

Review

The rise of mitochondria in medicine

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ABSTRACT

Once considered exclusively the cell's powerhouse, mitochondria are now recognized to perform multiple essential functions beyond energy production, impacting most areas of cell biology and medicine. Since the emergence of molecular biology and the discovery of pathogenic mitochondrial DNA defects in the 1980's, research advances have revealed a number of common human diseases which share an underlying pathogenesis involving mitochondrial dysfunction. Mitochondria undergo function-defining dynamic shape changes, communicate with each other, regulate gene expression within the nucleus, modulate synaptic transmission within the brain, release molecules that contribute to oncogenic transformation and trigger inflammatory responses systemically, and influence the regulation of complex physiological systems. Novel mitopathogenic mechanisms are thus being uncovered across a number of medical disciplines including genetics, oncology, neurology, immunology, and critical care medicine. Increasing knowledge of the bioenergetic aspects of human disease has provided new opportunities for diagnosis, therapy, prevention, and in connecting various domains of medicine. In this article, we overview specific aspects of mitochondrial biology that have contributed to – and likely will continue to enhance the progress of modern medicine.

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1. Introduction

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Mitochondrial research is on the rise across the medical sciences. As evidence, the number of mitochondria-related medical publications has outgrown those related to other organelles, including the endoplasmic

reticulum, Golgi apparatus, and the nucleus. In particular, the nucleus where the autosomal genes are housed has experienced a steady decline in the “post-genomic era” since completing the sequencing of the human genome in 2001 (Fig. 1). Reflecting the fact that mitochondria have received increasing attention in recent decades, biomedical scientists across disciplines frequently appear to ‘fortuitously’ encounter mitochondria at one point or another through the natural development of their research program. Likewise, recent discoveries of unsuspected pathophysiological mechanisms involving this organelle abound across medical disciplines (Wallace, 2013). Is this a fad doomed to fade sooner or later? We argue that this growing attention for mitochondrial biology, and its increasing relevance to modern medicine (McBride, 2015; Pagliarini and Rutter, 2013), is attributable to the convergence of key signaling pathways and biological processes onto the mitochondrion.

As life evolved from unicellular organisms over the last 1.2–1.5 billion years, mitochondria played a permissive role in the evolution of multicellular organisms (Lane and Martin, 2010; Wallace, 2010), even though the exact timing of endosymbiosis is under debate (Pittis and Gabaldon, 2016). Most likely as a result of this evolutionary connection to the basic cellular circuitry (Chandel, 2015), mitochondria are intimately linked to a number of basic cellular and physiological functions (Nunnari and Suomalainen, 2012). The present article focuses on classical and emerging aspects of mitochondrial biology and their relevance to specific areas of medicine, including inherited genetic disorders, neurology, oncology, immunology, endocrinology, and critical care medicine. Cases are outlined where considering emerging facets of mitochondrial biology has yielded new opportunities for diagnosis and/or therapy. We also discuss evidence that mitochondria exert systemic effects upon various organ systems, and the potential of bioenergetics research to the bridging enterprise with other medical theories.

In relation to disease, the emerging bioenergetic paradigm posits that mitochondrial defects contribute, often independently from energy production, to the development of age- and stress-related diseases by altering complex cellular and physiological functions.

1.1. Mitochondrial genetics and disease

Mitochondria contain their own genetic material – the mitochondrial DNA (mtDNA), which encodes essential molecular elements required

for electron transport by the respiratory chain where oxygen is consumed (Mitchell and Moyle, 1967). Driving this process justifies the existence of the cardiorespiratory systems (i.e., the lungs, heart, and vascular system), which transport oxygen and nutrients down to the cellular level. Ingested substrates initiate electron flow across the respiratory chain where breathed oxygen acts as the terminal electron acceptor. The cardio-pulmonary system thus provides the oxidizing agent (oxygen) and the gastrointestinal system provides the reducing agents (food substrates). This molecular sequence of events generates the electrochemical transmembrane potential across the inner mitochondrial membrane ultimately harnessed for adenosine triphosphate (ATP) synthesis, which fuels most life-sustaining cellular reactions (Nicholls and Ferguson, 2013).

Three decades have passed since the discovery of mtDNA is uniquely inherited from the maternal side (Giles et al., 1980). In the 1980's, it was discovered that mtDNA point mutations (Wallace et al., 1988) and deletions (i.e., the loss of a mtDNA segment encoding one or more mtDNA genes) (Holt et al., 1988) could cause human disease; a breakthrough for molecular medicine. Since these landmark discoveries, it has been established that inherited and acquired mtDNA defects, in addition to mutations in autosomal mitochondrial genes in the nucleus, are at the origin of heterogeneous and previously intractable pediatric and adult diseases. These are estimated to affect approximately 1:4300 individuals (Gorman et al., 2015b). Genetic mitochondrial disorders have principally remained the domain of neurology, but a now growing list of >300 monogenic autosomal defects at the origin of an even broader range of clinically complex diseases have pushed mitochondrialopathies into the realm of other medical specialties including endocrinology, oncology, cardiology, immunology, gastroenterology, and others (Koopman et al., 2012; Turnbull and Rustin, 2015). However, the origin of pleiotropic and multisystemic symptoms in mitochondrial disorders are, as yet, still poorly understood.

Even milder mtDNA sequence variants, or single nucleotide polymorphisms (SNPs) can confer disease risk. MtDNA SNPs have historically segregated as groups—called haplogroups—during human evolution and migration. Mitochondrial haplogroups have been found to be important in normal physiological adaptation as well as in modulating risk of developing disease across organ systems (Anglin et al., 2012; Hudson et al., 2014; Wallace, 2015; Latorre-Pellicer et al., in press). Specific selected examples are provided in Table 1.

Single mtDNA SNPs may also influence pathophysiology. For example, the “non-pathogenic” mtDNA variant m.16,189T>C confers risk for diabetes (Poulton et al., 2002), but possibly only in those with high BMI (i.e., in the presence of metabolic stress) (Liou et al., 2007) indicating mtDNA gene x environment interaction. mtDNA haplogroups may also influence the penetrance of autosomal genetic defects, such as ANT1-associated cardiomyopathy that progresses more rapidly in the context of certain mtDNA haplogroup than others

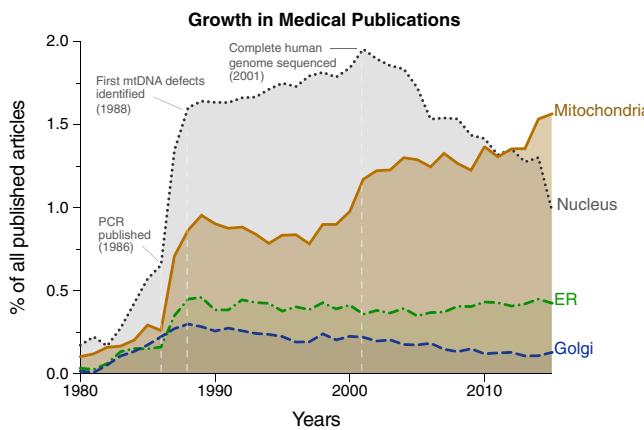


Fig. 1. Normalized proportions of published Medline-indexed medical articles from 1980 to January 1, 2016, related to various cellular components: mitochondria, nucleus, endoplasmic reticulum (ER), and Golgi apparatus. Note the increase in mitochondria-related publications following the publication of polymerase chain reaction (PCR) in 1986, the discovery of the first pathogenic mtDNA mutation/deletion in the 1988, and steady rise since the year 2000. In comparison, the number of publications about the cell nucleus has steadily decreased in the ‘post-genomic era’ following the completion of the human genome project in 2001, which demonstrated that the long searched genetic origin of common chronic diseases is likely not encoded in nuclear genes. Data for this figure was extracted from Medline/PubMed by searching the term “medicine” in combination with either “nucleus”, “mitochondria”, “endoplasmic reticulum”, or “Golgi”.

Table 1
Selected physiological conditions and common chronic diseases associated with mtDNA haplogroups.

Condition/disease	References
Longevity	De Benedictis et al. (1999); Feng et al. (2011); Rose et al. (2001); Tanaka et al. (1998)
Athletic performance	Eynon et al. (2011); Maruszak et al. (2014); Scott et al. (2009)
Adaptation to high altitude	Ji et al. (2012)
Diabetes	Crispim et al. (2006); Fuku et al. (2007)
Neurodegenerative disorders (Alzheimer and Parkinson)	Ghezzi et al. (2005); Liou et al. (2016); van der Walt et al. (2004); van der Walt et al. (2003)
Psychiatric disorders	Rollins et al. (2009); Sequeira et al. (2012)
Macular degeneration	Jones et al. (2007); Udar et al. (2009)
AIDS progression	Hendrickson et al. (2008)
Cancer	Booker et al. (2006); Darvishi et al. (2007); Fang et al. (2010)

(Strauss et al., 2013). These effects may be explained biochemically by the fact that the same mutation can cause varying degree of enzymatic deficiency depending upon the mtDNA haplogroup on which it is present (Ji et al., 2012). The genetic context of a mutation matters. These effects may arise from modest but functionally relevant differences in respiratory chain protein content and mtDNA copy number between haplogroups (Gomez-Duran et al., 2010; Kenney et al., 2014).

Next generation sequencing technologies affording greater sensitivity to detect low levels of mtDNA heteroplasmy have also revealed that pathogenic mtDNA mutations are common in the general population (Samuels et al., 2013; Ye et al., 2014). Their accumulation may be tissue specific (Burgstaller et al., 2014; Maeda et al., 2016; Samuels et al., 2013; Sharpley et al., 2012), suggesting that non-genetic factors across tissues may apply selective pressure influencing the segregation of certain mtDNA mutations (Picard and Hirano, 2016). Even in inherited pathogenic mutations such as the m.3243A>G mutation, heteroplasmy levels vary widely between tissues. A recent study of 24 postmortem tissues of monozygotic twins with the m.3243A>G mutation showed that heteroplasmy levels varied between 5 and 99%, but were highly similar in matched tissues from both brothers (Maeda et al., 2016). Genetic and non-genetic, possibly epigenetic, processes must therefore interact to influence mtDNA heteroplasmy and mitochondrial disease progression.

Improved diagnostics through advances in mtDNA and whole-exome sequencing has enabled the identification of a growing number of pathogenic mitochondrial mutations (Taylor et al., 2014). However, except for few defined disorders where nutritional interventions can offer partial symptomatic relief, clinicians mostly face a lack of consistently effective treatments (Parikh et al., 2015). The long-recognized fact that oxidative stress within mitochondria is a hallmark of mitochondrial dysfunction has stimulated the development of mitochondria-targeted antioxidant therapies. Subsequent to showing promise in pre-clinical studies and safety in phase 1 clinical trials in humans, phase 2 trials are now ongoing for mitochondria-targeted antioxidant molecules including MitoQ (ubiquinone mesylate, NCT02597023), the peptide SS-31 (d-Arg-2',6'-dimethyltyrosine-Lys-Phe-NH₂, NCT02245620), and other compounds. Other druggable mitochondrial components, particularly energy exchange systems and the pro-apoptotic function of the permeability transition pore (PTP), constitute new potential targets for mitochondrial medicine (Wang et al., 2016).

Recently, efforts have also been expanded to prevent the transmission of mitochondrial diseases. The UK approved a resolution aiming to legalize the clinical use of mitochondrial replacement therapy (MRT), which could soon enable women with mutated mtDNA to have children with normal mitochondria (Gorman et al., 2015a). Two related procedures are currently being pursued – maternal spindle transfer (Tachibana et al., 2010), and pronuclear transfer (Craven et al., 2010). Both techniques combine the nuclear genetic material of the two parents with the mitochondrial genome of a donor woman with healthy mitochondria, representing a breakthrough in the prevention of genetic diseases. Preclinical studies have now established the feasibility and minimized carryover of mutant mtDNA in pronuclear transfer (Hyslop et al., 2016).

Nevertheless, this preventative approach is not without creating debate due to potential long-term effects of the mixture of two different mitochondrial genomes within cells, a state termed heteroplasmy (Burgstaller et al., 2015; Reinhardt et al., 2013). In the U.S., where the procedure also remains controversial (Cohen et al., 2015), the Federal Drug Administration (FDA) recently mandated the Institute of Medicine (IOM) to establish a committee on "Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases" (Institute of Medicine, 2016). Significant steps for medicine are thus being taken towards the prevention of mitochondrial diseases, simultaneously raising new ethical and scientific challenges (Falk et al., 2016).

1.2. Genetic mitochondrial diseases: from ATP to genetic reprogramming

Because of the historical tenet of mitochondria as the cell's powerhouse, mitochondrial disease pathogenesis and patient symptomatology has naturally been attributed to an ATP production defect. But independent of energy production capacity, mitochondria produce signals that affect a number of cellular processes. Notably, mitochondrial signals alter the expression of several thousands of genes linked to diverse cellular functions (Elstner and Turnbull, 2012; Zhang et al., 2013; Latorre-Pellicer et al., in press). Thus, pathogenic mutations impairing mitochondrial functions may result in broad transcriptional reprogramming within the cell nucleus.

Mitochondrial reprogramming of the nuclear genome is rendered particularly complex because 100's to 1000's of copies of mtDNA exist within each cell, such that normal and mutated mtDNA genomes can coexist in a state of heteroplasmy within the same person, and within single cells (Fig. 2) (Taylor and Turnbull, 2005). Inherited differences in the proportion of mutant and normal mtDNA molecules, or increasing mutation load over time, may account for some of the variance in disease progression, where higher ratios of mutant/normal mtDNA cause more severe pathology in affected organs (Grady et al., 2014; Wallace and Chalkia, 2013). However, clinical and phenotypic variability exists among patients affected with the same mtDNA defect at similar heteroplasmy levels (Grady et al., 2014; Parikh et al., 2015), suggesting that other factors impact the complexity and progression of mitochondrial diseases.

Two recent studies investigated the dose-response consequence of increasing heteroplasmy for the most common human mtDNA mutation m.3243A>G tRNA^{Leu(UUR)} (Chae et al., 2013; Picard et al., 2014b). This mutation affects mitochondrial protein synthesis and causes respiratory chain dysfunction (Sasarman et al., 2008). One study examined the full spectrum of heteroplasmy from 0% (only normal mtDNA) to 100% (all mutant mtDNA) in syngenic cytoplasmic hybrid (cybrid) cell lines. Although these cells originate from a single clone, they vary in their levels of mtDNA heteroplasmy. Strikingly, whole-transcriptome analysis by RNA-sequencing revealed that mitochondria have the ability to regulate the expression of the majority (>66%) of genes within the human genome (Fig. 2), including the epigenetic/chromatin remodeling machinery (Picard et al., 2014b). Analysis of nuclear responses across the full spectrum of mtDNA heteroplasmy indicated that depending upon the mutation load – but not ATP levels – contrasting genetic programs were turned on while others were shut down (Picard et al., 2014b). This bi-phasic pattern of nuclear reprogramming is in contrast with the expectation that increasing mitochondrial dysfunction would cause a linear dose-response shift in the transcriptome.

In addition, different mtDNA haplogroups that confer disease risk have also been associated with different gene expression profiles in stem cells (Kelly et al., 2013) and cytoplasmic hybrid cells (Kenney et al., 2014). Conplastic mice with the same nuclear genome but with different mtDNAs also show profound transcriptomic, proteomic, and metabolomic differences (Latorre-Pellicer et al., in press). This demonstrates that both pathogenic defects such as the m.3243A>G point mutation, as well as evolutionary defined and combinations of mtDNA single nucleotide polymorphisms (i.e., haplogroups) generate signals that modulate the expression of nuclear genes.

Signals that convey information between mitochondria and the nucleus include reactive oxygen species (ROS) (Reczek and Chandel, 2015; Shadel and Horvath, 2015) and reactive metabolic intermediates derived from mitochondrial metabolism (Gut and Verdin, 2013; Wallace and Fan, 2010). These metabolites constitute the required substrates and co-factors for chromatin remodeling via post-translational modifications, including AcCoA and NAD⁺ for acetylation/deacetylation reactions by histone acetylase/deacetylases, s-adenosylmethionine and α-ketoglutarate for methylation/demethylation by DNA methyltransferases/demethylases, and others (Gut and Verdin, 2013). The resulting epigenetic marks impact nuclear gene expression via changing the

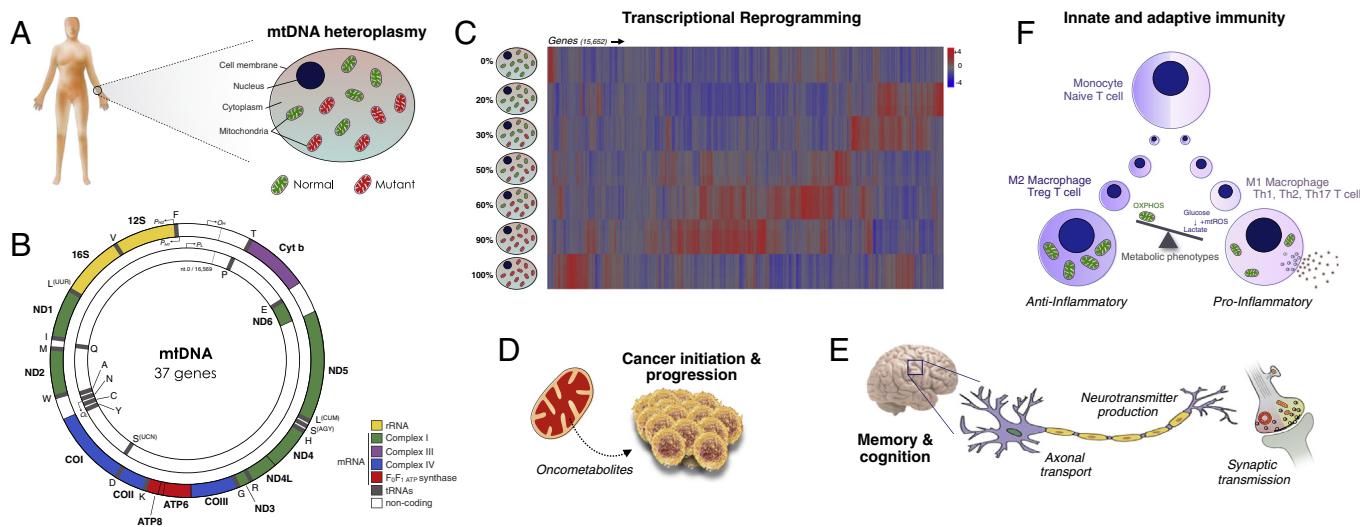


Fig. 2. Multifaceted mitochondrial pathogenesis. (A) Somatic tissues contain 100–1000's of mitochondrial DNA (mtDNA) molecules each, such that a mixture of normal and mutated copies can coexist in a state of heteroplasmy. (B) The mitochondrial genome, containing 37 genes essential to respiratory chain assembly and function. (C) mtDNA heteroplasmy for the most common pathogenic MELAS-causing m.3243A>G mutation of the tRNA^{Leu(UUR)} gene causes genome-wide transcriptional reprogramming; data adapted from (Picard et al., 2014b). (D) Mitochondrial signals promoting cancer initiation and progression. (E) Abnormal mitochondrial function and positioning alters multiple components of the nervous system. (F) Metabolic programming of immune cell differentiation and proliferation into anti- and pro-inflammatory phenotypes, driven by the balance of oxidative phosphorylation (OXPHOS) vs. glycolysis and mitochondrial reactive oxygen species (mtROS).

epigenetic landscape responsible for silencing and activating specific genes across genome (Bird, 2007).

Not surprisingly, mitochondria-nuclear crosstalk must also interact with cell- and tissue-specific features (Hamalainen et al., 2013), which are themselves epigenetically determined (Meissner et al., 2008). Mito-nuclear crosstalk and the link with the epigenome provides a potential explanation for tissue-specific affections in mitochondrial diseases. As a clinical entity, mitochondrial disorders exemplify the notion that a specific genetic defect can yield pleiotropic clinical manifestations, and that mitochondrial signals beyond energetics contributes to these pathogenic mechanisms. Further research is required to elucidate the underlying mechanisms, and the particular vulnerability of specific organs such as the brain, to mitochondrial dysfunction.

1.3. Mitochondrial dynamics, quality control and the brain

Mitochondria do not sit idle within the cell cytoplasm as suggested by the traditional static bean-like textbook picture. Visualizing live cells under the microscope reveals mitochondria undergoing constant dynamic processes of fusion and fission with each other, leading to shape changes and molecular exchange within seconds to minutes (Archer, 2013; Twig et al., 2010). Supplementary video S1 shows mitochondrial dynamics in a cultured human myoblast, where the mitochondrial network undergoes extensive remodeling. Although this process is slowed in mature differentiated cells *in vivo*, mitochondrial fusion occurs and enables the exchange of molecular content between organelles (Mishra et al., 2015).

Mitochondrial morphology transitions are regulated via multiple inputs including fluctuations in the metabolic state, in which substrate oversupply promotes network fragmentation (Molina et al., 2009; Yu et al., 2008), and metabolic undersupply promotes elongation (Gomes et al., 2011; Rambold et al., 2011). In fact, mitochondrial fission, fusion, transport, and degradation are collectively regulated by energy metabolism and respiratory chain function (Mishra and Chan, 2016), the conserved energy sensing intracellular signaling pathways AMP-activated protein kinase (AMPK) signaling (Toyama et al., 2016), adrenergic signaling (Chang and Blackstone, 2007; Wikstrom et al., 2014), among others (Mishra and Chan, 2016). Because mitochondrial morphology appears to regulate various aspects of mitochondrial function such as oxygen consumption, ROS production, and susceptibility to apoptotic

signaling (Picard et al., 2013), changes in mitochondrial shape impact both cell energetics (Benard and Rossignol, 2008) and other cellular functions ranging from differentiation to death (Kasahara and Scorrano, 2014).

Although long-believed to behave as independent organelles, new evidence is changing this solitary view of mitochondria. Not unlike their “social” bacterial ancestors mitochondria undergo a form of quorum sensing (Picard and Burelle, 2012), specialized inter-mitochondrial junctions also exist between adjacent mitochondria where cristae ultrastructure becomes coordinated between neighboring organelles, indicating the exchange of information across mitochondria (Picard et al., 2015b). This may account for rapid information exchange between organelles reported to occur in the absence of organelle fusion (Santodomingo et al., 2013), and possibly other forms of communication. The transfer of whole mitochondria from one cell to another – intercellular mitochondrial transfer – has also been described (Rogers and Bhattacharya, 2013), and may have significant functions for stem cell behavior and functional interactions between cancer and stromal cells (Ahmad et al., 2014; Tan et al., 2015). Immune-to-endothelial cell mitochondrial transfer (Islam et al., 2012), and mitochondrial transplantation (Masuzawa et al., 2013), may also confer protection against injury. The discovery of mechanisms enabling the communication of bioenergetic states within and across cells is thus blurring the boundaries previously imagined to separate mitochondria as independent energy-producing powerhouses.

Likewise, as the proteins enabling dynamic processes of mitochondrial fusion and fission were discovered, new opportunities arose to understand disease (Chan, 2012). Multiple clinical conditions primarily affecting the neuromuscular systems involve impaired mitochondrial dynamics (Archer, 2013; Friedman and Nunnari, 2014). Fusion/fission dynamics in concert with mitochondrial biogenesis also enable the selective removal of dysfunctional mitochondria as part of intracellular quality control – or autophagy (from the Greek “self-eating”); the “life cycle” of mitochondria (Twig et al., 2008). In the brain where synaptic mitochondria are often positioned several hundred microns and centimeters away from the cell body, neurons may outsource mitophagy by shedding damaged mitochondria followed by uptake and degradation by adjacent astrocytes (Davis et al., 2014).

Whereas disrupting this mitochondrial life cycle and quality control processes may lead to disease, targeting it may have clinical therapeutic

applications. In diabetes for example, pharmacologically preventing excessive glucose- and lipid-induced mitochondrial fission may confer protection against insulin resistance (Jheng et al., 2012). In muscular dystrophy, pharmacological activation of autophagy may preserve mitochondrial function and attenuate myofiber degeneration (Grumati et al., 2010). Likewise in mouse models of mitochondrial disease, overexpression of the core component of the mitochondrial fusion machinery OPA1 (optic atrophy 1) partially restores skeletal muscle function (Civiletti et al., 2015). Overexpression of OPA1 also partially alleviates ischemic damage in heart and brain (Varanita et al., 2015), with potential therapeutic implications for a number of acute and chronic medical conditions such as retinopathy, diabetic angiopathy, stroke, myocardial infarction, and others where ischemic insult likely contributes to tissue damage through mitochondria-dependent mechanisms (Chouchani et al., 2014).

Among the organ systems affected by mitochondrial dysfunction, the brain and the nervous system are particularly harmed by alterations of both mitochondrial shape and function (McFarland et al., 2011). Notably, electron microscopic studies position abnormal mitochondrial shape as an emerging disease biomarker and potential cause of neurodegenerative disorders (Burte et al., 2015), along with oxidative stress and inflammation (Lin and Beal, 2006). In non-human primates, abnormal donut-shaped (i.e., toroid) mitochondria in brain presynaptic terminals are associated with loss of synaptic structure and function, and are correlated to age-related memory decline in the living animal (Hara et al., 2014), thus linking abnormal organelle shape to a higher-level cognitive function. These findings could be explained by the fact that the presence or absence of mitochondria in presynaptic boutons directly modulate synaptic neurotransmitter release (Sun et al., 2013). mtDNA heteroplasmy also impact memory formation in mice (Sharpley et al., 2012).

Clinically, a neurobiological subtype of autism spectrum disorder and other neurological disorders in humans involve mitochondrial dysfunction (Goh et al., 2014), although the cause-effect relationship in these cases remains to be established. Potential mechanisms involve the production of abnormal mitochondrial signals that may contribute intracellularly to cytoplasmic protein aggregates, epigenetic anomalies and gene expression dysregulation in the cell nucleus, as well as systemic neuroendocrine and metabolic effects that feedback on the brain (Picard and McManus, 2016). Notably, mitochondria-targeted antioxidant treatment has successfully prevented early pathological changes in preclinical studies of Alzheimers' disease (McManus et al., 2011), suggesting that abnormal mitochondrial shape and function may precede and contribute to neurodegenerative processes, rather than being a secondary consequence.

Interrelated aspects of mitochondrial dynamics, quality control, and their non-energetic functions thus bear functional consequences on multiple organ systems including the heart, skeletal muscles, liver, kidneys, and the brain in particular. Our growing understanding of the role of the processes responsible for maintaining optimal mitochondrial functions, and their failure in disease, may eventually translate into opportunities for prevention and treatment of age-related diseases affecting the brain and other physiological processes.

1.4. The bioenergetics of immunity

Immune processes and inflammation are conserved biological functions linked to diseases that span multiple areas of medicine. In mammalian cells, mitochondria contribute to immune processes in four major ways.

First, systemic inflammatory cellular responses involve mitochondrial signaling. Following mitochondrial damage due to oxidative stress or other insult, the bacteria-like circular mtDNA can leak out into the cytoplasm through mechanisms that remain to be established. As a result, the NLRP3 inflammasome can be triggered by mtDNA outside the mitochondria (Lu et al., 2014). In neutrophils, mitochondrial damage may

also lead to extrusion of mtDNA nucleoids, which when oxidized, can trigger interferon production and contribute to autoimmune processes in lupus (Caielli et al., 2016).

Second, mitochondria act as an immune signaling platform to orchestrate the anti-viral response intracellularly. This involves the recruitment and aggregation of MAVS (mitochondria antiviral signaling) proteins at the mitochondrial surface to engage innate antiviral signaling in a mitochondrial membrane potential-dependent manner (Koshiba et al., 2011; Seth et al., 2005). Mitochondrial ROS can also potentiate toll-like receptors (TLRs) signaling involved in macrophage bactericidal activity (West et al., 2011), thus priming the anti-viral machinery for action. In the cytoplasm, the mtDNA also engages the DNA sensor cGAS and activates downstream signaling components culminating in transcriptional regulation that modulate resistance to viral infection (West et al., 2015). The role of mitochondria in anti-viral cellular signaling could contribute to explain why mtDNA sequence variants (i.e., haplogroups) across individuals infected with HIV/AIDS clinically impact disease progression and mortality (Hendrickson et al., 2008).

Third, the mtDNA can also leak into the systemic circulation where it is recognized by TLR9 and may ultimately lead to tissue lesions and degenerative cardiovascular and neurological conditions (Mathew et al., 2012; Oka et al., 2012; Zhang et al., 2010). Circulating "cell-free" mtDNA (ccf-mtDNA) and other mitochondria-derived damage-associated proteins (DAMPs) and pathogen-associated molecular proteins (PAMPs) that are free-floating in the blood thus represent putative biomarkers of prodromal stages of disease either produced by or involving mitochondrial stress (Picard et al., 2014a). Studies also indicate that ccf-mtDNA increase with aging, representing a potential contributor to "inflammaging" (Pinti et al., 2014). Importantly for our understanding of the role of mitochondria in human health is the emerging notion that mitochondria-derived factors can trigger inflammatory and pathologic processes known to underlie many of the most common age-related chronic diseases. But whether mitochondria act as primary drivers of inflammation in various conditions remains to be established.

Finally, mitochondrial energetics and adaptive immunity are connected via regulating immune cell type differentiation into pro- and anti-inflammatory phenotypes. The acquisition of specific effector functions in monocyte/macrophages, lymphocytes and dendritic cells cannot proceed without specific metabolic and mitochondrial reprogramming (Pearce et al., 2013). Differentiation of macrophages (M0) into distinct pro- (M1) and anti-inflammatory (M2) phenotypes involves specific bioenergetic signatures (see Fig. 2). Recent findings also suggest that in professional antigen-presenting cells such as macrophages and dendritic cells, inflammatory stress can lead to the production of small mitochondrial-derived vesicles (MDVs), which deliver mitochondrial antigen at the cell surface for presentation on MHC class-1 molecules (Matheoud et al., 2016). This mechanism, which may promote activation of autoimmune processes, is potently repressed by PINK1/PARKIN-dependent mitophagy (Matheoud et al., 2016), illustrating the importance of proper mitochondrial quality control for the maintenance of normal immunity. Thus, mitochondrial dysfunction in immune cells could contribute to an increased susceptibility to infection and autoimmune disorders in patients with mitochondrial disorders (Walker et al., 2014a; Walker et al., 2014b), and opens the possibility to modulate both innate and adaptive immune responses by targeting mitochondrial function (Weinberg et al., 2015). Mitochondrial modulation of various immune processes further illustrates the organelle's broad physiological effects beyond energy production.

1.5. Non-energetic mitochondrial functions and systemic diseases

Beyond their energetic role in ATP synthesis, mitochondria engage in "non-energetic" intracellular signaling that reprogram nuclear gene expression as described above and are found at the nexus of multiple cellular metabolic pathways leading to disease when disrupted. Through bioenergetic processes, enzymatic reactions within mitochondria re-

route carbohydrates, amino-acids and lipids into cellular pathways destined either to macromolecule biosynthesis (e.g., heme and steroid hormones), de-novo lipid or nucleotide synthesis for DNA replication, and cellular antioxidant defenses, among others (Nicholls and Ferguson, 2013). As a result, defects in specific mitochondrial enzymes cause the accumulation of intermediary metabolites, several of which are the substrates for enzymatic reactions that regulate gene expression (Gut and Verdin, 2013). In addition, mitochondrial metabolic intermediates including fumarate, succinate and D-2-hydroxyglutarate can also act as ‘onco-metabolites’ that can induce or promote carcinogenic transformation (Yang et al., 2013) (Fig. 2). Mitochondrial metabolites may also reach the systemic circulation, acting peripherally upon other cells via G-protein coupled receptors (GPCRs). For instance, succinate is a metabolic intermediate of the Krebs cycle that can trigger a “pseudo-hypoxic state” by stabilizing the hypoxia-responsive element HIF-1a, with downstream Nf- κ B activation (Tannahill et al., 2013). Selected examples of recently discovered “non-energetic” syndromes and diseases caused by defects in mitochondrial genes are listed in Table 2.

Beyond the confine of cells, mtDNA defects also dysregulate complex physiological processes at the organ and systems level. The growth of blood vessels for oxygen delivery (i.e., angiogenesis) is selectively promoted around skeletal muscle fibers with defective mitochondria (Taivassalo et al., 2012), indicating that information about OXPHOS defects in the affected muscle cells influence the behavior of surrounding capillary cells. Systemically, mtDNA mutations have been found to cause abnormal autonomic nervous system regulation of heart rate (Bates et al., 2013; Taivassalo et al., 2003), and to exaggerate catecholamine release during exercise in humans (Jeppesen et al., 2013). Mitochondrial functions also modulate neuroendocrine (cortisol, catecholamines), hippocampal gene expression, and downstream metabolic responses to psychological stress in mice with different mitochondrial defects (Picard et al., 2015c), demonstrating that mitochondrial disorders impact multiple levels of functioning from organelle to organism (Fig. 3). These systemic mitochondrial effects may contribute to the multisystemic deterioration associated with chronic or repeated stressors, and thus shape the organism's resilience and vulnerability in the face of various stressors (Morava and Kozicic, 2013; Picard et al., 2014a). Evidence so far indicates that mitochondria modulate responses to increased energy demand during exercise, psychosocial stress, as well as critical life-threatening medical conditions that activate multiple stress systems, as discussed below.

Table 2

Selected examples of diseases and syndromes associated with defects in mitochondrial functions not directly involving energy production.

Disease/syndrome	Mitochondrial defect (gene)	References
Early-onset proximal muscle weakness accompanied by learning difficulties	Calcium uptake (MICU1)	Logan et al. (2014)
Early-onset fatigue and lethargy	Calcium uptake (MICU1)	Lewis-Smith et al. (2016)
Deafness	Intramitochondrial methylation (TFB1M)	Bykhovskaya et al. (2004); Raimundo et al. (2012)
Adrenocortical cell loss and hypocortisolemia	Redox regulation, intra-mitochondrial antioxidant systems (NNT)	Meimardou et al. (2012)
Multi-system neurological disease	Mitochondrial fusion and cristae organization (OPA1, MFN2)	Burte et al. (2015); Yu-Wai-Man et al. (2010)

MICU1: mitochondrial calcium uptake 1, a regulator of the mitochondrial calcium uniporter (MCU).

NNT: nicotinamide nucleotide transhydrogenase.

TFB1M: mitochondrial transcription factor B1.

OPA1: optic atrophy 1.

MFN2: mitofusin 2.

1.6. Mitochondria in critical care medicine

Within the realm of critical care medicine, severe pathological states often overwhelm the body's stress response systems. Recent research has defined certain principles of mitochondrial bioenergetics, notably related to how mitochondria respond to stressors – bioenergetically, morphologically, and genetically – and the downstream impact of resulting mitochondrial signals on key aspects of cellular function such as gene expression. This section outlines some of these bioenergetic principles that enhance our grasp of resilience/vulnerability and of its cellular determinants, which are beginning to inform medical practice in the intensive care unit (ICU).

One such principle is that metabolic “oversupply” leads to mitochondrial toxicity. Metabolic oversupply is the excess supply of energy substrates, mainly glucose and lipids, relative to cellular demand (Picard and Turnbull, 2013). In the critically ill adult patient who naturally exhibits low energy requirements due to bedrest and physical inactivity, early-onset intravenous feeding (i.e., parenteral nutrition) promotes metabolic oversupply and is consequently associated with greater morbidity than later-onset feeding (Casaer et al., 2011). More food is not better, and may even be damaging. The detrimental effect of metabolic oversupply is thought to result from mitochondrial substrate overload (Fisher-Wellman and Neufer, 2012), which entails excessive reduction of the respiratory chain and consequent ROS production (Anderson et al., 2009), mitochondrial fission and oxidative stress culminating in mtDNA damage, and possibly cellular aging indexed by telomere shortening (Picard and Turnbull, 2013).

In patients receiving ventilatory support, hyperglycemia (excess circulating glucose levels) is associated with longer length of hospitalization, prolonged weaning time, and increased mortality (Bilotta and Rosa, 2012; Van den Berghe et al., 2006). As in other instances of bioenergetic disturbance, ventilator-induced diaphragmatic dysfunction (VIDD) involves metabolic stress and mitochondrial fragmentation in muscle fibers (Picard et al. 2015a). This condition is exacerbated by systemic metabolic oversupply (Picard et al., 2012b), and associated with mtDNA damage with consequent mitochondrial respiratory chain dysfunction (Picard et al., 2012b). In patients with sepsis, a life-threatening clinical syndrome following infection or injury, mitochondrial function is also acutely impaired (Weiss et al., 2014). In this context, molecular induction of mitochondrial biogenesis, which increases or preserves mitochondrial content and function, predicts survival in critically ill patients (Carre et al., 2010), consistent with the notion that mitochondrial functional capacity contributes to shaping adaptive capacity in the face of acute stressors (Picard et al., 2014a). mtDNA haplogroups also predict survival in septic patients (Baudouin et al., 2005), illustrating the clinical significance of both biochemical and genetic aspects of mitochondrial biology in critical care medicine. Understanding the interplay between the metabolic state and mitochondria will help design optimal treatment strategies that will aim to preserve mitochondrial functions, prevent the accumulation of damage, and secondarily enhance clinical outcomes.

In the context of treatment and prevention, it is illuminating to understand that mitochondria mediate the effects of metabolic stress and determine resilience to septic conditions. This suggests that targeting mitochondrial functions, pharmacologically or through other means, may yield measurable clinical outcomes (Wang et al., 2016). Preserving normal cellular bioenergetics through optimal glycemic control reduces incidence of critical illness polyneuropathy (CIP)/myopathy (CIM), which otherwise compromises weaning from mechanical ventilation and hospital discharge (Hermans et al., 2009). Optimal glycemic control with intensive insulin therapy also preserves mitochondrial integrity and decreases co-morbidity in bedridden individuals (Van den Berghe et al., 2006), underscoring the deleterious effect of metabolic oversupply on mitochondria, and the downstream systemic outcomes.

In preclinical studies, the genetic overexpression of the antioxidant enzyme Prx3 (peroxiredoxin 3) prevents VIDD in mice (Picard et al., 2012b). Similarly, administration of the mitochondrial-targeted

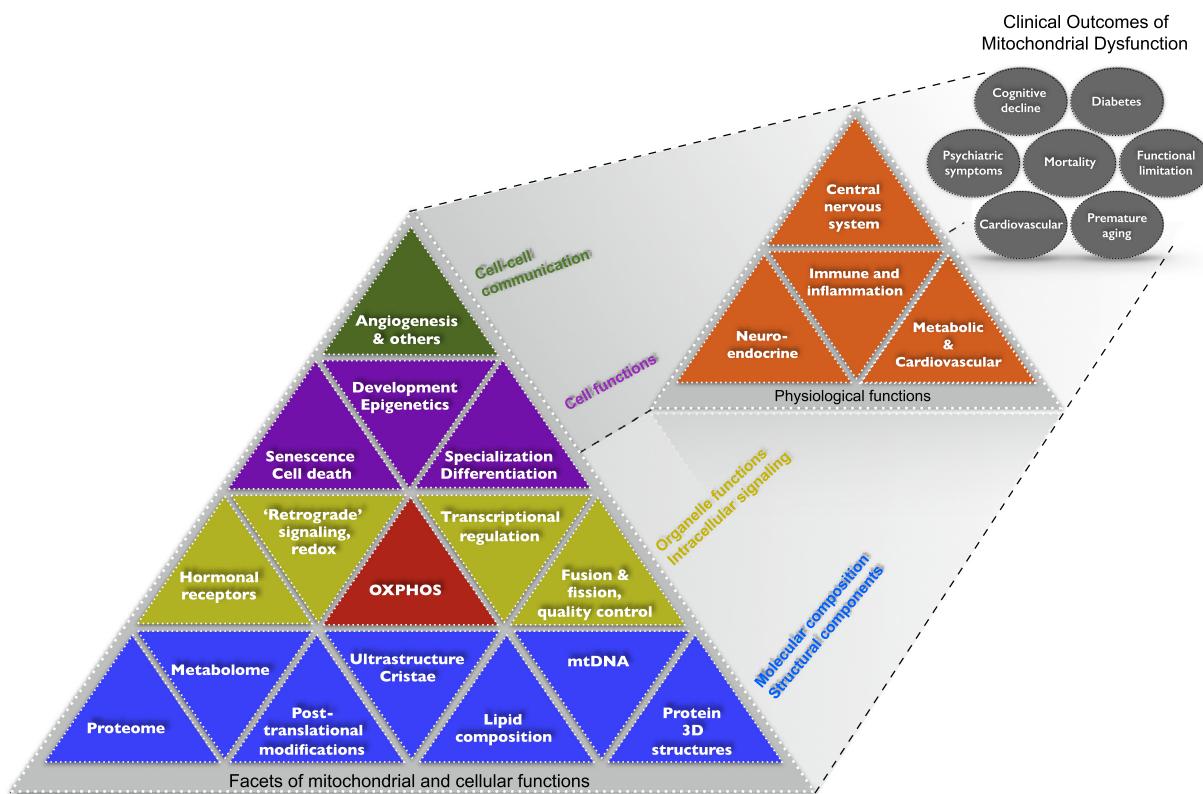


Fig. 3. Multi-level organization of mitochondrial molecular composition, structures, functions, and signaling roles within the cell. These nested facets of mitochondrial functions are depicted hierarchically in a Maslow-type pyramidal model with the most basic determinants at the bottom and more complex emergent processes above. These facets of mitochondrial and cellular functions (first dimension) are regarded as determinants of higher-level physiological functions (second dimension), which in turn influence systems-level functions (third dimension) that contribute to clinical outcomes and mortality. Figure adapted from (Juster et al., 2011).

antioxidant SS-31 has shown promise pre-clinically in preventing the mitochondrial dysfunction in the mechanically-ventilated diaphragm, and thus mitigating the ensuing reduction in muscle mass and contractility (Powers et al., 2011). These data position mitochondria-derived oxidative stress as an early mediator of the effect of metabolic oversupply on skeletal muscle function, and possibly in other tissues. Based on our rapidly evolving understanding of mitochondrial bioenergetics, morphology, and genetics in critical care illness, clinical strategies aimed at reducing “mitochondrial overload”, mitigating excessive mitochondrial oxidative stress, and mitochondrial apoptotic signaling should thus represent suitable avenues to optimize recovery and reduce mortality in the ICU.

1.7. Disease prevention, the health benefits of physical activity, and mitochondria

Advances in mitochondrial biology may also inform strategies, such as exercise, to prevent and treat non-communicable diseases that burden modern medicine. Aerobic exercise is among the few therapies capable of improving medical conditions refractory to conventional treatments, such as major depressive disorder (Rethorst et al., 2013), and remission from type 2 diabetes (Gregg et al., 2012). Exercise has also been shown to affect the brain, and possibly reverse age-related atrophy of the hippocampus along with increasing relational memory (Erickson et al., 2011). How so? Vigorous exercise increases whole-body oxygen consumption 5 to 20-fold above resting levels in humans (Weibel and Hoppeler, 2005), reflecting accelerated mitochondrial energy conversion. At the cellular level, increased energy demand engages adaptive intracellular signaling pathways to increase mitochondrial content and optimize their function via mitochondrial biogenesis, inducing the expression of genes that buffer against inflammation systemically (Handschin and Spiegelman, 2008), and may, therefore, counteract deleterious pro-aging mitochondrial signaling (Safdar et al., 2011).

Specifically for the brain, social interactions and other forms of mental stimulation that increase neuronal activity confer protection against neurodegeneration and age-related cognitive decline (Anguera et al., 2013). It is well established that repeated contraction of muscle fibers triggers mitochondrial biogenesis in working muscles (Cartee et al., 2016). Likewise, neuronal activity may produce similar effects in neurons and glia. Exercise stimulates mitochondrial biogenesis in the brain (Steiner et al., 2011). Moreover, neuronal activity triggered by either exercise or mental stimulation, entails energy-dependent cellular processes and enzymatic reactions (ion transport, neurotransmitter release and reuptake, gene expression, protein synthesis, etc.) that increase energy flow within brain mitochondria, enhancing cellular oxygen consumption (Huchzermeyer et al., 2013).

Interestingly, impaired mitochondrial biogenesis is a feature of neurodegenerative conditions including Alzheimer's disease (AD) (Qin et al., 2009). It has been estimated that 20–22% of AD cases in developed countries could be prevented by physical activity alone (Norton et al., 2014). In other words, physical *inactivity* (i.e., sedentary behavior) is a major risk factor for AD. This might be explained by the fact that physical inactivity promotes metabolic stress that predisposes to disease, possibly via disruption of normal mitochondrial dynamics and the accumulation of mtDNA damage (Picard and Turnbull, 2013). Based on these and other data, a leading hypothesis proposes that the protective effects of exercise against AD and other neurodegenerative diseases arise from exercise-induced increase in mitochondrial content, quality, and function (Mattson, 2012).

1.8. Bridging medical disciplines

Our increasing understanding of mitochondrial structures and functions coupled with a general fascination for mitochondrial energetics across medical sciences has caused mitochondrial biology to take roots

in various conventional and non-conventional areas of medicine. Conventional medical disciplines (e.g., neurology, oncology, cardiology) are based on established diagnostic categories, which mitochondrial research extend and deepen by adding insight into the molecular aspects of pathogenesis. As a result, mitochondrial biology provides mechanistic insights into well-defined medical problems such as mitochondrial disease, cancer, immune disorders, critical care illness, and neurodegenerative conditions (see sections above). Conversely, non-conventional or “integrative” medical disciplines are based on systems of knowledge that differ substantially from that of Western biomedicine, most of which are rooted in Eastern philosophy. These include but are not limited to Qi Gong, Tai Chi, biofield therapy, homeopathy, osteopathy, and acupuncture ([NIH National Center for Complimentary and Integrative Health, 2016](#)).

Recently, these complimentary care approaches have been applied to increasing numbers in the U.S. medical system (e.g., 70% of cancer patients) ([Horrigan, 2012](#)), yet knowledge of their underlying mechanisms remains poor. Within the U.S. health care system where >\$30 billion is spent annually on integrative medicine, following increasing public demand and partial supportive evidence ([NIH National Center for Complimentary and Integrative Health, 2016](#)), several medical institutions have developed and are currently offering programs of training, research, and health care involving complimentary care approaches and integrative medicine.

The theoretical foundation for integrative medicine practices largely derives from traditional Eastern philosophy where biological processes are conceptualized not in molecular terms, but in terms of ‘vital energy’, ‘biofield’, and the flow of ‘Qi’ between organ systems. In this framework, ‘dissonance’ in energetic states is assumed to underlie or drive pathophysiological states or disease ([Amri and Abu-Asad, 2011](#); [Hammerschlag et al., 2015](#)). Whether conditions such as “excess heat” or “deficient lung Qi” from traditional Chinese medicine have measurable bioenergetic correlates remains unknown. It would be valuable to evaluate the molecular and bioenergetic aspects of “energetically” defined disease states, as well as pathological cellular and organ disturbances. This kind of systematic comparison could possibly lead to discoveries of non-molecular correlates of disease states defined clinically, and promote dialogue among researchers and practitioners with a common interest to assess usefulness and safety of integrative medicine therapies.

It has been proposed that principles of mitochondrial biology may serve to create a common basis to logically connect existing concepts in non-conventional approaches with the major tenets of biomedicine ([Amri and Abu-Asad, 2011](#); [Pokorny et al., 2013](#); [Wallace, 2008](#)). This proposition is based on two main arguments. The first is that non-conventional medical approaches have produced observations based on “energy flow” that have lead to complex therapeutic systems supporting the same concepts as those that promote mitochondrial function outlined above. This includes the deleterious effects of excess food intake, the positive effects of physical activity and “conditioning of the body”, and body-mind practices that reduce stress arousal systems. The second argument relies on the semantic similarities between related concepts, such as “heat”. Heat is used in traditional Chinese medicine to define one’s dynamic physical and mental state. For example, excess “heat” would define someone with physical and mental hyperactivity, flushed face, rapid heart rate, and increased core body temperature. In Western biomedicine, heat is a physical-chemical concept confined to body temperature. Biologically, bodily heat or temperature is derived in large part from energy dissipation secondary to uncoupled mitochondrial respiration, driven by electron leak across inner mitochondrial membrane ([Nedergaard et al., 2001](#); [Chouchani et al., 2016](#)). The putative connection between mitochondrial heat dissipation and physical-mental states defined holistically remains to be explored. Based on these notions and with the goal to overcome differences in language and terminology across these domains, emerging roles and functions of mitochondria could eventually enable the

formulation of testable scientific hypotheses reaching across conventional Western and non-conventional Eastern theoretical models.

This integration between the Western and Eastern perspectives in medicine should be facilitated by the development and application of non-invasive and minimally invasive technologies to measure mitochondrial (dys)function ([Goh et al., 2014](#); [Minh Tdo et al., 2012](#); [Roede et al., 2012](#); [Wallace et al., 1988](#); [Zand et al., 2013](#)). Mitochondria are not all created equal but are functionally specialized across cell types and organs, both in their composition ([Pagliarini et al., 2008](#)) and functions ([Picard et al., 2012a](#)). This must ensure that mitochondria are functionally matched to the demand of the cell types they reside in. In some disease states mitochondria can exhibit qualitative physiological differences in multiple facets of their functions despite normal energy production capacity (e.g., [Picard et al., 2008](#)). Thus, it will be important in the context of integrative medicine to measure and integrate functional measures beyond energy production capacity, and investigate both quantitative and qualitative aspects of mitochondria functions to better grasp complex mitochondrial phenotypes which might bear functional consequences for the organism.

2. Conclusions

Medicine progresses via discoveries of pathophysiological mechanisms for diseases that undermine patients’ health. A mechanistic understanding of disease not only yields new diagnostic opportunities, but also enables the development of targeted therapeutic and preventative strategies. For mitochondrial medicine, discoveries that mtDNA defects are at the origin of certain human diseases contributed novel diagnostic information for rare inherited monogenic metabolic disorders. This initiated a profound and still ongoing shift in focus away from the anatomical aspects of disease towards the underlying energetic determinants ([Wallace, 2013](#)). More recently, a growing body of research has continued to uncover aspects of mitochondrial biology beyond energy production, including transcriptional remodeling within the nucleus, mitochondrial dynamics and quality control, inter-mitochondrial communication, the inter-cellular transfer of mitochondria, mitochondrial regulation of inflammatory processes and immune function, mitochondrial regulation of brain functions, and modulation of systemic physiological processes across organ systems, among others discussed here.

From these findings have arisen new insights into the biological mechanisms underlying critical care illness, metabolic disease, and the health effects of physical activity and inactivity. Together, this growth of knowledge around the role of mitochondria in various cellular functions has engendered renewed excitement and momentum for mitochondrial research across the medical sciences, as evidenced from the rise in the number of publications in medical sciences related to mitochondria. These and other discoveries are expanding the relevance of mitochondria across medical disciplines, possibly representing an opportunity to bridge the divide that separates academic disciplines ([Picard, 2011](#)), as well as concepts from Eastern and Western medicine.

Mitochondrial functions respond to a number of genetic, metabolic, neuroendocrine signals by undergoing functional and morphological changes, and in turn generate signals that influence a large number of cellular functions contributing to disease complexity. This places mitochondria in a privileged position, as a “portal” at the intersection of the cell and its environment. Because they contain numerous potential druggable components ([Andreux et al., 2013](#); [Wang et al., 2016](#)), mitochondria provide an unusual number of opportunities, and challenges, to translate arising discoveries into therapeutic interventions ([Hersh, 2014](#)). With the tools of molecular biology and the “omics” in hand ([McBride, 2015](#)), and a growing recognition of bioenergetics aspects of modern chronic diseases, the rise of mitochondria in medicine appears likely to continue. With it should come further insights into disease pathogenesis, as well as new strategies to intervene on a number of medical conditions through targeted behavioral,

pharmacological, and other interventions rooted in the principles of mitochondrial bioenergetics.

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Competing interests

The authors have no competing interest.

Author's contributions

All authors edited and revised the manuscript.

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