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Mitochondrial synapses: intracellular communication and signal integration

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Communication is a central theme in biology. Consequently, specialized structures have evolved to permit rapid communication among cells, tissues, organs, and physiological systems, thus enhancing the overall function and adaptation of the organism. A prime example is the neuronal synapse. In the brain, synaptic communication establishes neuronal networks with the capacity to integrate, process, and store information, giving rise to complex output signals capable of orchestrating functions across the organism. At the intracellular level, discoveries now reveal the existence of 'mitochondrial synapses' establishing mitochondrial networks, with defined chromatin-modifying mitochondrial output signals capable of orchestrating gene expression across the genome. These discoveries raise the possibility that in addition to their role as powerhouses and neuromodulators, mitochondria behave as intracellular signal-processing networks.

> 'The organism is integrated into a larger system of information exchange [. . .]. The brain and the rest of the organism are not qualitatively different in their ability to compute information, but show only qualitative differences in their purposiveness.' Weiner, H. (1992) *Perturbing the Organism: The Biology of Stressful Life Experience*, University of Chicago Press

The evolution of communication

Communication among cells, organs, and organisms is a far-reaching principle in biology [1]. As complex multicellular organisms evolved from unicellular life forms 1.5 billion years ago, the acquisition of specialized structures to enable and facilitate information exchange between cells and organs provides mechanistic evidence of the evolutionary advantage – or requirement – for communication in multicellular systems.

At the systemic level, a multitude of small molecules and peptide hormones, for which an even larger number of receptors exist, carry information between organ systems to coordinate their functions. Between most cells, gap junctions (see Glossary) and transmembrane receptors also enable efficient exchange of information between cells, thus coordinating their behavior. In fact, disorders of intercellular communication is a hallmark of cancer and other disease states [2].

In the brain, an organ optimized for signal integration, there are billions of synapses establishing complex neuronal networks which process and store information. Considering the parallel with synaptic function that defines brain activity, this opinion article discusses the emerging notion that within the cell cytoplasm, mitochondria are connected by similar physical structures – mitochondrial synapses – permitting electrochemical information exchange, and thus the opportunity to process, integrate, and transduce environmental information into signals that regulate gene expression and function (Figure 1).

Case study: the brain

The brain derives its processing power not from its constituent neurons but from the interconnections among them: the chemical and electrical synapses. Likewise, although information can be retained by single cells [3],

Glossary

Biofilm: matrix-enclosed multicellular bacterial cell collective whose behavior is controlled by cell–cell communication [32,35].
Chromatin: DNA–RNA–proteins complexes within the nucleus whereby chromosomes are packaged and gene expression is regulated without changes in the DNA sequence [66].
Cytoplasmic hybrid cells: or 'cybrids', are generated by the complementary fusion of two cells, one in which the nucleus is removed, and one depleted of its mitochondrial DNA.
Epigenetic: structural adaptations of chromosomal regions which register, signal, or perpetuate altered activity states [18].
Gap junction: an electrical synapse, or pathway of low resistance for the spread of electrical current (i.e., ions) and other small molecules from one cell to another [47].
Heteroplasmy: the mixture of different mtDNA molecules (e.g., mutant and normal) within a single cell [9]. This is possible because cells each contain 100s to 1000s of mtDNA molecules.
mtDNA: the mitochondrial DNA, a circular DNA molecule found in each cell by hundreds, localized in the mitochondrial matrix, and encoding 37 genes essential for respiratory chain function [9].
Neural ensemble: a population of functionally connected neuronal cells acting as a 'closed' system, involved in a specific neural computation process (e.g., [4]).
Quorum sensing: a cell–cell communication process where bacteria produce and detect extracellular chemicals to monitor cell population density and complexity, enabling the synchronization of gene expression within the group, and thus coordinated action [31].

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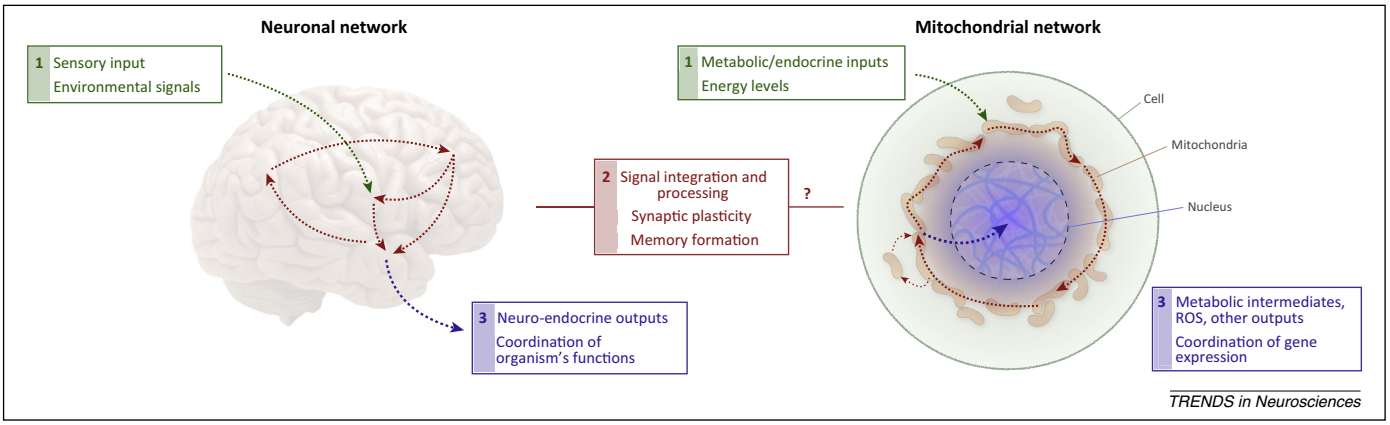

Figure 1. Conceptual model of signal sensing, integration, and signaling by neuronal and mitochondrial networks. Abbreviation: ROS, reactive oxygen species.

evidence suggests that memories are stored and retrieved in the patterned activation of neural ensembles [4]. Such information processing entails fast-acting, efficient, and moldable communication among large neuronal networks. Chemical and electrical coupling of neurons afforded by the synapse thus transforms a potentially inert mass of cells into one of the most sophisticated signal-processing system. The power of connections!

Importantly for the organism, neuronal connections confer upon the brain the possibility to rapidly and simultaneously process inputs of various nature: chemical, electrical, metabolic, and others. Information traveling within neuronal networks is also integrated with existing information – memories, stored within the state of these same networks. Under the influence of neuromodulators regulating synaptic transmission, including mitochondria (Box 1), emerge complex outputs, or signals. The ultimate outcome is the production of 'intelligent' patterns of response, transmitted via nerve fibers, secreted peptides, and neuroendocrine mediators to various organ systems of the body. The brain thus establishes 'integrated' patterns of function across the organism that ensure survival and adaptation to an ever-changing environment [5]. The evolutionary advantage of intercellular communication is thus used to coordinate functioning of multiple interrelated body systems. Likewise, within individual cells, coordinating the expression of interrelated genes across the genome entails complex subcellular regulatory mechanisms, which have recently been shown to involve mitochondria.

Box 1. Mitochondria modulate neuronal synaptic function and animal behavior

In neurons, neurotransmitter release by the presynaptic terminal requires mitochondrial ATP [67]. Because mitochondria contribute to synaptic vesicle release and recycling [68], the presence, absence, and movement of mitochondria in or out of the presynaptic terminal dynamically modulates neurotransmitter release [69]. Mitochondria also regulate spine morphogenesis and synaptic plasticity, and synaptic activity impacts mitochondrial positioning [70]. In the aging monkey brain dorsolateral prefrontal cortex, abnormal mitochondrial shape (donut-shaped) within presynaptic terminals is associated with smaller active zone size, fewer docked synaptic vesicles, and impaired short-term memory [71]. The heteroplasmic mixture of two different mtDNA types in mice impairs memory retention and anxiety behavior [72]. In the honey bee, mitochondrial respiratory chain function in neurons, but not astrocytes, modulates aggressive behavior [73]. Mitochondrial dysfunctions also initiate and/or contribute to neurodegeneration [74,75]. Collectively, via their positioning, shape, and function, mitochondria are potent neuromodulators.

Mitochondria regulate gene expression

At the subcellular level, mitochondria coordinate the function of genes within the cell nucleus. In the same way that the brain regulates basic organ functions and behaviors, mitochondria impact fundamental cell functions and behaviors including growth and differentiation [6,7], migration, autophagy, and death [8]. This is possible because mitochondria are positioned, both topologically and functionally, in close proximity to the nucleus where they generate chromatin remodeling, epigenetic metabolites affecting gene expression (Figure 2). Signals from the totality of mitochondria within a cell can thus generate complex patterns of gene expression.

Somatic cells such as neurons contain hundreds of mitochondria and an even greater number of mitochondrial DNA (mtDNA) copies. Within a single cell, a portion of mtDNAs can harbor a specific pathogenic mutation whereas the remaining mtDNAs are normal, leading to an intracellular state of heteroplasmy [9]. Clinically, increasing mtDNA mutation load leads to varying disease phenotypes for reasons that remain to be fully elucidated.

In cytoplasmic hybrid cells (i.e., cybrids), by manipulating mtDNA heteroplasmy levels along the full spectrum – from 0% (all normal mtDNA) to 100% (all mutated mtDNA) – the dose–response effect of mitochondrial dysfunction on nuclear gene expression was recently mapped. Increasing levels of the most common human mtDNA mutation ($tRNA^{Leu(UUR)}$ 3243A>G) caused complex transcriptional patterns impacting >17 000 genes, demonstrating that the majority of the human genome is subject to mitochondrial regulation [10]. Whereas high (60–90%) mtDNA mutation load activated transcriptional pathways associated with neurodegeneration and senescence, when only a small proportion (20–30%) of the mitochondria of the cell were affected, directionally 'opposite' transcriptional responses emerged notably leading to growth inhibition and decreased cell size [10]. Cells with the same nuclear genetic material can thus acquire vastly different transcriptomes and contrasting cellular phenotypes depending on mitochondrial signaling [10,11].

The nature of the signals by which mitochondria regulate the plastic (epi)genome are the subject of intense

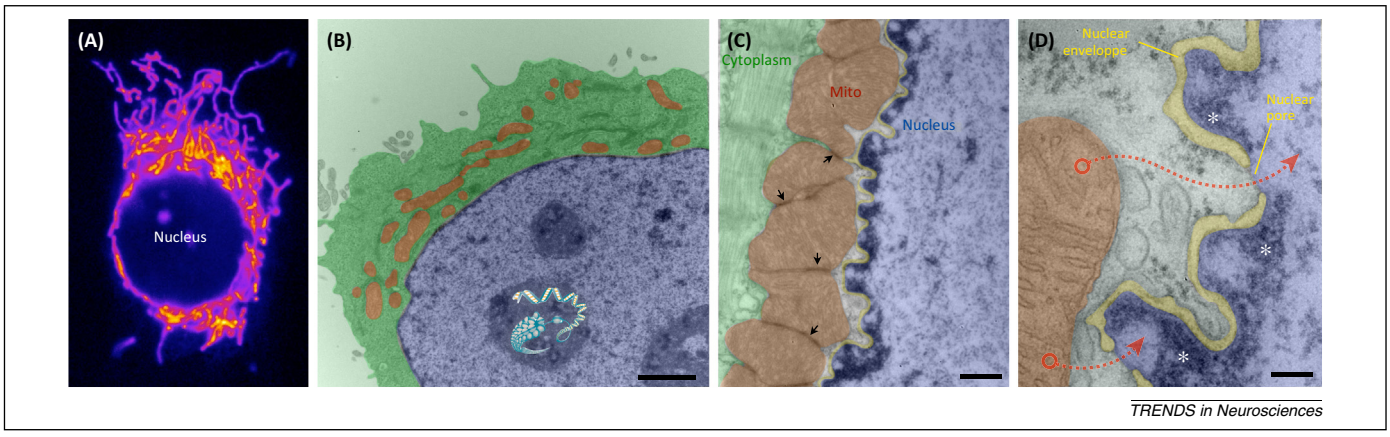

Figure 2. Mitochondria are in close proximity to the cell nucleus and the (epi)genome. **(A)** Light microscopy image showing the mitochondrial network around the nucleus in a human myoblast labeled with MitoTracker Green. See Video S1 in the supplementary material online for the corresponding live cell imaging movie. **(B)** Electron micrograph showing the perinuclear positioning of mitochondria (brown) around the nucleus (blue). Cytoplasm is green. Gene products (proteins, RNA) from both nuclear and mitochondrial genomes interact closely within mitochondria [76–78]. **(C)** Higher magnification of the mitochondria–nuclear interface in a skeletal muscle cell. Note the perinuclear clustering of mitochondria, here tethered by electron-dense inter-mitochondrial junctions (IMJs; see Figure 4 for details). **(D)** High-resolution imaging of a mitochondrion positioned nanometers away from nuclear pores, formed by discontinuities in the nuclear envelope (yellow). Condensed heterochromatin within the nucleus is indicated by *. Dotted arrows indicate theoretical diffusion of mitochondria-derived reactive metabolites and other signals, which can affect nuclear chromatin regulation to impact gene expression. Scale bars: (B) 1 μm, (C) 500 nm, (D) 100 nm.

investigation. They consist at least of reactive oxygen species (ROS) and reactive metabolic intermediates such as acetyl-coenzyme A (Ac-CoA), succinyl-CoA, α-ketoglutarate, NAD^+ (nicotinamide adenine dinucleotide), FAD (flavin adenine dinucleotide), SAM (S-adenosyl methionine), and others [12–17]. These metabolites are required substrates and cofactors for enzymatic reactions that modify the chromatin enclosed within the cell nucleus (Figure 3). The resulting chromatin post-translational modifications either promote or repress gene expression depending on interacting epigenetic components and the DNA sequence itself [18]. Notably, expression levels of the chromatin-modifying enzymatic machinery, including DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), are themselves under mitochondrial regulation [10]. Other canonical mitonuclear signaling pathways, including those responding to cellular energy levels such as AMPK (AMP-activated protein kinase) and PGC-1α (peroxisome proliferator gamma coactivator 1α) [10,11,19], involve the activation and translocation of transcription factors and coactivators within the nucleus [20]. Multiple signaling pathways thus contribute to transducing the functional state of mitochondria into transcriptional changes within the cell nucleus.

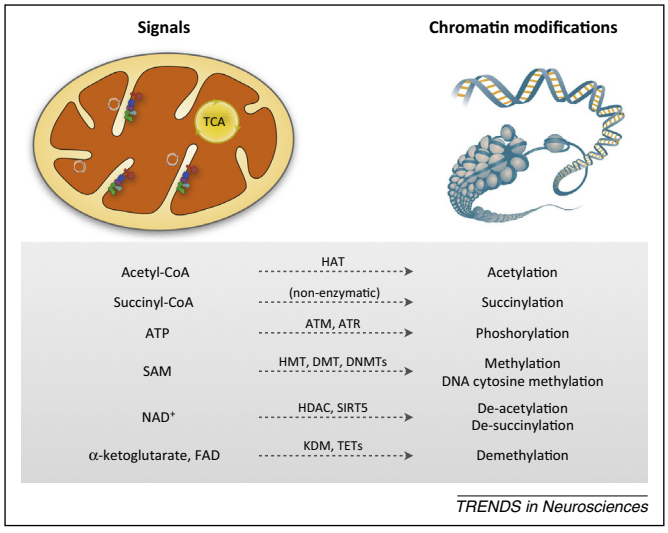

Figure 3. Reactive metabolites from mitochondria are the substrates for post-translational modifications regulating the chromatin structure and gene expression. Abbreviations: HAT, histone acetyltransferase; ATM, ataxia telangiectasia mutated; ATP, adenosyl triphosphate; ATR, ATM- and RAD3-related; DNMTs, DNA methyltransferases 1–3; FAD, flavin adenine dinucleotide; HDAC, histone deacetylase; HMT, histone methyltransferase; KDM, lysine demethylase; NAD^+, nicotinamide adenine dinucleotide; SAM, S-adenosyl methionine; TCA, tricarboxylic acid cycle (Krebs's cycle); SIRT5, sirtuin 5; TETs, ten–eleven translocation enzymes 1–3.

Even more interesting is the question on how such signals are generated. Do individual mitochondria release gene-regulatory signals based on their own state-of-the-moment? Or, as for brain neurons, whose function is contingent on the activity of other neurons to which they are functionally connected, can signal integration leading to complex-patterned outputs emerge within the mitochondrial network? It is established that fluctuations in the metabolic environment lead to mitochondrial morphology transitions via fusion/fission processes, which affect mitochondrial functions and resulting signals [8,21]. Mitochondrial fusion notably enables a certain form of molecular information exchange, although on a slow time scale, in the form of proteins, RNA, and other biomolecules. Individual units thus become an interconnected network.

From units to networks: insight from bacterial ancestors of mitochondria

Discoveries that mitochondria interact with each other and with other organelles, including the endoplasmic reticulum, Golgi, and peroxisomes [23–25,38], combined with molecular insights into mitochondrial fusion [26] have challenged the traditional conception of mitochondria as bean-shaped singular organelles operating independently from one another. Mitochondria are even exchanged between cells in a process termed 'intercellular mitochondrial transfer' [27,28] for reasons that remain unresolved [29],

but may represent an attempt of cells to communicate their intracellular bioenergetics states. This brings us back to our central question. Why communicate? As among brain neurons, does inter-mitochondrial communication enable signal processing within the mitochondrial network?

In pondering these questions, it is enlightening to consider the evolutionary history of the organelle. Notably, the bacterial ancestors of mitochondria possess sophisticated systems to communicate with each other. One such process is termed 'quorum sensing', which occurs via the exchange of diffusible or vesicle-bound chemical signals between individual units [30]. Membrane projections also enable transfer of antibiotic-resistance plasmids between neighboring bacteria – the communication of 'stable' information. Through quorum sensing, large numbers of individual bacteria synchronize their gene expression patterns, effectively behaving as a unified colony [31,32]. The slime mold, also a 'unicellular' organism, exhibits similar coordinated behavior arising from cell–cell communication (see http://www.youtube.com/watch?v=bkVhLJLG7ug, 'John Bonner's slime mold movies', for examples). In lower organisms, as in more complex ones, external signals such as food abundance, affect not only a proportion of the cells of the colony in direct contact with food scarcity but is also rapidly transmitted to the whole. In so doing, a collective and more appropriate adaptive response is initiated. Communication thus creates new 'emergent' population-level behaviors among the system [33]. As a result, simple 'unicellular' quorum-sensing bacteria form complex tridimensional structures called the biofilm, enhancing virulence and host invasion [34]. Through communication, the whole becomes more than the sum of its parts.

Assuming that bacterial quorum-sensing mechanisms evolved before the endosymbiotic incorporation of mitochondria's α-proteobacterial ancestor into the proto-eukaryotic cells, mitochondria may at the minimum have retained some of their bacterial communication/integration systems [35]. In addition, 1.5 billion years of community living within the eukaryotic cytoplasm and a major shift in the mitochondrial genome, whereby the majority of the ancestral mitochondrial genome was transferred and now resides in the nucleus, might have enabled the evolution of new means to exchange information between mitochondria, synchronize their behavior, and process information as an integrated system analogous to the plastic brain [36]. As in the brain, could synapse-like structures also exist to functionally connect mitochondria to one another, facilitating rapid communication, integration, and memory formation?

The mitochondrial synapse exists

In light of their somewhat privileged level of control on gene expression and cell functions, it is reasonable to ask whether mitochondria are only capable of individualistic action or whether they, similar to neurons, cooperate to generate integrated outputs that enhance the process of cellular adaptation. In the cell cytoplasm, it has been proposed that mitochondria act as 'power-transmitting cables', with evidence that electrochemical potential indeed propagates along mitochondrial tubules, and between each other [37,38].

Recent studies using time-lapse live-cell fluorescence microscopy with cells expressing a pH-sensitive reporter dye further demonstrated that electrochemical information (pH flashes) rapidly travels between physically-apposed mitochondria [25], implying the presence of structures to transmit electrochemical information. In cardiomyocytes, the electrical coupling of mitochondria was first suggested in the 1980s [38]. Since then, wave-like intracellular propagation of calcium, ROS, and mitochondrial permeability transition (a trigger of apoptosis) from mitochondrion to mitochondrion have also been reported, spreading through the mitochondrial network [39,40]. Furthermore, similar to neural ensembles, clusters of adjacent organelles in cardiomyocytes exhibit coordinated oscillations in membrane potential [41], further substantiating rapid electrochemical communication between neighboring mitochondria.

Upon investigation of mitochondrion–mitochondrion contacts by electron tomography, which affords enhanced resolution and three-dimensionality, synapse-like structures connecting mitochondria to one another were recently documented [22]. These inter-mitochondrial junctions (IMJs) are present across the animal kingdom from mollusks to mammals, suggesting their evolutionary significance [22]. On electron micrographs, IMJs are electron-dense membrane structures analogous to neuronal tight junctions, exhibiting a linear apposition of outer mitochondrial membranes from adjacent organelles (Figure 4) [22,38].

Within the space enclosed by the outer mitochondrial membrane (OMM), the inner mitochondrial membrane (IMM) forms invaginations called cristae, within which is embedded the respiratory chain. There, oxygen is coupled to electron transport to generate the life-sustaining membrane potential across the IMM. Interestingly, the number of cristae junctions with the outer membrane, which constitute an important site of metabolite exchange between mitochondrial compartments, is selectively enhanced at IMJs [22]. More surprisingly still is the fact that the cristae of two mitochondria bound by an IMJ become coordinated in space, often exhibiting significant curvature within a single organelle to enable their parallel alignment with cristae of the neighboring mitochondria (Figure 4). Information about the spatial orientation or mitochondrial ultrastructure is thus exchanged across mitochondria. IMJs and trans-mitochondrial cristae alignment do not require the profusion proteins Mitofusins 1 or 2 [22]. Consistent with earlier findings showing that mitochondria united by IMJs are electrically coupled [38], these data suggest that IMJs constitute electrical synapses between mitochondria.

In addition to rapid synaptic events of mitochondria–mitochondria communication [25] likely enabled by IMJs, other mechanisms involving slower-acting diffusible signals such as ROS-induced–ROS release [42], and exchange of matrix components via mitochondrial fusion [43,44], also contribute to inter-mitochondrial communication. In the brain, an analogous process would be the release of trophic factors between nerve cells. As for other aspects of physiology [45], 'redundant' mechanisms always exist to ensure robustness of essential biological functions such as communication.

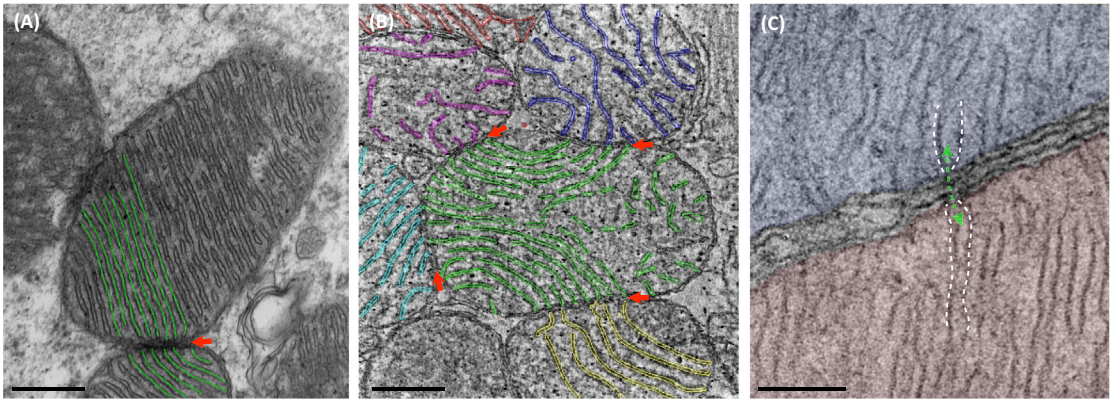

Figure 4. Mitochondrial synapses. **(A,B)** Inter-mitochondrial junctions (IMJs; red arrows) and associated trans-mitochondrial cristae coordination in skeletal (A) and cardiac muscle (B). **(C)** Higher magnification of IMJ, with gap junction-like juxtaposition of mitochondrial outer membranes, and juxtaposition of cristae (dotted lines) in a cardiomyocyte. Green arrow denotes theoretical exchange of electrochemical information at the apposed cristae junctions. Scale bars: (A,B) 300 μm, (C) 100 μm. Images reproduced, with permission, from [22].

Synaptic plasticity

An element that confers the brain with the capacity to learn and adapt is the plasticity of its synaptic connections. Chemical synapses can come and go, strengthened or weakened by their activation, or the lack thereof. Electrical synapses (i.e., gap junctions) are also dynamically modulated [46,47]. Likewise, mitochondrial synapses appear to be dynamically modulated.

At first glance, the mitochondrial network is fairly dynamic, with the shape and number of mitochondria subject to constant processes of fusion, fission, and transport [26]. Time-lapse images of living cultured cells with fluorescently labeled mitochondria provide a visceral and compelling picture of the dynamic nature of the mitochondrial network (see Video S1 in the supplementary material online). However, it is notable that differentiated cells and tissues *in vivo*, where the cytoplasm is more crowded and may chemically inhibit fusion [48], mitochondrial dynamics is slowed and the network assumes a more stable configuration.

An optimized biological solution to functionally connect physically constrained units, such as brain neurons, consists in establishing and dynamically remodeling specialized structures that hold membranes of adjacent cells in close proximity to facilitate molecular exchanges (i.e., synapses). In living cultured cells, bringing mitochondrial membranes in close proximity using a synthetic linker system that physically tethers organelles to one another induced mitochondrial synapses (IMJs) within less than 30 min [22]. In living animals, tissues that rely more heavily on mitochondrial oxidative metabolism for energy production and have higher mitochondrial density, such as the heart and muscles, also contain more IMJs, even when normalized to the total number of mitochondria–mitochondria contacts [22]. From an evolutionary standpoint, that the number of IMJs is in proportion to the density of mitochondria within cells is in line with the requirement for high population density to initiate quorum sensing in bacteria [30].

Preliminary evidence also suggests that as neuronal firing strengthens brain synapses, mitochondrial energy flux modifies mitochondrial synapse numbers. Whereas IMJs are practically absent from cells relying only minimally on mitochondria for energy production (i.e., cultured cells grown in high-glucose medium), their numbers in skeletal muscle dynamically increase with energy demand during exercise [49], and may decrease with inactivity [50]. Among neuronal mitochondria, presynaptic terminals of more metabolically demanding tonic synapses also contain more IMJs than phasic synapses [51], suggesting that mitochondria–mitochondria synapses are modulated by metabolic signals in neurons and other cell types. The 'use it or lose it' concept that characterizes the plasticity of neuronal networks may therefore represent one more parallel with mitochondrial networks driven by the plasticity of synapse-like IMJs.

Overview

It is proposed in this opinion article that interorganelle communication provides mitochondria, as do synapses between neurons of the brain, with the ability to collectively integrate information about the environment (Figure 1). An implicit aspect of this model not discussed in detail here is that mitochondria receive or sense incoming signals. Indeed, mitochondria contain functional hormonal receptors for glucocorticoids [52], cannabinoids [53], estrogen [54,55], and other molecular signaling platforms, including G-protein-coupled receptors (GPCRs) [56,57]. Mitochondria also undergo function-defining dynamic shape changes within seconds to minutes in response to the abundance of energetic substrates [21,58]. These evolved features likely ensure that mitochondria can sense a wide set of biological, psychosocial, and other signals, or 'stressors' [59].

In the context of signal processing, the establishment of a 'mitochondrial collective' [36] through mitochondrial synapses could have two major roles: (i) generate more temporally coordinated (coherent) and potent signals to impact nuclear gene expression [35]; and (ii) process and store information – a natural property of biological networks [60]. By sensing and integrating environmental signals with information stored in their functional and morphological states, mitochondria could thus effectively

interpret environmental signals to subsequently inform the production of appropriate chromatin-modifying metabolic intermediates, and possibly other adaptive signals.

Concluding remarks

A central role of communication within biology in general and neuroscience in particular is the coordination of elements within the organism as a whole – from genes to organs [61,62]. In accordance with this principle, mitochondria regulate functions across organizational levels. As discussed above, mitochondrial signals coordinately regulate the most part of the human genome at the intracellular level [10], in addition to influencing local organ-level processes such as angiogenesis [63], and systems-level cardiorespiratory responses [64]. Mitochondrial defects have both cell-autonomous and cell-nonautonomous effects on the organism [65]. This raises the intriguing possibility that mitochondrial energetics, in conjunction with the nervous system, serve to coordinately regulate central physiological functions across multiple levels of organization.

The relevance of mitochondria to brain function and cognition has been increasingly evident through the impact of the organelle on synaptic transmission (Box 1). But the role of mitochondria–mitochondria communication for learning, memory, and other neural activity remains unknown. Whether mitochondrial networks and mitochondrial synapses could contribute to storing information in single cells (i.e., 'grandmother cells' theory [3]), both within and outside the brain, is a matter of speculation. Likewise, whether disease states, such as diabetes and neurodegeneration, are associated with deficient mitochondrial communication, or impaired intracellular signal integration, remains to be tested. Some outstanding questions will need to be addressed to further test this hypothesis (Box 2). Nevertheless, the discovery of a dynamically remodeled inter-mitochondrial communication system and of defined mitochondria–nuclear signaling mechanisms to regulate gene expression opend new avenues to unravel the mechanisms by which organisms perceive, integrate, and adapt to an ever-changing environment.

Box 2. Outstanding questions

The impact of IMJs and cristae alignment (i.e., mitochondrial synapses) on cell function remains to be established. Nevertheless, their regulation by cellular energy demand, inducibility by stable mitochondrial contacts, and their evolutionary conservation across species suggest an important functional role [22]. Deciphering IMJ molecular composition and the nature of processes that orchestrate trans-mitochondrial coordination of cristae will provide cues of their functional regulation and physiological significance. The objective will be to manipulate mitochondrial synapses with the same precision that synaptic transmission can be manipulated in neurons so as to understand their role in neurons and other cell types. A few questions are particularly intriguing:

- As for neurons, can interconnected networks of mitochondria store information, that is, form 'memories'?
- Do mitochondrial synapses potentiate mitochondrial energy output in a manner consistent with the arrangement of batteries in series with one another?
- Other than electrochemical potential, what other information/molecules are passed through mitochondrial synapses?
- Are there nonmolecular (i.e., electromagnetic) mechanisms involved in regulating IMJs and trans-mitochondrial cristae coordination?

Insight from the field of bacterial quorum sensing may provide cues into both the regulatory mechanisms and the functional significance of mitochondria–mitochondria interactions for neuronal and brain function.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tins.2015.06.001.

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