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Review

Pathogenic mitochondrial dysfunction and metabolic abnormalities

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ABSTRACT

Herein we trace links between biochemical pathways, pathogenesis, and metabolic diseases to set the stage for new therapeutic advances. Cellular and acellular microorganisms including bacteria and viruses are primary pathogenic drivers that cause disease. Missing from this statement are subcellular compartments, importantly mitochondria, which can be pathogenic by themselves, also serving as key metabolic disease intermediaries. The breakdown of food molecules provides chemical energy to power cellular processes, with mitochondria as powerhouses and ATP as the principal energy carrying molecule. Most animal cell ATP is produced by mitochondrial synthase; its central role in metabolism has been known for >80 years. Metabolic disorders involving many organ systems are prevalent in all age groups. Progressive pathogenic mitochondrial dysfunction is a hallmark of genetic mitochondrial diseases, the most common phenotypic expression of inherited metabolic disorders. Confluent genetic, metabolic, and mitochondrial axes surface in diabetes, heart failure, neurodegenerative disease, and even in the ongoing coronavirus pandemic.

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1. Introduction

In mythology, Tyche (Τύχη) is the Greek goddess of a combination of chance, (good) luck, fate, fortune, providence, and success [1]. Some people are born with the genes and behaviors that provide them with good health throughout life. Clearly Tyche must be looking out for them. But others, indeed many human beings, ultimately fall ill beyond the ability of medicine to save them from pain, suffering and ultimately death.

Let food be thy medicine and medicine be thy food. Although there is no evidence in the surviving works of Hippocrates [2] that he ever communicated this paradigm verbally or in writing [3], the popular colloquial saying, nonetheless, gets widely attributed to him [3–7].

Thus, we will in this overview attempt to outline a common theme — of mitochondria and metabolism and of health and medicine — that could aid in the development of new therapies for a wide range of major diseases. In the meantime, for those of us who need or take medicines now, or will later in life, there may be no better path than to stay in Tyche's good graces and to follow the advice attributed to Hippocrates, because many diseases lack the efficacious therapeutics that are desired now or will be required in due course.

2. Mitochondrial dysfunction and metabolic disorders

Mitochondrial dysfunction is at the heart of age-related metabolic disorders [8,9]. Through a myriad of metabolic processes that drive and support cellular function and work, living systems depend on their ability to transfer, store and utilize energy derived directly from the sun (photosynthesis) or indirectly from a proxy in the food chain [10,11]. ATP is the principal energy-carrying molecule found in the cells of all living things. It is essential for sustaining life and each day approximately 65 kg of ATP is produced and recycled in the adult human body [12,13]. The human heart, the most metabolically active organ in the body, has the highest content of mitochondria of any tissue, 25–30% of cell volume in mammals [12,13]. It is a voracious consumer of ATP — using more than 6 kg per day pumping blood [14,15]. To produce this quantity of ATP, the adult healthy heart relies predominantly on mitochondrial fatty acid oxidation and to a much lesser extent on utilizing glucose, lactate, branched chain amino acids and ketone bodies [12,16,17]. Heart failure (HF) is a leading cause of death in the developed world [18–21] and there is a general consensus that energy deprivation caused by mitochondrial dysfunction in the heart is a key contributing factor [12,18,22–25]. Current treatments for heart failure, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, hydralazine, ivabrabine, mineralocorticoid receptor antagonists (aldosterone antagonists), soluble guanylyl cyclase inhibitors and nitrates, do not address mitochondrial dysfunction, effectively lowering energy demand but also lowering energy supply. Future therapies will ideally restore mitochondrial function, thereby preserving cardiac function and increasing energy supply [12]. See Fig. 1 and Table 1 [26,27]. However, there is much more to this story than just heart disease. Major diseases are listed in Fig. 2.

3. Pathogenic mitochondrial Dysfunction, mitochondrial diseases and inherited metabolic disorders

Progressive pathogenic mitochondrial dysfunction is a signature feature of the genetic mitochondrial diseases. Mitochondrial diseases represent the most common phenotypic expression of the inherited metabolic disorders [9,28–36]. In metabolic disorders, circulating hormones such as fibroblast growth factors (FGFs) 19, 21 and 23 that normalize critical metabolic processes [37–43] are susceptible to being dysregulated. FGF21 [38,40,44] (also called mitokine [9,45]) is secreted mainly by the liver and is highly expressed in the heart, brown adipose tissue [46,47] and exocrine pancreas where it acts directly on acinar cells in an autocrine/paracrine manner to stimulate digestive enzyme secretion [48]. It triggers and coordinates the response to metabolic, oxidative, nutritional, hormonal and environmental challenges,

Table 1
Heart and skeletal muscle abnormalities in the context of mitochondrial physiology that needs to be normalized or rebalanced to treat heart failure.

Heart and skeletal muscle abnormalities in heart failure	Mitochondrial physiology requiring normalization or rebalancing
Dynamics	Biogenesis, fission, fusion, mitocytosis, mitophagy
Function	ATP synthesis, cardiolipin, complex activity, membrane potential, respiration, permeability transition pore
Structure	Matrix, membrane disruption, number, size, cristae density
ROS production	Levels of reactive species, expression of detoxifying systems

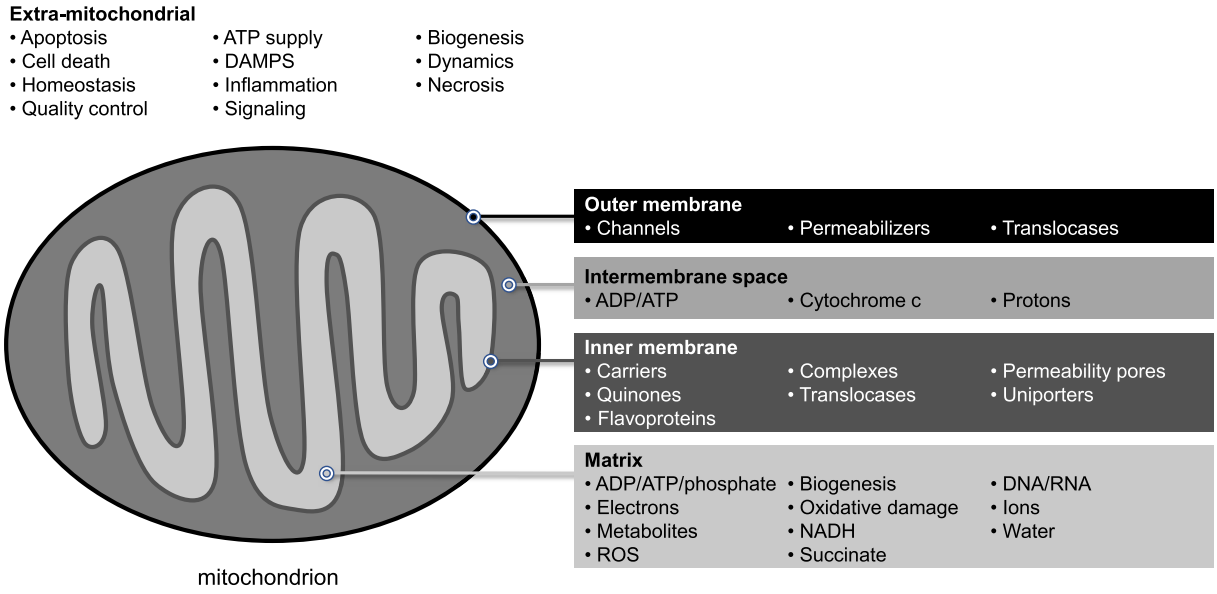

Fig. 1. The many components of mitochondrial function and dysfunction. DAMPS, disease-associated molecular patterns; ROS, reactive oxygen species.

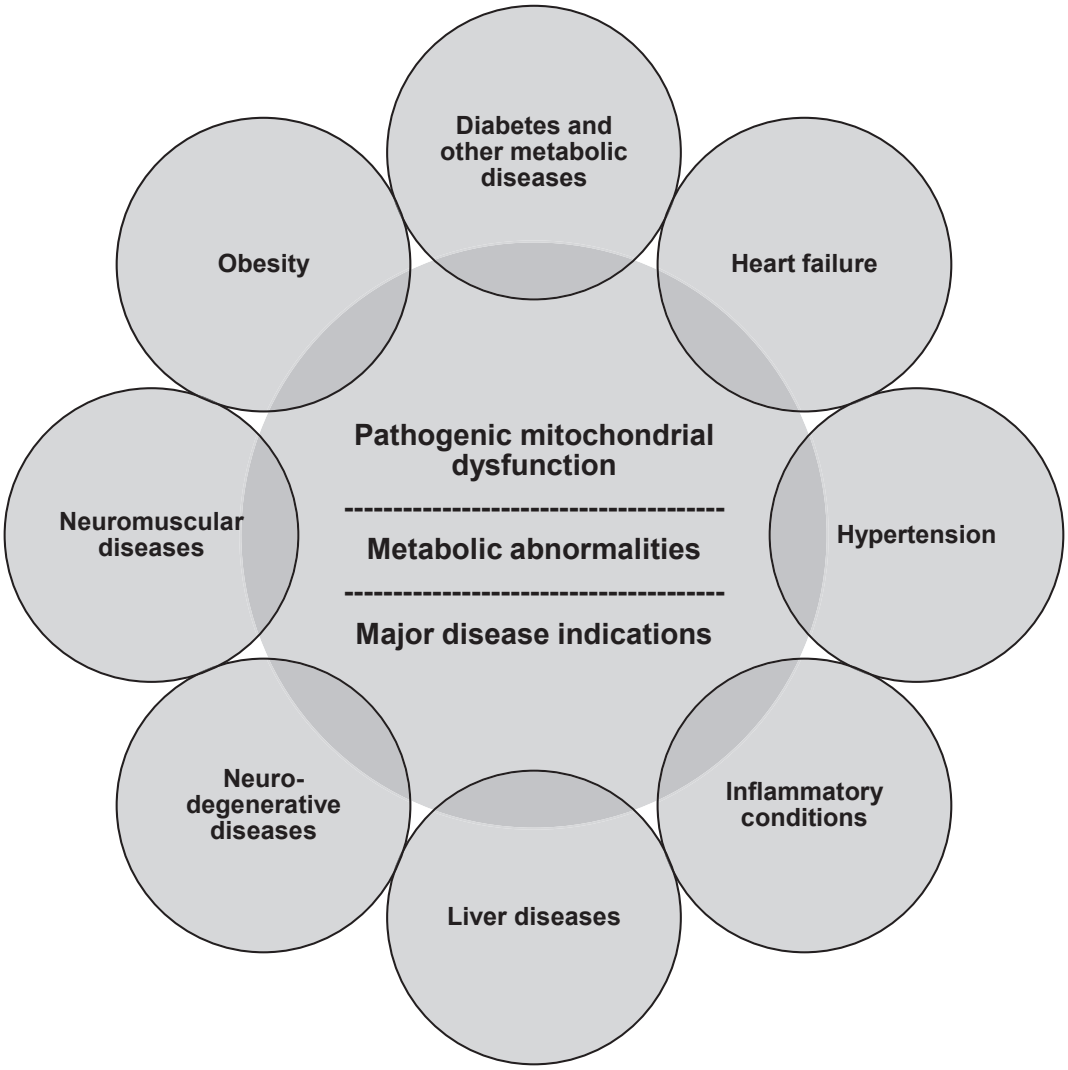

Fig. 2. Major disease indications associated with metabolic abnormalities.

reinforcing its vital role in restoring metabolic homeostasis [49–52]. The biological activity of FGF21 is empowered when conjoined with β-Klotho [40,53–55] and FGF receptor 1c (FGFR1c) [40,48,51–53,56] to regulate carbohydrate and lipid metabolism [38,40,57]. FGF21 modulates mitochondrial function [40,52,58–60] and is upregulated in mitochondrial myopathies and abnormal metabolic conditions [50,59,61]. It acts as a stress-response hormone in humans [53,57,60]. The stress serum response concentration level is promoted as a specific biomarker for a wide range of mitochondrial disorders [29,30,38,49,51,60,62,63], particularly those presenting with muscle-manifesting defects of mitochondrial translation and/or mitochondrial transfer-RNA mutations and primary and secondary mitochondrial DNA deletions, which also tend to be the most familiar causes of mitochondrial disease [64]. See Fig. 3 for a sampling of health challenges from young to old that are increasingly associated with the axis of mitochondrial dysfunction and metabolic disorders.

FGF21 aligns with β-Klotho and its FGFR co-receptor to help foster the removal of damaged cellular mitochondria through mitophagy [59,65]. Mitophagy is an organelle selective form of autophagy [66–71] cells utilize to remove all or parts of damaged mitochondria [66,71–73]. This represents a cell-survival process that is especially important in non-regenerative tissues and the CNS, which includes the retina, optic nerve, brain, brainstem and spinal cord [74]. Cellular mitochondrial turnover is modulated by mitocytosis [75,76], mitophagy [9,71,77–79], biogenesis [72,80], mitochondrial dynamics [72,75,80–83], cellular nutrient levels and a variety of stress response mechanisms [71,75,80,82,84–88]. Mitochondria cannot be synthesized *de novo* [88]. Dysfunctional mitochondria are transported into lysosomes where they are degraded, allowing for the mitochondrial population to be rejuvenated by undergoing continuous fusion and fission events with adaptive morphology according to cellular need [9,66,69,72,78,89–91]. In fact, an imbalance between mitochondrial fusion and fission can often be indicative of disease. A shift toward fission is usually associated with deleterious processes while a shift toward fusion reflects compensatory mechanisms [92,93].

There is overwhelming evidence that mitochondrial dysfunction plays a leading role in the progression of metabolic diseases [24,30,36,94–103]. Hopefully, new therapies for some of these conditions are on the horizon.

4. Metabolic homeostasis and mitochondrial function in the CNS

The control of metabolic homeostasis is fundamental for normal physiology as well as during stress-induced and disease-related episodes [104]. Gestational diabetes mellitus resulting in insulin resistance increases the risk for maternal hyperglycemia and neonatal hypoglycemia, which can instigate seizures and brain damage if glucose levels are inadequate [105]. During pregnancy, the highly metabolic placenta

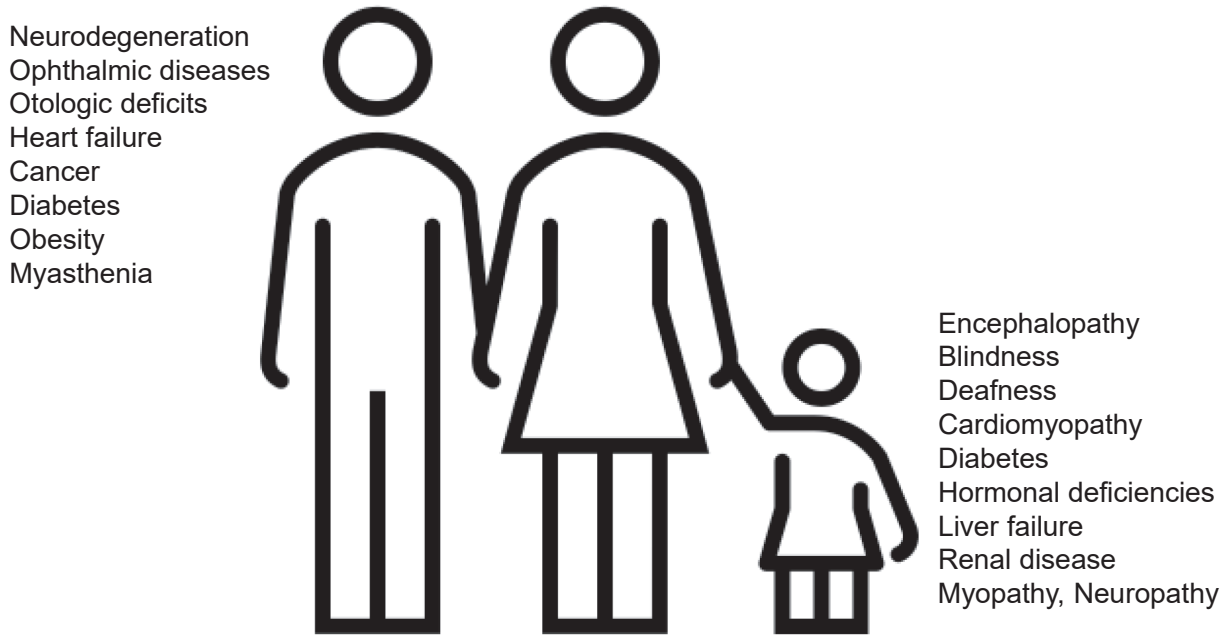

Fig. 3. Common manifestations of inherited mitochondrial diseases and mitochondrial dysfunction in children and adults.

relies on efficient mitochondrial function to produce the requisite energy for supporting a developing fetus through the transport of nutrients, gases and wastes [105]. With the exception of adipose tissues, the brain is the organ with the highest lipid content in the human body [106], consumes more oxygen than any other organ and is critically dependent on intact and well-functioning mitochondria to provide a continuous supply of ATP [107]. Astrocytes are metabolically active cells that deliver necessary neuronal support in the CNS [108], including via an inherent ability to donate their mitochondria to deficient neurons [106,107,109–112]. Consequently, astrocytic mitochondrial dysfunction can lead to insufficient energy production, calcium and potassium dysregulation, inflammatory response induction, blood-brain barrier impairment and glutamate dysregulation causing irreparable damage to the surrounding brain and neural tissues [110,111]. The retina, the innermost light-sensitive layer of tissue of the eye, is a highly active metabolic neural and vascular tissue with tightly-packed photoreceptors [113] that have the greatest density of mitochondria of all CNS neurons [86,114–119]. Not surprisingly, metabolic disorders such as diabetes — a disease marked by impaired glucose metabolism — will frequently manifest symptoms of retinal degeneration [114,117,119,120–125] with destructive effects most noticeable in the macula, a small, cone-rich area of the retina responsible for high acuity, central and color vision [125–127].

The presence of diabetic retinopathy — the most common microvascular complication of diabetes and the leading cause of visual impairment and blindness in the working-age population in the United States [128,129] — is characterized by disruption of neurovascular coupling due to alterations in both neural and vascular structures, which accumulate with increased disease severity and visual dysfunction. In healthy eyes, neuronal and Müller cell signals elicit vascular responses mediated by contractile pericytes and responsive endothelial cells in order to maintain appropriate perfusion. Hyperglycemia, inflammation and hypoxia in diabetes are key factors for endoplasmic reticulum-mitochondria miscommunication and mitophagy dysregulation and play a major role in the impairment of neurovascular coupling [130–132]. See Fig. 4 for a schematic view of the eye.

5. Mitochondrial dysfunction in metabolic pathogenesis of COVID-19

Deterioration of mitochondrial function is a pathogenic driver in age-related metabolic abnormalities characteristic of diseases that range from heart failure to diabetes, cancer and neurodegenerative disorders among a long list of other health challenges [9,133–136]. Compromised metabolic pathways involved with energy and nutrient metabolism such as glucose, fatty acid and nucleic acid are also increasingly being

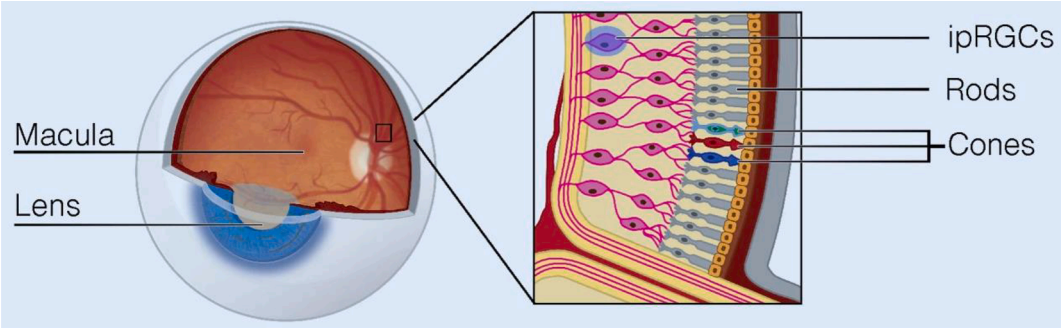

Fig. 4. Photoreceptors in retina: Schematic view of eye, retina at back (fundus), with cones, rods and intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing melanopsin, a photopigment. (This file is licensed under the Creative Commons Attribution 4.0 International license. Page URL: https://commons.wikimedia.org/wiki/File:Overview_of_the_retina_photoreceptors_(a).png. Attribution: Christine Blume, Corrado Garbazza & Manuel Spitschan.)

associated with the severity and lethality of COVID-19 [45,137–142]. The ongoing COVID-19 pandemic is directing attention to the central role mitochondria play in the innate immune response to viral infection [9,45,140,143–155]. Results from metabolomic studies suggest that dysregulated oxidative phosphorylation (OXPHOS) and/or suppression of mitophagic pathways leading to cellular accumulation of damaged and dysfunctional mitochondria facilitate immune evasion by the severe acute respiratory SARS-CoV-2 coronavirus — the novel 2019 virus responsible for COVID-19 [45,146,151,152]. Immunity and infection engage mitochondria in numerous ways, influencing mitochondrial cell death pathways, mitochondrial dynamics and mitochondrial metabolism. The effects of selected bacteria and viruses on mitochondria are outlined in Table 2 [156].

Table 2
Effect of infectious agents on mitochondrial function. DRP1, dynamin-related protein 1; GLUT1, glucose transporter 1; TCA, tricarboxylic acid; VacA, vacuolating cytotoxin; HIV, human immunodeficiency virus; SARS, severe acute respiratory syndrome.

Infectious agents	Mitochondrial cell death pathways	Mitochondrial dynamics leading to mitochondrial fragmentation	Mitochondrial metabolism
Brucella			Lactate production via aerobic glycolysis, suppressed TCA cycle
Chlamydia	Cell death blocked to increase intracellular proliferation of bacteria	Induced mitochondrial fusion, required for intracellular proliferation	Increased GLUT1 levels, glucose uptake, glycolytic flux
Dengue		DRP1 inhibition induces mitochondrial fragmentation	
Helicobacter	Apoptosis	VacA-induced mitochondrial fragmentation, cytochrome *c* release into cytosol, cell death	
Hepatitis C			Perturbed fatty acid oxidation
Herpes			Induced TCA cycle, increased mitochondrial respiration
HIV		DRP1 degradation, leading to mitochondrial fragmentation	
Influenza A	Enhanced cell death	Fragmentation caused by loss of mitochondrial membrane potential	
Legionella	Cell death blocked to increase intracellular proliferation of bacteria	DRP1-dependent mitochondrial fragmentation	Enhanced aerobic glycolysis
Listeria		DRP1-independent mitochondrial fragmentation	
Mycobacteria	Apoptosis		Enhanced aerobic glycolysis
SARS		DRP1 degradation, leading to mitochondrial fragmentation	
Shigella	Apoptosis	DRP1-dependent mitochondrial fragmentation	
Zika virus	Cell death blocked		

Thankfully, knowledge gained from years of basic research in vaccine technologies converged to help produce effective vaccines [157–165] that were quickly deployed to mitigate the unbridled expansion of the pandemic in conjunction with an unprecedented cooperative global effort to prevent the spread of SARS-CoV-2 infection [166,167]. However, in spite of an extraordinary ongoing effort to screen for biologics, new small-molecule therapeutics and repurposed or repositioned approved drugs, an effective antiviral therapeutic specific to COVID-19 has yet to stand out [162,168–174]. Since all pathogens are obligated to acquire their nutritional needs from the host's body [175–178], alternative and attractive mechanistic targets that are drawing attention are modified adaptations in SARS-CoV-2 lipid metabolism [148,151,175,179–186].

Preliminary results from a study examining a cohort of 551 patients hospitalized for COVID-19 in Italy suggest that the persistence of aberrant glycometabolic control is associated with "long-COVID" in patients who recovered from COVID-19 disease [187]. Diabetes and hypertension are among the most prominent risk factors for COVID-19 [188–191]. As noted, symptoms of retinal degeneration are common in diabetic subjects and there is mounting evidence of retinal microangiopathy in some patients with confirmed COVID-19 infection [192]. Fortunately, a COVID Symptom Study of UK school-aged children tested for SARS-CoV-2 showed that it is only a minority of school-aged children who experienced longer illness duration and most of these children recovered with time [193].

6. Altered mitochondrial function and cellular metabolic reprogramming in cancer

In the vast majority of countries, cancer remains a leading cause of death among people younger than 70 years of age [194]. An undisputed hallmark of cancer [195–199] is the ability of tumor cells to alter their metabolism in order to support the increased energy needs required for exponential growth, rapid proliferation and other attributes typical of neoplastic cells [196,200–204]. It is almost one hundred years since Otto Heinrich Warburg published on the metabolic association of cancer cells [205,206], now known as the "Warburg effect" [202,203,207–210]. [^{18}F]-Fluorodeoxyglucose taken up by cancer cells with enhanced metabolic and glycolytic rates in positron emission tomography (PET) scans [211,212] is an indispensable diagnostic tool for determining metastasis in cancer therapy. Yet, in practice, leveraging the Warburg effect in cancer treatments that target glycolysis alone has limited therapeutic success [213–215].

Both glycolytic and mitochondrial metabolic pathways are elevated in most tumor cells to support anabolism. There are some tumor cells in which glucose uptake exceeds lactate release and ATP production shifts significantly toward aerobic glycolysis, particularly in those tumors bearing succinate dehydrogenase, fumarate hydratase and von Hippel-Lindau defects [207]. The tumor cell TCA cycle may shift toward acting as an anabolic hub that includes enhanced use of glutamine as a carbon source. Advances in studies of tumor cell metabolism suggest the field is increasingly adapting to a more nuanced understanding of the changes in tumor cell metabolism, which often can be heavily reliant on specific tumor-causing mutations [207].

Tumor metabolic adaptations often present specific vulnerabilities that can be exploited in cancer treatment. Examples of these vulnerabilities include a reliance on pathways mitigated by FGF21 endocrine regulation of systemic homeostasis of lipid and energy metabolism in contrast to insulin as a direct regulator of glucose metabolism [37,216–218]. With or without the influence of FGF21, other dependencies include the high levels of glutamine needed for tumor growth, one to two orders of magnitude more than any other amino acid [215,219–222]. These and specific vulnerabilities, such as metabolic aberrations in cancer persister cells that arise from different cell lineages with distinct transcriptional and metabolic programs [223,224], among many others, offer actionable opportunities to be exploited in cancer

treatment [211,225–232], particularly in combination with the new and emerging immunotherapies [208,222,233–239]. It is known that profuse changes in tissue metabolism, including the depletion of nutrients, increased oxygen consumption and the generation of reactive nitrogen and oxygen species will provoke an immune response [240] affecting immunometabolism [222,241–243].

Advanced renal cell carcinoma, for example, presents with an extensively altered metabolic profile [244–246] and in many ways behaves like a metabolic disease [247,248]. In some cancers, such as hereditary leiomyomatosis and renal cell carcinoma (HLRCC), mitochondrial dysfunction drives metabolic remodeling that favors anabolic pathways utilizing glutamine — endowing the tumor with bioenergetic and biosynthetic advantages for growth and metastasis [244]. Metabolism of the amino acid tryptophan through the kynurenine pathway is upregulated to generate elevated levels of immunosuppressants, which help the tumors to evade the natural immune system [245,247]. A serious drawback to the clinical utility of immune checkpoint inhibitors is often a high incidence of immune-related adverse events associated with treatment [249,250]. Nevertheless, immunotherapies using checkpoint inhibitors [208,234,251–254] are rapidly becoming a mainstay treatment for many cancers [255,256]. Pembrolizumab (Keytruda; Merck, Sharp & Dohme) is a programmed cell death 1 (PD-1)–blocking antibody that inhibits the formation of immunosuppressants, clearing the way for the immune system to attack the cancer [257,258]. In combination with a tyrosine kinase inhibitor [251,254,259–261] pembrolizumab was approved by the US Food and Drug Administration (FDA) as a first-line treatment of patients with advanced renal cell carcinoma [262].

Nonetheless, optimal tumor attributes for a favorable response to immunotherapy are not fully understood [263–273]. Although metabolic reprogramming in metastatic renal cell carcinoma elicits a good response to checkpoint immunotherapy [251,274], in cancers such as urinary bladder cancer [256,272], metabolic reprogramming and/or mitochondrial dysfunction related to reduced OXPHOS [275] have been recently associated with a poor response to immune checkpoint inhibition [276]. The potential role of the microbiome in checkpoint inhibitor response is most intriguing [245,277–280].

7. Mitochondrial dysfunction and metabolic pathogenesis of aging

A recent analysis of aging as a disease target suggests that a slowdown in aging that increases life expectancy by only one year could be worth US$38 trillion to society and by 10 years it could be worth US $367 trillion [281]. The continuous accumulation of degenerative processes that damage and/or alter molecular pathways exacerbating systemic pathologies characterize the natural course of aging as a disease phenomenon [282–286]. Every year, more than 70% of disease-related deaths globally are from chronic, noncommunicable diseases — the deadliest being cardiometabolic syndrome [94,287]. The cardiometabolic diseases, which include atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome, metabolic-cognitive syndrome and cerebrovascular dementia, are age-associated and have in common dysregulated mitochondrial function and atypical levels of nutritional, immune, neurotrophic and metabotrophic support [23,287,288].

New insights derived from an elegantly executed study on the daily energy expenditure through the human life course suggest that metabolism may be a driver in aging biology [289,290]. In aging populations, dementia is becoming a primary contributor to disability and dependence in the elderly. An overwhelming body of evidence associates failing mitochondrial function [291–295] and disrupted microbiome-assisted metabolism [86,292,296–298] with the neuropathology of aging. The brain ages with increasingly dysregulated CNS lipid metabolism and a slow but progressive decline in its lipid content [299]. Numerous published studies based on animal models have demonstrated that pharmaceuticals which act to ameliorate mitochondrial metabolic pathways, like the antidiabetic drug metformin, may have a geroprotective effect in increasing lifespan [300–308]. Natural products derived from marine organisms are a promising source of novel anti-aging compounds [309] and breakthrough pharmaceutical research in developing synthetic analogues of FGF21 to treat obesity and/or compounds that increase the bioavailability of FGF21/β-Klotho indicate these compounds have great potential in delaying aging by mitigating adverse metabolic pathways in the aging process [217,310–313]. See Fig. 5 for selected molecules that have been reported to exhibit anti-aging or geroprotective effects [314].

A recent analysis of epidemiological data on SARS-CoV-2 infections in Italy illustrates that COVID-19 has many of the characteristics of an age-related disease [315]. Indeed, in a very large OpenSAFELY study searching the records of more than 17 million patients in England that were linked to 10,926 COVID-19-related deaths, advanced age and pre-existing age-related diseases, such as hypertension, diabetes, cancer, heart failure and chronic obstructive pulmonary disease, were found to be more prevalent among hospitalized COVID-19 patients [316]. Although current research is understandably focused on developing antiviral therapeutics, there is a suggestion that a broader effort targeting the aging process itself can be a viable orthogonal strategy against COVID-19 and other deadly respiratory diseases [315].

8. Concluding remarks

In this review we have tried to weave a thread through the metabolic commonalities of a wide range of diseases, acquired or inherited, with the common theme being the key roles that mitochondria play in all of them. We have learned a great deal about how mitochondria and metabolism interweave their strengths and weaknesses in this story of the successes and failures of medicines to date. Unfortunately, therapeutic efficacy has remained elusive in far too many patients to declare victory. While we hope that readers will find new paths forward, we do still have healthy habits that may yield substantial benefit to people around the world. Returning to the theme at the start of this paper — if “food be thy medicine” — then in the absence of a silver bullet against Alzheimer’s disease, cancer, diabetes, diabetic retinopathy, inherited mitochondrial diseases and sadly even more largely untreatable ailments, then perhaps food represented by the Mediterranean Diet [317] and regimens that alter the microbiome [318–320] are the active pharmaceutical ingredients (APIs) of potentially significant interest.

Authorship Contribution Statement

Authorship has been based on the principles of the International Committee of Medical Journal Editors: substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

Walter H. Moos, in addition to academic and nonprofit roles, is a managing director of Pandect Bioventures, is compensated by Shang-Pharma Innovation as chairman emeritus, receives royalty and equity sharing benefits from SRI International, has stock or other financial interests in Azkarra Therapeutics, Chinook Therapeutics, Circle Pharma, Rigel Pharmaceuticals, Valitor and Walden Biosciences, and serves on the boards of directors and/or scientific advisory boards of Aprinoia Therapeutics, Circle Pharma, Global Blood Therapeutics, Rigel Pharmaceuticals and Valitor. Douglas V. Faller, in addition to academic and nonprofit roles, is employed by Viracta Therapeutics, Phoenicia

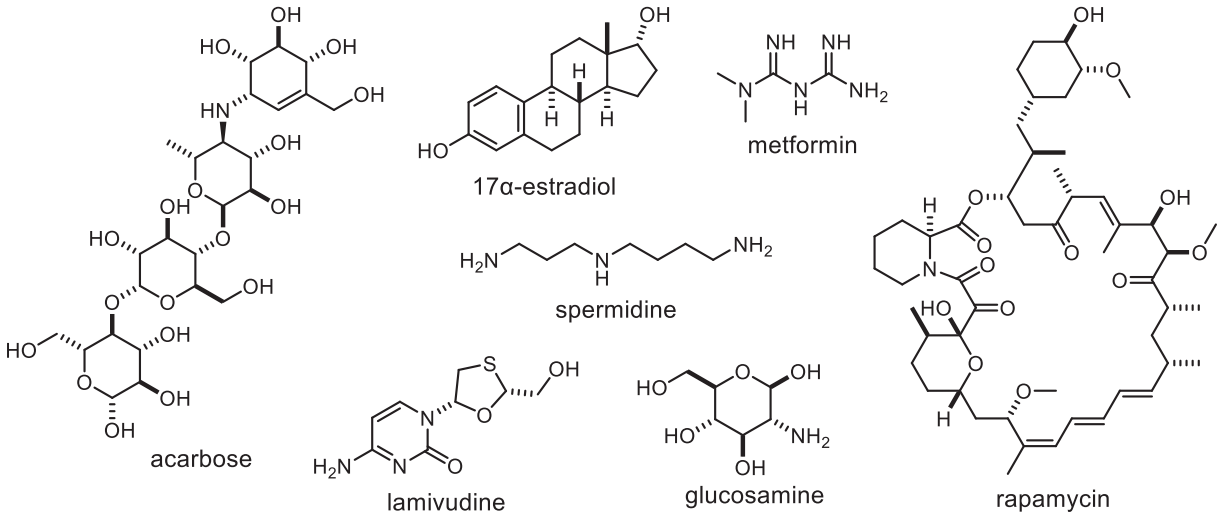

Fig. 5. A diverse chemical array of potential geroprotective agents that target everything from mitochondrial dysfunction to nutrient sensing, cellular senescence, DNA damage, epigenetic pathways, intercellular signaling, proteostasis, stem cells, telomeres, and more.

Biosciences and Takeda Pharmaceuticals and serves as a consultant to Briacell Therapeutics. Kosta Steliou, in addition to academic and nonprofit roles, is the founder and chief scientific officer of PhenoMatriX. Krishna Kodukula consults with and/or serves as an executive or on the boards of various biotechnology and pharmaceutical companies from time to time, where he may receive compensation and/or stock options, and he is eligible to receive compensation from Pandect Bioventures and ShangPharma Innovation, venture capital and healthcare venture incubator organizations.

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