary intervention with broccoli (source of glucoraphanin, a sulforaphane precursor) improved the integration of fatty acid oxidation and TCA cycle activity[91]. Since many diseases have an oxidative stress component, the Nrf2-dependent up-regulation of cytoprotective genes is considered a therapeutic target[92].

Complex I inhibition. Complexes I and III are mainly responsible for superoxide anion yield in mitochondria; therefore, their inhibition affects redox status homeostasis. Recent *in vitro* and *ex vivo* studies have indicated that polyphenols can modulate mitochondrial superoxide production via ETC complexes[81,93,94]. Thus, quercetin may suppress H_2O_2 production by modulating complex I activity[95].

CoQ pre-treatment reduced the inhibitory effect of quercetin on complex I, suggesting that quercetin competitively binds the quinone-binding site of complex I due to structural similarity with the quinone moiety of CoQ. It has been demonstrated that quercetin (10 μM) stimulates complex I activity in a very similar manner to CoQ in an experimental model using mitochondria isolated from rat duodenum epithelium[87]. Importantly, complex I inhibition could lead to electron leakage from the ETC and the increased generation of superoxide anions, which are H_2O_2 precursors[96].

Activation of Nrf2-mediated antioxidant/detoxifying enzymes. An increasingly recognised mechanism by which some polyphenols can exert antioxidant effects *in vivo* is by up-regulating antioxidant enzyme systems. Moreover, some polyphenols can induce certain phase I and II enzymes that detoxify potentially pro-oxidant xenobiotics[97].

Numerous natural products originating from plants, including isothiocyanates (for example, phenethyl isothiocyanate and sulforaphane), alkaloids (for example, berberine and betanin), flavonoids (for example, epigallocatechin gallate and quercetin), stilbenes (for example, resveratrol and piceatannol), diferuloylmethanes (for example, curcumin and caffeic acid phenethyl ester) and organosulfur compounds (for example, allicin and diallyl trisulfide), have been reported to activate antioxidant/detoxifying defences via an indirect mechanism (Nrf2)[98]. Despite their structural diversity, these molecules share the ability to activate this molecular mechanism due to their pro-oxidant and electrophilic properties[99]. At doses ingested by humans, these phytochemicals can induce adaptive responses by inducing Nrf2-driven antioxidant gene expression[100], which improves defensive mechanisms to better protect cells and organs against further toxic insults. Like the hormetic mechanism activated by Nrf2, the pro-oxidant effects exhibited by these chemopreventative phytochemicals are not unexpected.

The ability of polyphenols (for example, stilbenes: resveratrol; and flavonoids: epigallocatechin gallate) and curcumin to activate the Nrf2 pathway has been investigated thoroughly[101–104]. In particular, the ability of quercetin to improve antioxidant defences and bioenergetic parameters in mitochondria was demonstrated *in vivo* using experimental models consisting of the brain, heart, gastric and liver tissues of experimental animals. Quercetin was reported to exert antioxidant effects by decreasing lipid peroxidation and protein carbonylation (important consequences of increased oxidative stress) and preventing GSH oxidation[105]. This flavonoid also protects mitochondria by activating Nrf2 pathways in cultured cells and animal tissues[106], and attenuates hepatic lipid accumulation in mice fed a high-fat diet[107]. Moreover, dietary quercetin supplementation (100 mg/kg administered orally for 90 d) up-regulated SOD2 and GPx activity and restored GSH levels in the liver mitochondria of ethanol-treated rats, with the authors observing that quercetin alleviated the effects of ethanol on mitochondrial ROS production and lipid peroxidation[108].

Similar effects have been suggested for resveratrol, which exerts antioxidant activity by increasing the expression of mitochondrial proteins or ROS-scavenging enzymes. In fact, dietary supplementation with resveratrol appeared to improve mitochondrial function in mice, with those treated with resveratrol also tolerating oxidative stress induced by exposure to various chemical agents better than untreated mice[109]. This stilbene decreases mitochondrial ROS levels and inhibits lipid peroxidation by

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

scavenging ROS (superoxide anions, H_2O_2 and hydroxyl radicals) and replenishing GSH[110]. Moreover, another study revealed that resveratrol can dose-dependently activate antioxidant defences by activating the Nrf2 pathway[111].

Several studies have shown that curcumin exerts significant antioxidant activities by ameliorating lipid peroxidation and oxidative stress in different tissues[112]. Moreover, curcumin exerts its antioxidant properties via both direct and indirect mechanisms. This polyphenol effectively scavenges free radicals, such as hydroxyl radicals, superoxide anions, NO, H_2O_2 and peroxynitrite[113,114], and is able to up-regulate cytoprotective cell responses by modulating the expression of genes encoding antioxidant proteins, such as SOD, CAT and HO-1, or proteins that replenish the glutathione pool, such as GR, GPx and GST[115]. Improved mitochondrial function has also been associated with preventing reduced aconitase activity, a marker of oxidative stress[116]. Curcumin exerts cytoprotective effects against toxic compounds that can generate ROS and cause lipid peroxidation and DNA damage, including potassium dichromate ($K_2Cr_2O_7$). Curcumin prevents $K_2Cr_2O_7$-induced decreases in body weight, increases liver weight and the liver:body ratio, and exerts protective effects against oxidative damage in liver tissue by preventing $K_2Cr_2O_7$-induced decreases in hepatic antioxidant enzyme levels. These effects appear to be mediated by its protective effects in mitochondria. Studies on isolated organelles have shown that curcumin reduces mitochondrial dysfunction by preventing $K_2Cr_2O_7$ from reducing complex I activity and opening the mitochondrial permeability transition pore (mPTP), thus inhibiting mitochondria-induced apoptosis[117].

By investigating antioxidant efficacy, lycopene, a lipid–soluble carotenoid compound, was found to exert a strong protective effect against brain damage. Lycopene pre-treatment was shown to protect SH–SY5Y neuroblastoma cells against H_2O_2-induced death by inhibiting apoptosis and improving the activity of Nrf2-activated antioxidant enzymes (SOD and CAT). Additionally, lycopene prevented H_2O_2-induced mitochondrial dysfunction by mitochondrial permeability transition pore (mPTP) opening and attenuating the decline in mitochondrial membrane potential[118].

Sulforaphane activates Nrf2, which induces the expression of cytoprotective genes that play key roles in cellular defence mechanisms, including redox status and detoxification. Both its high bioavailability (higher than polyphenols) and significant ability to induce Nrf2 contribute towards the therapeutic potential of sulforaphane-yielding supplements[119].

Nrf2–sirtuins. The association between the health benefits of several polyphenolic compounds, such as resveratrol, fisetin and quercetin, and their ability to activate SIRT1, was recently reviewed[120] and their effects on cancer cells have been associated with AMPK activation[121].

Resveratrol reduces mitochondrial ROS generation by increasing SIRT3 levels in the mitochondria of endothelial cells, in turn increasing complex I activity and ATP synthesis by up-regulating the mitochondrial proteins ATP6, CO1, Cyt*b*, ND2 and ND5[122]. Moreover, resveratrol can up-regulate the expression of the scavenging enzymes GPx, CAT[123] and SOD2 in endothelial cells in a SIRT1-dependent manner[124]. Resveratrol treatment has also been shown to stimulate SIRT1 and AMPK activity *in vivo*, both of which influence redox homeostasis in multiple tissues[125,126].

Nrf2–PPARγ coactivator-1α. The effects of a phenolic acid on Nrf2–PGC-1α have been studied; in particular, high dietary hydroxytyrosol intake appears to increase PGC-1α expression, indirectly improving mitochondrial function by interacting with and enhancing enzymes that protect cells against oxidative damage due to excessive ROS levels. In fact, mice lacking PGC-1α suffer greater drug-induced oxidative damage in the brain and neural tissues, suggesting that hydroxytyrosol exerts cytoprotective effects by increasing PGC-1α levels and improving mitochondrial and cellular ROS-related functions[48]. Similarly, quercetin was recently reported to enhance hepatic mitochondrial oxidative metabolism and biogenesis (PGC-1α) by activating Nrf-2/HO-1[127].

Nrf2–uncoupling proteins. As mentioned previously, Nrf2 activation may be triggered by mild stress conditions via the oxidation of Keap1 cysteine residues; however, Nrf2 may also be activated in an AMPK-dependent manner by the flavonoid-related compound xanthohumol *in vitro* or the alkaloid berberine *in vivo*[128,129]. UCP can modulate mitochondrial superoxide anion generation by decreasing mitochondrial inner membrane potential via their uncoupling activity. The uncoupling effect exerted by flavonoids has been attributed to their weakly acidic and highly lipophilic nature. Flavonoids can be protonated on the low-pH external side of the inner mitochondrial membrane, but when they pass through the lipid layer they are deprotonated in the high-pH mitochondrial matrix milieu; thus, the proton gradient across the inner mitochondrial membrane is dissipated. However, a more recent study proposed that the uncoupling effect exerted by the isoflavone genistein (1 μM) might be mediated by up-regulated UCP2 expression[130]. The mechanisms that induce OXPHOS uncoupling remain unknown; however, several studies have suggested that the effect could be associated with decreased ROS formation via the ETC[131]. Thus, the uncoupling effect of some polyphenols could be viewed as an ROS scavenging-independent mechanism via which they exert their antioxidant activity.

Summary

Mitochondria play pivotal roles in numerous cellular processes and are considered the main source of ROS whilst simultaneously being a major target for these potentially noxious molecules. In fact, excess oxidants can cause oxidative stress which is known to play a causal role in many diseases, such as cancer, metabolic, degenerative and hyper-proliferative diseases, as well as ageing[132,133].

Several mechanisms are involved in modulating mitochondrial function, with numerous proteins and protein complexes in specific pathways allowing crosstalk between mitochondrial metabolism and oxidoreductive homeostasis. Recent studies have demonstrated that many bioactive dietary compounds, such as polyphenols and carotenoids, could be used alone or

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

in combination to prevent and control disease development[134]. Most of these molecules can target mitochondria to improve and/or restore their function by indirectly modulating redox status. Therefore, we believe that further investigation and an improved understanding of the molecular and biochemical mechanisms underlying the action of these natural compounds are necessary to develop new therapeutic approaches that improve mitochondrial function and restore redox homeostasis.

Acknowledgements

The present review received no specific grant from any funding agency, commercial or not-for-profit sectors.

P. B., M. D. G. and A. F. drafted the manuscript; A. F., P. B. and V. Z. made critical revisions.

There are no conflicts of interest.

References

1. Duchen MR (2004) Mitochondria in health and disease: perspectives on a new mitochondrial biology. *Mol Aspects Med* **25**, 365–451.
2. Galluzzi L, Morselli E, Kepp O, *et al.* (2011) Mitochondrial liaisons of p53. *Antioxid Redox Signal* **15**, 1691–1714.
3. Galluzzi L, Kepp O & Kroemer G (2012) Mitochondria: master regulators of danger signaling. *Nat Rev Mol Cell Biol* **13**, 780–788.
4. Galluzzi L, Kepp O, Trojel-Hansen C, *et al.* (2012) Mitochondrial control of cellular life, stress, and death. *Circ Res* **111**, 1198–1207.
5. Zhou L, Chen P, Peng Y, *et al.* (2016) Role of oxidative stress in the neurocognitive dysfunction of obstructive sleep apnea syndrome. *Oxid Med Cell Longev* **2016**, 9626831.
6. Islam MT (2017) Oxidative stress and mitochondrial dysfunction linked neurodegenerative disorders. *Neurol Res* **39**, 73–82.
7. Bergman O & Ben-Shachar D (2016) Mitochondrial oxidative phosphorylation system (OXPHOS) deficits in schizophrenia: possible interactions with cellular processes. *Can J Psychiatry* **61**, 457–469.
8. Cadonic C, Sabbir MG & Albensi BC (2016) Mechanisms of mitochondrial dysfunction in Alzheimer's disease. *Mol Neurobiol* **53**, 6078–6090.
9. Zulian A, Schiavone M, Giorgio V, *et al.* (2016) Forty years later: mitochondria as therapeutic targets in muscle diseases. *Pharmacol Res* **113**, 563–573.
10. Ferramosca A, Conte A & Zara V (2015) Krill oil ameliorates mitochondrial dysfunctions in rats treated with high-fat diet. *Biomed Res Int* **2015**, 645984.
11. Ferramosca A, Conte A, Guerra F, *et al.* (2016) Metabolites from invasive pests inhibit mitochondrial complex II: a potential strategy for the treatment of human ovarian carcinoma? *Biochem Biophys Res Commun* **473**, 1133–1138.
12. Hu H, Tan CC, Tan L, *et al.* (2017) A mitocentric view of Alzheimer's disease. *Mol Neurobiol* **54**, 6046–6060.
13. Lunetti P, Di Giacomo M, Vergara D, *et al.* (2019) Metabolic reprogramming in breast cancer results in distinct mitochondrial bioenergetics between luminal and basal subtypes. *FEBS J* **286**, 688–709.
14. Forbes-Hernández TY, Giampieri F, Gasparrini M, *et al.* (2014) The effects of bioactive compounds from plant foods on mitochondrial function: a focus on apoptotic mechanisms. *Food Chem Toxicol* **68**, 154–182.
15. Vasam G, Reid K, Burelle Y, *et al.* (2019) Nutritional regulation of mitochondrial function. In *Mitochondria in Obesity and Type 2 Diabetes Comprehensive Review on Mitochondrial Functioning and Involvement in Metabolic Diseases*, chapter 4, pp. 93–126 [B Morio, L Penicaud and M Rigoulet, editors]. Cambridge, MA: Academic Press.
16. Wesselink E, Koekkoek WAC, Grefte S, *et al.* (2019) Feeding mitochondria: potential role of nutritional components to improve critical illness convalescence. *Clin Nutr* **38**, 982–995.
17. Martin-Montalvo A & de Cabo R (2014) Mitochondrial metabolic reprogramming induced by calorie restriction. *Antioxid Redox Signal* **19**, 310–320.
18. Stefanovic-Racic M, Perdomo G, Mantell BS, *et al.* (2008) A moderate increase in carnitine palmitoyltransferase 1a activity is sufficient to substantially reduce hepatic triglyceride levels. *Am J Physiol Endocrinol Metab* **294**, E969–E977.
19. Ferramosca A, Savy V & Zara V (2008) Olive oil increases the hepatic triacylglycerol content in mice by a distinct influence on the synthesis and oxidation of fatty acids. *Biosci Biotechnol Biochem* **72**, 62–69.
20. Park SH, Gammon SR, Knippers, JD, *et al.* (2002) Phosphorylation-activity relationships of AMPK and acetyl-CoA carboxylase in muscle. *J Appl Physiol (1985)* **92**, 2475–2482.
21. Srivastava RA, Pinkosky SL, Filippov S *et al.* (2012) AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res* **53**, 2490–2514.
22. Cohen HY, Miller C, Bitterman KJ, *et al.* (2004) Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* **305**, 390–392.
23. Cantó C & Auwerx J (2011) Calorie restriction: is AMPK as a key sensor and effector? *Physiology (Bethesda)* **26**, 214–224.
24. Sugden MC, Caton PW & Holness MJ (2010) PPAR control: it's SIRTainly as easy as PGC. *J Endocrinol* **204**, 93–104.
25. Lin J, Handschin C & Spiegelman M (2005) Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab* **1**, 361–370.
26. Bouchez C & Devin A (2019) Mitochondrial biogenesis and mitochondrial reactive oxygen species (ROS): a complex relationship regulated by the cAMP/PKA signaling pathway. *Cells* **8**, E287.
27. Lombard DB, Tishkoff DX & Bao J (2011) Mitochondrial sirtuins in the regulation of mitochondrial activity and metabolic adaptation. *Handb Exp Pharmacol* **206**, 163–188.
28. Valero T (2014) Mitochondrial biogenesis: pharmacological approaches. *Curr Pharm Des* **20**, 5507–5509.
29. Bhatti JS, Bhatti GK & Reddy PH (2017) Mitochondrial dysfunction and oxidative stress in metabolic disorders – a step towards mitochondria based therapeutic strategies. *Biochim Biophys Acta Mol Basis Dis* **1863**, 1066–1077.
30. Austin S & St-Pierre J (2012) PGC1α and mitochondrial metabolism – emerging concepts and relevance in ageing and neurodegenerative disorders. *J Cell Sci* **125**, 4963–4971.
31. Karamanlidis G, Lee CF, Garcia-Menendez L, *et al.* (2013) Mitochondrial complex I deficiency increases protein acetylation and accelerates heart failure. *Cell Metab* **18**, 239–250.
32. Jones DP & Sies H (2015) The Redox Code. *Antioxid Redox Signal* **23**, 734–746.
33. Rydström J (2006) Mitochondrial NADPH, transhydrogenase and disease. *Biochim Biophys Acta* **1757**, 721–726.
34. Sazanov LA & Jackson JB (1994) Proton-translocating transhydrogenase and NAD-linked and NADP-linked isocitrate dehydrogenases operate in a substrate cycle which contributes to fine regulation of the tricarboxylic-acid cycle activity in mitochondria. *FEBS Lett* **344**, 109–116.

Nutrition Research Reviews

35. Jo SH, Son MK, Koh HJ, *et al.* (2001) Control of mitochondrial redox balance and cellular defense against oxidative damage by mitochondrial NADP$^+$-dependent isocitratedehydrogenase. *J Biol Chem* **276**, 16168–16176.
36. Garcia J, Han D, Sancheti H, *et al.* (2010) Regulation of mitochondrial glutathione redox status and protein glutathionylation by respiratory substrates. *J Biol Chem* **285**, 39646–39654.
37. Treberg JR, Quinlan CL & Brand MD (2010) Hydrogen peroxide efflux from muscle mitochondria underestimatesmatrix superoxide production – a correction using glutathione depletion *FEBS J* **277**, 2766–2778.
38. Aon MA, Stanley BA, Sivakumaran V, *et al.* (2012) Glutathione/thioredoxin systems modulate mitochondrial H_2O_2 emission: an experimental–computational study. *J Gen Physiol* **139**, 479–491.
39. Starkov AA (2008) The role of mitochondria in reactive oxygen species metabolism and signalling. *Ann N Y Acad Sci* **1147**, 37–52.
40. Dröse S, Brandt U & Wittig I (2014) Mitochondrial respiratory chain complexes as sources and targets of thiol-based redox-regulation. *Biochim Biophys Acta* **1844**, 1344–1345.
41. Brand MD, Affourtit C, Esteves TC, *et al.* (2004) Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. *Free Radic Biol Med* **37**, 755–767.
42. Echtay KS, Roussel D, St-Pierre J, *et al.* (2002) Superoxide activates mitochondrial uncoupling proteins. *Nature* **415**, 96–99.
43. Korshunov SS, Skulachev VP & Starkov AA (1997) High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. *FEBS Lett* **416**, 15–18.
44. Miwa S & Brand MD (2003) Mitochondrial matrix reactive oxygen species production is very sensitive to mild uncoupling. *Biochem Soc Trans* **31**, 1300–1301.
45. Mailloux RJ & Harper ME (2011) Uncoupling proteins and the control of mitochondrial reactive oxygen species production. *Free Radic Biol Med* **51**, 1106–1115.
46. Puigserver P & Spiegelman BM (2003) Peroxisome proliferator-activated receptor-γ coactivator 1 α (PGC-1 α): transcriptional coactivator and metabolic regulator. *Endocr Rev* **24**, 78–90.
47. St-Pierre J, Lin J, Krauss S, *et al.* (2003) Bioenergetic analysis of peroxisome proliferator-activated receptor γ coactivators 1 α and 1 β (PGC-1α and PGC-1β) in muscle cells. *J Biol Chem* **278**, 26597–26603.
48. St-Pierre J, Drori S, Uldry M, *et al.* (2006) Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* **127**, 397–408.
49. Rabinovitch RC, Samborska B, Faubert B, *et al.* (2017) AMPK maintains cellular metabolic homeostasis through regulation of mitochondrial reactive oxygen species. *Cell Rep* **21**, 1–9.
50. Cantó C, Houtkooper RH, Pirinen E, *et al.* (2012) The NAD$^+$ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab* **15**, 838–847.
51. Jin L, Galonek H, Israelian K, *et al.* (2009) Biochemical characterization, localization, and tissue distribution of the longer form of mouse SIRT3. *Protein Sci* **18**, 514–525.
52. Nemoto S, Fergusson MM & Finkel T (2005) SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α. *J Biol Chem* **280**, 16456–16460.
53. Kong X, Wang R, Xue Y, *et al.* (2010) Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PLoS ONE* **5**, e11707.
54. Sundaresan NR, Gupta M, Kim G, *et al.* (2009) Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice. *J Clin Invest* **119**, 2758–2771.
55. Qiu X, Brown K, Hirschey MD, *et al.* (2010) Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab* **12**, 662–667.
56. Someya S, Yu W, Hallows WC, *et al.* (2010) Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell* **143**, 802–812.
57. Calabrese V, Cornelius C, Dinkova-Kostova AT, *et al.* (2010) Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxid Redox Signal* **13**, 1763–1811.
58. Taguchi K, Motohashi H & Yamamoto M (2011) Molecular mechanisms of the Keap1–Nrf2 pathway in stress response and cancer evolution. *Genes Cells* **16**, 123–140.
59. Sarsour EH, Kalen AL & Goswami PC (2014) Manganese superoxide dismutase regulates a redox cycle within the cell cycle. *Antioxid Redox Signal* **20**, 1618–1627.
60. Finkel T (2011) Signal transduction by reactive oxygen species. *J Cell Biol* **194**, 7–15.
61. Sies H, Berndt C & Jones DP (2017) Oxidative stress. *Annu Rev Biochem* **86**, 715–748.
62. Kensler TW, Wakabayashi N & Biswal S (2007) Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu Rev Pharmacol Toxicol* **47**, 89–116.
63. Calabrese V, Cornelius C, Dinkova-Kostova AT, *et al.* (2012) Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity. *Biochim Biophys Acta* **1822**, 753–783.
64. Trewavas A & Stewart D (2003) Paradoxical effects of chemicals in the diet on health. *Curr Opin Plant Biol* **6**, 185–190.
65. Holmström KM, Kostov RV & Dinkova-Kostova AT (2016) The multifaceted role of Nrf2 in mitochondrial function. *Curr Opin Toxicol* **1**, 80–91.
66. Dinkova-Kostova AT & Abramov AY (2015) The emerging role of Nrf2 in mitochondrial function. *Free Radic Biol Med* **88**, 179–188.
67. Wegiel B, Nemeth Z, Correa-Costa M, *et al.* (2014) Hemeoxygenase-1: a metabolic nike. *Antioxid Redox Signal* **20**, 1709–1722.
68. Ryter SW, Alam J & Choi AM (2006) Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiol Rev* **86**, 583–650.
69. Suliman HB, Carraway MS, Ali AS, *et al.* (2007) The CO/HO system reverses inhibition of mitochondrial biogenesis and prevents murine doxorubicin cardiomyopathy. *J Clin Invest* **117**, 3730–3741.
70. Piantadosi CA, Carraway MS, Babiker A, *et al.* (2008) Heme oxygenase-1 regulates cardiac mitochondrial biogenesis via Nrf2-mediated transcriptional control of nuclear respiratory factor-1. *Circ Res* **103**, 1232–1240.
71. Kawai Y, Garduño L, Theodore, M, *et al.* (2011) Acetylation–deacetylation of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) regulates its transcriptional activity and nucleocytoplasmic localization. *J Biol Chem* **286**, 7629–7640.
72. Zhang W, Wei R, Zhang L, *et al.* (2017) Sirtuin 6 protects the brain from cerebral ischemia/reperfusion injury through NRF2 activation. *Neuroscience* **366**, 95–104.
73. Ka SO, Bang IH, Bae EJ, *et al.* (2017) Hepatocyte-specific sirtuin 6 deletion predisposes to non-alcoholic steatohepatitis by up-regulation of Bach1, a Nrf2 repressor. *FASEB J* **3**, 3999–4010.
74. Oh JY, Choi GE, Lee HJ, *et al.* (2019) 17β-Estradiol protects mesenchymal stem cells against high glucose-induced mitochondrial oxidants production via Nrf2/Sirt3/MnSOD signaling. *Free Radic Biol Med* **130**, 328–342.

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

75. Yu J, Sun W, Song Y, *et al.* (2019) SIRT6 protects retinal ganglion cells against hydrogen peroxide-induced apoptosis and oxidative stress by promoting Nrf2/ARE signaling via inhibition of Bach1. *Chem Biol Interact* **300**, 151–158.
76. Ashabi G, Khalaj L, Khodagholi F, *et al.* (2015) Pretreatment with metformin activates Nrf2 antioxidant pathways and inhibits inflammatory responses through induction of AMPK after transient global cerebral ischemia. *Metab Brain Dis* **30**, 747–754.
77. Wang F, Shang Y, Zhang R, *et al.* (2018) A SIRT1 agonist reduces cognitive decline in type 2 diabetic rats through anti-oxidative and anti-inflammatory mechanisms. *Mol Med Rep* **19**, 1040–1048.
78. Anedda A, Lopez-Bernardo E, Acosta-Iborra B, *et al.* (2013) The transcription factor Nrf2 promotes survival by enhancing the expression of uncoupling protein 3 under conditions of oxidative stress. *Free Radic Biol Med* **61**, 395–407.
79. Lesnefsky EJ & Hoppel CL (2006) Oxidative phosphorylation and aging. *Ageing Res Rev* **5**, 402–433.
80. Franco JL, Braga HC, Stringari J, *et al.* (2007) Mercurial-induced hydrogen peroxide generation in mouse brain mitochondria: protective effects of quercetin. *Chem Res Toxicol* **20**, 1919–1926.
81. Lagoa R, Graziani I, Lopez-Sanchez C, *et al.* (2011) Complex I and cytochrome *c* are molecular targets of flavonoids that inhibit hydrogen peroxide production by mitochondria. *Biochim Biophys Acta Bioenerg* **1807**, 1562–1572.
82. Zou X, Ratti BA, O'Brien JG, *et al.* (2017) Manganese superoxide dismutase (SOD2): is there a center in the universe of mitochondrial redox signaling? *J Bioenerg Biomembr* **49**, 325–333.
83. Sandoval-Acuña C, Ferreira J & Speisky H (2014) Polyphenols and mitochondria: an update on their increasingly emerging ROS-scavenging independent actions. *Arch Biochem Biophys* **559**, 75–90.
84. Decker EA (1997) Phenolics: prooxidants or antioxidants? *Nutr Rev* **55**, 396–398.
85. Galati G & O'Brien PJ (2004) Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. *Free Radic Biol Med* **37**, 287–303.
86. Bors W & Michel C (2002) Chemistry of the antioxidant effect of polyphenols. *Ann N Y Acad Sci* **957**, 57–69.
87. Crozier A, Jaganath IB & Clifford MN (2009) Dietary phenolics: chemistry, bioavailability and effects on health. *Nat Prod Rep* **26**, 1001–1043.
88. Chow HH & Hakim IA (2011) Pharmacokinetic and chemoprevention studies on tea in humans. *Pharmacol Res* **A64**, 105–112.
89. Czank C, Cassidy A, Zhang Q, *et al.* (2013) Human metabolism and elimination of the anthocyanin, cyanidin-3-glucoside: a ^{13}C-tracer study. *Am J Clin Nutr* **97**, 995–100.
90. Espín JC, González-Sarrías A & Tomás-Barberán FA (2017) The gut microbiota: a key factor in the therapeutic effects of (poly)phenols. *Biochem Pharmacol* **139**, 82–93.
91. Armah CN, Traka MH, Dainty JR, *et al.* (2013) A diet rich in high-glucoraphanin broccoli interacts with genotype to reduce discordance in plasma metabolite profiles by modulating mitochondrial function. *Am J Clin Nutr* **98**, 712–722.
92. Cuadrado A, Manda G, Hassan A, *et al.* (2018) Transcription factor NRF2 as a therapeutic target for chronic diseases: a systems medicine approach. *Pharmacol Rev* **70**, 348–383.
93. Carrasco-Pozo C, Gotteland M & Speisky H (2011) Apple peel polyphenol extract protects against indomethacin-induced damage in Caco-2 cells by preventing mitochondrial complex I inhibition. *J Agric Food Chem* **59**, 11501–11508.
94. Sandoval-Acuña C, Lopez-Alarcón C, Aliaga ME, *et al.* (2012) Inhibition of mitochondrial complex I by various non-steroidal anti-inflammatory drugs and its protection by quercetin via coenzyme Q-like action. *Chem Biol Interact* **199**, 18–28.
95. Murphy M (2009) How mitochondria produce reactive oxygen species. *Biochem J* **417**, 1–13.
96. Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? *J Neurochem* **97**, 1634–1658.
97. Tsuji PA, Stephenson KK, Wade KL, *et al.* (2013) Structure–activity analysis of flavonoids: direct and indirect antioxidant, and antiinflammatory potencies and toxicities. *Nutr Cancer* **65**, 1014–1025.
98. Iranshahy M, Iranshahi M, Abtahi SR, *et al.* (2018) The role of nuclear factor erythroid 2-related factor 2 in hepatoprotective activity of natural products: a review. *Food Chem Toxicol* **120**, 261–276.
99. Surh YJ (2011) Xenohormesis mechanisms underlying chemopreventive effects of some dietary phytochemicals. *Ann N Y Acad Sci* **1229**, 1–6.
100. Son TG, Camandola S & Mattson MP (2008) Hormetic dietary phytochemicals. *Neuromolecular Med* **10**, 236–246.
101. Scapagnini G, Vasto S, Abraham NG *et al.* (2011) Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. *Mol Neurobiol* **44**, 192–201.
102. Eggler AL & Savinov SN (2013) Chemical and biological mechanisms of phytochemical activation of Nrf2 and importance in disease prevention. *Recent Adv Phytochem* **43**, 121–155.
103. Stefanson AL & Bakovic M (2014) Dietary regulation of Keap1/Nrf2/ARE pathway: focus on plant-derived compounds and trace minerals. *Nutrients* **6**, 3777–3801.
104. Trujillo J, Granados-Castro LF, Zazueta C, *et al.* (2014) Mitochondria as a target in the therapeutic properties of curcumin. *Arch Pharm (Weinheim)* **347**, 873–884.
105. Waseem M & Parvez S (2015) Neuroprotective activities of curcumin and quercetin with potential relevance to mitochondrial dysfunction induced by oxaliplatin. *Protoplasma* **253**, 417–430.
106. Ji LL, Sheng YC, Zheng ZY, *et al.* (2015) The involvement of p62–Keap1–Nrf2 antioxidative signaling pathway and JNK in the protection of natural flavonoid quercetin against hepatotoxicity. *Free Radic Biol Med* **85**, 12–23.
107. Jung CH, Cho I, Ahn J, *et al.* (2013) Quercetin reduces high-fat diet induced fat accumulation in the liver by regulating lipid metabolism genes. *Phytother Res* **27**, 139–143.
108. Tang Y, Gao C, Xing M, *et al.* (2012) Quercetin prevents ethanol induced dyslipidemia and mitochondrial oxidative damage. *Food Chem Toxicol* **50**, 1194–1200.
109. Kovacic P & Somanathan R (2010) Multifaceted approach to resveratrol bioactivity: focus on antioxidant action, cell signaling and safety. *Oxid Med Cell Longev* **3**, 86–100.
110. Guha P, Dey A, Dhyani MV, *et al.* (2010) Calpain and caspase orchestrated death signal to accomplish apoptosis induced by resveratrol and its novel analog hydroxstilbene-1 in cancer cells. *J Pharmacol Exp Ther* **334**, 381–394.
111. Ungvari Z, Bagi Z, Feher A, *et al.* (2010) Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. *Am J Physiol Heart Circ Physiol* **299**, H18–H24.
112. Ak T & Gülçin I (2008) Antioxidant and radical scavenging properties of curcumin. *Chem Biol Interact* **174**, 27–37.
113. Barzegar A & Moosavi-Movahedi AA (2011) Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin. *PLoS ONE* **6**, e26012.
114. Derochette S, Franck T, Mouithys-Mickalad A, *et al.* (2013) Curcumin and resveratrol act by different ways on NADPH

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press

oxidase activity and reactive oxygen species produced by equine neutrophils. *Chem Biol Interact* **206**, 186–193.
115. Reyes-Fermín LM, González-Reyes S, Tarco-Álvarez NG, *et al.* (2012) Neuroprotective effect of α-mangostin and curcumin against iodoacetate-induced cell death. *Nutr Neurosci* **15**, 34–41.
116. Granados-Castro LF, Rodríguez-Rangel DS, Fernández-Rojas B, *et al.* (2016) Curcumin prevents paracetamol-induced liver mitochondrial alterations. *J Pharm Pharmacol* **68**, 245–256.
117. García-Niño WR, Tapia E, Zazueta C, *et al.* (2013) Curcumin pretreatment prevents potassium dichromate-induced hepatotoxicity, oxidative stress, decreased respiratory complex I activity, and membrane permeability transition pore opening. *Evid Based Complementary Altern Med* **2013**, 424692.
118. Feng C, Luo T, Zhang S, *et al.* (2016) Lycopene protects human SH–SY5Y neuroblastoma cells against hydrogen peroxide-induced death via inhibition of oxidative stress and mitochondria–associated apoptotic pathways. *Mol Med Rep* **13**, 4205–4214.
119. Houghton CA, Fassett RG & Coombes JS (2016) Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? *Oxid Med Cell Longev* **2016**, 7857186.
120. Bai X, Yao L, Ma X, *et al.* (2018) Small molecules as SIRT modulators. *Mini-Rev Med Chem* **18**, 1151–1157.
121. Giovannini L & Bianchi S (2017) Role of nutraceutical SIRT1 modulators in AMPK and mTOR pathway: evidence of a synergistic effect. *Nutrition* **34**, 82–96.
122. Zhou X, Chen M, Zeng X, *et al.* (2014) Resveratrol regulates mitochondrial reactive oxygen species homeostasis through Sirt3 signaling pathway in human vascular endothelial cells. *Cell Death Dis* **5**, e1576.
123. Ungvari Z, Orosz Z, Rivera A, *et al.* (2007) Resveratrol increases vascular oxidative stress resistance. *Am J Physiol Heart Circ Physiol* **292**, H2417–H2424.
124. Ungvari Z, Labinskyy N, Mukhopadhyay P, *et al.* (2009) Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. *Am J Physiol Heart Circ Physiol* **297**, H1876–H1881.
125. Moskaug JØ, Carlsen H, Myhrstad MC, *et al.* (2005) Polyphenols and glutathione synthesis regulation. *Am J Clin Nutr* **81**, 277S–283S.
126. Sarubbo F, Esteban S, Miralles A, *et al.* (2018) Effects of resveratrol and other polyphenols on Sirt1: relevance to brain function during aging. *Curr Neuropharmacol* **16**, 126–136.
127. Kim CS, Kwon Y, Choe SY, *et al.* (2015) Quercetin reduces obesity-induced hepatosteatosis by enhancing mitochondrial oxidative metabolism via heme oxygenase-1. *Nutr Metab (Lond)* **12**, 33.
128. Mo C, Wang L, Zhang J, *et al.* (2014) The crosstalk between Nrf2 and AMPK signal pathways is important for the anti-inflammatory effect of berberine in LPS-stimulated macrophages and endotoxin-shocked mice. *Antioxid Redox Signal* **20**, 574–588.
129. Zimmermann K, Baldinger J, Mayerhofer B, *et al.* (2015) Activated AMPK boosts the Nrf2/HO-1 signaling axis – a role for the unfolded protein response. *Free Radic Biol Med* **88**, 417–426.
130. Nadal-Serrano M, Pons DG, Sastre-Serra J, *et al.* (2013) Genistein modulates oxidative stress in breast cancer cell lines according to ERα/ERβ ratio: effects on mitochondrial functionality, sirtuins, uncoupling protein 2 and antioxidant enzymes. *Int J Biochem Cell Biol* **45**, 2045–2051.
131. Modrianský M & Gabrielová E (2009) Uncouple my heart: the benefits of inefficiency. *J Bioenerg Biomembr* **41**, 133–136.
132. Brand MD & Nicholls DG (2011) Assessing mitochondrial dysfunction in cells. *Biochem J* **435**, 297–312.
133. Demine S, Reddy N, Renard, P, *et al.* (2014) Unraveling biochemical pathways affected by mitochondrial dysfunctions using metabolomic approaches. *Metabolites* **4**, 831–878.
134. Pandey KB & Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev* **2**, 270–278.

Nutrition Research Reviews

https://doi.org/10.1017/S0954422419000210 Published online by Cambridge University Press