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REVIEW ARTICLE

Mitochondrial involvement in sarcopenia

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Abstract

Sarcopenia lowers the quality-of-life for millions of people across the world, as accelerated loss of skeletal muscle mass and function contributes to both age- and disease-related frailty. Physical activity remains the only proven therapy for sarcopenia to date, but alternatives are much sought after to manage this progressive muscle disorder in individuals who are unable to exercise. Mitochondria have been widely implicated in the etiology of sarcopenia and are increasingly suggested as attractive therapeutic targets to help restore the perturbed balance between protein synthesis and breakdown that underpins skeletal muscle atrophy. Reviewing current literature, we note that mitochondrial bioenergetic changes in sarcopenia are generally interpreted as intrinsic dysfunction that renders muscle cells incapable of making sufficient ATP to fuel protein synthesis. Based on the reported mitochondrial effects of therapeutic interventions, however, we argue that the observed bioenergetic changes may instead reflect an adaptation to pathologically decreased energy expenditure in sarcopenic muscle. Discrimination between these mechanistic possibilities will be crucial for improving the management of sarcopenia.

KEYWORDS

cellular bioenergetics, sarcopenia, skeletal muscle mitochondria

1 | INTRODUCTION

Populations are aging rapidly in all parts of the world, but extended lifetime is generally not spent in best health, because of age-related disorders that are linked to the functional decline of various organs.[1] Sarcopenia, for instance, may be defined as a progressive and generalized skeletal muscle disorder that involves accelerated loss of muscle mass and function,[2] and contributes significantly to the frailty that compromises the quality-of-life for millions of elderly individuals worldwide.[3,4] The underlying causes of sarcopenia include malnutrition, inactivity, and disease, as well as drugs and hospital admission.[2] Skeletal muscle quality is thus not only lost with old age (primary sarcopenia) but also in association with diseases such as cancer,[5] type 2 diabetes,[6] cardiovascular disease,[7] chronic obstructive pulmonary disease,[8] chronic kidney disease,[9] advanced liver disease,[10] as well as with acute and chronic critical illness.[11] Obesity is an important risk factor for these chronic disorders, and disease-related secondary sarcopenia also occurs in individuals with excess body fat.[12] The estimated global prevalence of sarcopenia is imprecise, between 10% and 27%, as epidemiology statistics are confounded by variable classification and cut-off points for skeletal muscle mass and function,[13,14] but loss of muscle quality with age clearly adds to overall healthcare costs.[15]

While functional and structural muscle phenotypes share some similarities between primary and secondary sarcopenias, differences in the underlying pathology are likely to complicate the clinical management of elderly people, who often suffer from sarcopenia with multiple causes.[2] Exercise is recommended as the primary treatment of sarcopenia,[16] possibly with dietary supplements to improve benefits,[14] while no single anti-sarcopenic drug has been approved to date.[2,14] Novel therapeutic solutions are much needed to treat sarcopenia in frail elderly and diseased individuals, who are unable to restore skeletal muscle quality through increased physical activity.

The notion that exercise and nutrition are major pillars in sarcopenia management[17] strongly suggests the involvement of bioenergetic failure in disease development. Indeed, compromised ATP synthesis capacity has been recognized as an important feature of primary and secondary sarcopenia for some time.[18,19] Many aspects of mitochondrial function and dysfunction have been implicated in different types of sarcopenia,[20–23] but causal interrelations with other cellular defects that are associated with this multifactorial muscle disorder have not been established conclusively. Such defects include loss of skeletal muscle insulin sensitivity[24] and a perturbed balance between myocellular protein synthesis and protein breakdown that favors muscle protein loss.[25] Since insulin resistance and perturbed proteostasis are both associated with inflammation[26] and oxidative stress,[27] these cellular defects are also likely functionally related to the observed changes in mitochondrial activity. Primary sarcopenia is further characterized by hormonal changes,[28] a decline in the number of skeletal muscle satellite cells,[29–32] muscle fiber type transitions,[33] the loss of neuromuscular junctions,[34] and by fat infiltration within and between muscle fibers.[2] Secondary sarcopenia is complicated by the pathological milieu, as muscle dysfunction may be triggered or exacerbated by therapeutics such as corticosteroids[35] and by disease-specific manifestations such as the toxic retention of solutes in chronic kidney disease.[36]

In this review, we give our perspective on mitochondrial involvement in sarcopenia, stressing the incompletely understood interrelation between myocellular proteostasis and bioenergetics. Citing human studies where possible, we explore how exercise and nutrition affect sarcopenic muscle mitochondria, and we briefly reflect on the promise and risk of emerging mitochondria-focussed management strategies.

2 | MITOCHONDRIAL CHANGES IN SARCOPENIC MUSCLE

Age-dependent decline in aerobic capacity coincides with changes in skeletal muscle energy metabolism,[37,38] and mitochondrial dysfunction has been identified as hallmark of aging.[39] Sarcopenia appears invariably linked with oxidative stress (Figure 1), a unifying pathological condition that is at least partly responsible for compromised mitochondrial quality control,[40,41] mitochondrial bioenergetics,[14,42] and mitochondrial redox biology[43] in sarcopenic muscle.

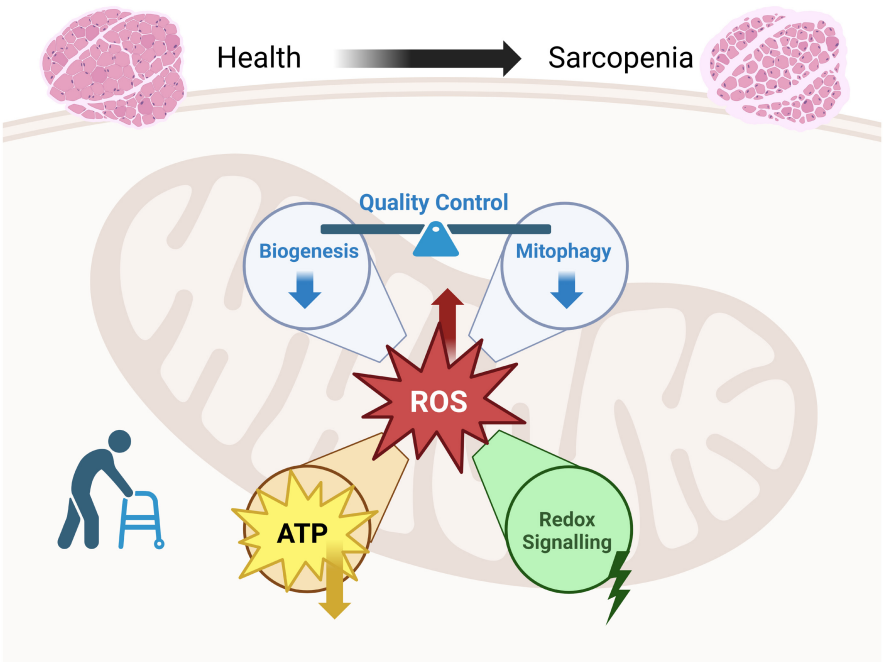

FIGURE 1 Mitochondrial changes in sarcopenic muscle. Loss of skeletal muscle mass and function with age is characterized by increased production of reactive oxygen species (ROS), decreased oxidative phosphorylation, mitochondrial biogenesis, and mitophagy, and perturbed redox signaling. Created with BioRender.com.

2.1 | Mitochondrial redox biology

Oxidative stress results from a decreased expression of antioxidant defense systems and from the increased formation of reactive oxygen species (ROS) that, to a large extent, is accounted for by mitochondria.[43–48] High ROS levels interfere with the mitochondrial redox biology that contributes to the physiological regulation of insulin[49] and other anabolic signaling pathways,[50] and thus inhibit protein synthesis.[51] Consequent perturbance of proteostasis[25] is made worse by stimulatory effects of high ROS levels on proteolysis: oxidation of proteins by ROS renders them generally more susceptible to proteasome-mediated breakdown, at least partly because oxidation causes unfolding.[52] Indeed, prevention by ROS of the activation of the mammalian target of rapamycin complex 1 (mTORC1) increases expression of muscle-specific E3 ligases that effect proteasome-mediated protein breakdown.[43] Increased autophagy through ROS-prevented activation of mTORC1[53] as well as ROS-induced expression of calcium-activated proteases[54] further tip the proteostasis balance toward loss of protein. ROS thus provokes skeletal muscle dysfunction and atrophy, and clinical studies have indeed demonstrated that oxidative damage increases with age[55] and is associated with impaired muscle strength.[56]

Oxidative stress that leads to sarcopenia during aging,[57] inactivity,[58] and chronic disease[59] is likely related to a persistent state of low-grade systemic inflammation[26] in which production of ROS is stimulated by proinflammatory cytokines.[60] Conditions in which sarcopenia develops are furthermore characterized by a perturbed bioenergetic balance where nutrient availability in muscle cells outweighs energy expenditure,[12] and nutrient catabolism creates a reduced cellular environment that permits ROS generation.[20] ROS likely exacerbate inflammation[61] and may thus reinforce their own formation. Preventing ROS levels in muscle tissue from becoming too high seems an attractive therapeutic option to combat sarcopenia, and certain nutritional and mitochondria-targeted pharmacological interventions (see below for detail) indeed have an antioxidant rationale. However, antioxidant-based therapies might be counterproductive, as insulin and anabolic signaling paths crucial for proteostasis are regulated physiologically by ROS.[49,50] Because of this ROS duality, the anti-sarcopenic promise of antioxidant therapies has been questioned.[62] Future antioxidant-based interventions will likely benefit from a more complete understanding of mitochondrial redox biology, and from more detailed insight in the molecular nature and origin of the ROS responsible for the progressive shift toward oxidative stress that is evident as primary and secondary sarcopenia develop.

2.2 | Mitochondrial quality control

Mitochondrial biogenesis, mitophagy and structural dynamics are important for mitochondrial quality control, as these processes maintain functional capacity,[63,64] remove redundant or dysfunctional organelles,[65] and remodel organelle morphology,[66] respectively. Regulation of these processes is reviewed in detail by others,[40,64] and it suffices to mention here that such regulation is disrupted in both primary and secondary sarcopenic skeletal muscle, at least partly owing to oxidative stress, such that the myocellular ability to replace dysfunctional with functional mitochondria is lowered.[67] Functional capacity furthermore depends on regulation of the highly variable turnover of individual mitochondrial proteins,[68] which may change in aging skeletal muscle. Compromised quality control of mitochondria likely contributes to the decreased oxidative capacity of sarcopenic muscle,[14,42] although it remains also possible that molecular signs of attenuated mitochondrial biogenesis reflect a lowered demand for oxidative capacity. It is, for example, possible that anabolic resistance of protein synthesis[69] lowers total energy expenditure, which is expected to decrease oxidative ATP synthesis given that control of skeletal muscle energy metabolism is demand-driven[70] (Figure 2) and given that a significant proportion of overall muscle ATP supply (approximately 20%) is generally allocated to protein synthesis.[71,72] In this respect, it is worth stressing that therapeutic interventions aimed at boosting oxidative capacity through improved mitochondrial biogenesis would be of limited success if demand for such increased capacity remained low.

2.3 | Mitochondrial bioenergetics

Skeletal muscle bioenergetics have been investigated extensively in human with phosphorus-31 magnetic resonance spectroscopy (^{31}P MRS).[73] For instance, in vivo measurements of the rate by which phosphocreatine (PCr) is recovered after exercise have provided much insight in the capacity of oxidative phosphorylation in healthy individuals as well as people living with chronic disease. Indeed, ^{31}P MRS established relatively early on that the PCr recovery rate of skeletal muscle decreases with age[19,74,75] as sarcopenia develops. Secondary sarcopenia is also associated with decreased PCr recovery rates, as, for example, revealed in patients with dialysis-dependent chronic kidney disease,[76] chronic lung disease,[77] thyroid disorders,[78] and heart failure.[77] These (patho)physiological observations are corroborated by studies on human skeletal muscle biopsies that

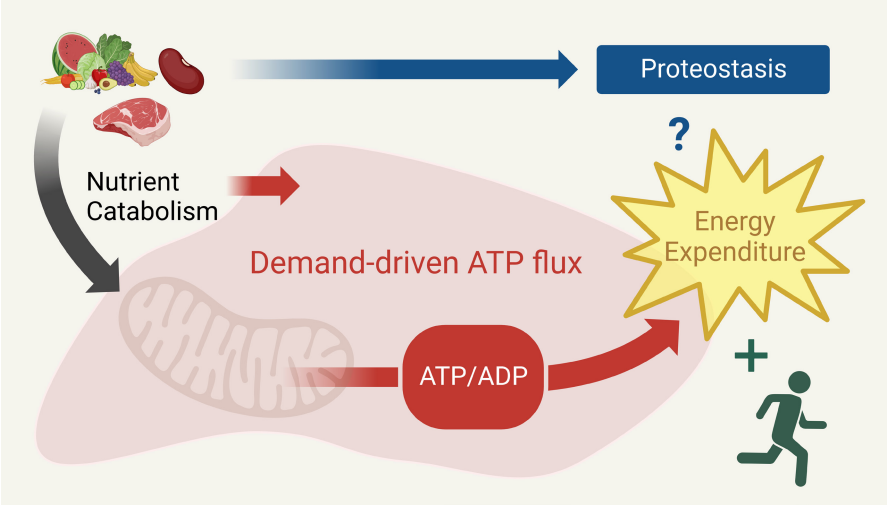

FIGURE 2 Demand-driven energy metabolism in skeletal muscle. Cellular energy metabolism may be viewed from a top-down perspective as the interaction between processes that supply ATP by substrate-level and oxidative phosphorylation, and processes that demand ATP. In healthy skeletal muscle, total ATP flux is largely controlled by energy expenditure, which is increased by physical activity. Nutrients are catabolic fuels for ATP synthesis and stimuli for anabolic ATP-consuming processes, such as protein synthesis. Created with BioRender.com.

also demonstrate an age-dependent decline in the rate of PCr recovery after exercise.[74,79] In vivo and ex vivo data thus both strongly suggest that the oxidative ATP synthesis capacity of sarcopenic skeletal muscle is lower than that of healthy muscle. Perturbed calcium handling in sarcopenic muscle[80] may further dysregulate oxidative metabolism. Notably, age effects on oxidative capacity remain generally heterogeneous.[81] Variable habitual physical activity as well as the sex of the studied individuals contribute to this heterogeneity, as does the variety of skeletal muscle groups probed[81]—these variables need to be taken into account when age effects on mitochondrial ATP synthesis are interpreted. Notably, age does not only decrease the capacity of skeletal muscle oxidative phosphorylation but also the efficiency by which mitochondrial respiration and ATP synthesis are coupled.[42,82]

PCr-recovery-after-exercise measurements remain arguably the most reliable, albeit indirect, way to quantify oxidative mitochondrial ATP supply in human,[83–85] but obtained information is restricted to bioenergetic capacity and offers limited insight in ATP synthesis activity under conditions of varying energy demand. In this respect, it is noteworthy that the causal relation between decreased oxidative capacity and perturbed proteostasis in aged skeletal muscle remains uncertain. Explicitly or implicitly, it is often argued that the rate of protein synthesis is lowered in sarcopenia because dysfunctional mitochondria are unable to sufficiently sustain this and other anabolic processes energetically,[20–23,86] but it is equally conceivable that the decreased oxidative phosphorylation capacity is an adaptation to lowered ATP demand from the depressed anabolism that follows from insulin and anabolic resistance[69,87] (Figure 2).

3 | RESPONSE OF SKELETAL MUSCLE MITOCHONDRIA TO THERAPEUTIC INTERVENTIONS

Current management of sarcopenia aims to build muscle mass by increasing physical activity, improving nutrition, and by optimizing hormonal homeostasis.[17] To date, exercise remains the sole proven therapy of these three management pillars.[88,89] Dietary supplementation seems only beneficial when combined with exercise,[2,14,90] and although the pharmacological use of vitamin D and testosterone is supported by evidence from human trials,[91] no anti-sarcopenic drugs have yet been approved. Next, we will explore how different sarcopenia management approaches affect skeletal muscle mitochondria (Figure 3).

3.1 | Exercise

Physical activity increases ATP consumption by skeletal muscle cells to fuel contraction. The consequent drop of the myocellular energy charge triggers AMP-activated kinase (AMPK),[92] a master regulator of cellular energy metabolism that helps adjust ATP supply to meet ATP demand.[93] Moreover, physical activity acutely stimulates the production of ROS by skeletal muscle mitochondria[94] and thus causes mild endogenous oxidative stress that activates AMPK further.[95,96] Exercise protects against

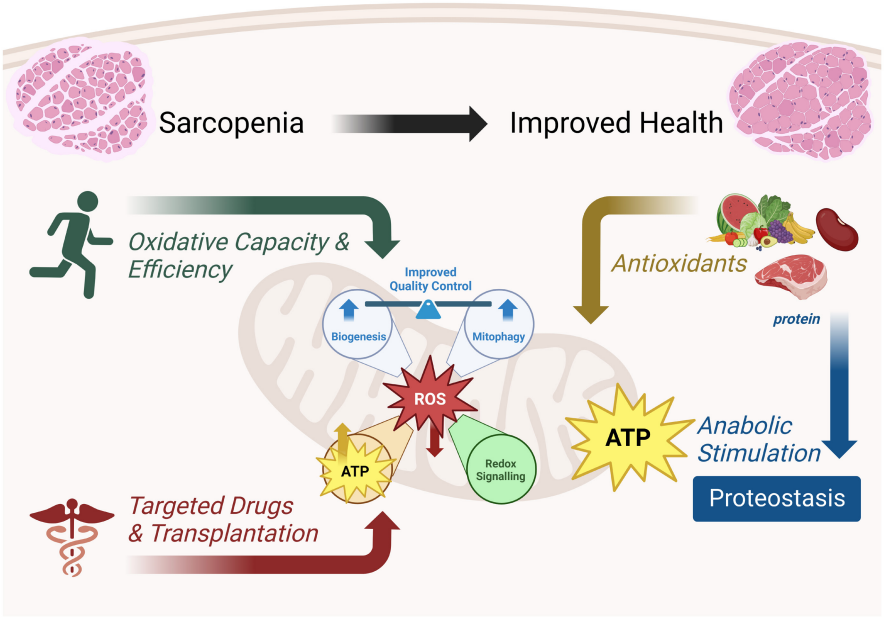

FIGURE 3 Effects of anti-sarcopenic interventions on skeletal muscle mitochondria. Exercise improves mitochondrial quality control and increases both the capacity and efficiency of oxidative phosphorylation, at least partly, through attenuation of oxidative stress. Some nutrient supplements contain antioxidants, while branched-chain amino acids, leucine, in particular, may improve proteostasis through energy-demanding anabolic stimulation. Mitochondria have been suggested as therapeutic targets. Created with BioRender.com.

oxidative stress in the longer term, however, because skeletal muscle cells upregulate expression of antioxidant defense systems in response to the acute increase in ROS.[97] This mitohormetic response[98] likely contributes to the benefits of physical activity for mitochondrial activity in aged skeletal muscle. Long-term positive effects of exercise include a boosted oxidative capacity,[99] with evidence for increased ATP synthesis capacity *in vivo*[100–102] and for an increased activity of mitochondrial respiratory complexes ex vivo.[103–107] Related to this oxidative benefit, exercise increases mitochondrial biogenesis[108] and mitochondrial mass,[106] and improves mitochondrial quality control[40] through effects on structural dynamics and autophagy.[104,109–111]

With ROS as important culprit of the mitochondrial defects in sarcopenic muscle (Figure 1), it is perhaps not surprising that exercise should rescue such defects, since it strengthens the cells' antioxidant defense. Interestingly, however, exercise-induced increases in muscle mass and function do not always involve increased oxidative capacity, as the nature of mitochondrial effects appears to depend on the type of exercise.[42] Both endurance and resistance training increase skeletal muscle quality in sarcopenia, but while the benefit of endurance exercise is consistently linked with clear stimulation of mitochondrial biogenesis and increased oxidative capacity,[112–116] mitochondrial effects of resistance exercise are less clear.[113,117–120] Resistance training does not affect mitochondrial biogenesis or mitochondrial content but does indeed alter intrinsic mitochondrial function.[121,122] For instance, resistance exercise changes the mitochondrial transcriptome[123] and increases specific abundance of mitochondrial respiratory complexes,[124] which is consistent with the observation that resistance exercise increases ATP synthesis capacity without changing mitochondrial content,[112,125] and may indicate increased coupling efficiency of oxidative phosphorylation.[42]

AMPK is activated during exercise by a decreased ATP/AMP ratio[92] and by increased ROS levels.[95,96] Skeletal muscle fibers demand much ATP during both endurance and resistance exercise[126] and increase their production of ROS in acute response to both types of physical activity.[127] The different mitochondrial effects of endurance and resistance training are thus unlikely related to these cellular signals per se but are more likely owing to differential fiber type recruitment during different types of exercise.[42] Resistance exercise draws predominantly on fast-twitch type 2 fibers, which obtain more of their ATP from glycolysis than their slow-twitch type 1 counterparts.[128] The type of exercise thus seems to dictate which skeletal muscle fiber type accounts most for the increased muscle mass and function provoked by physical activity. Endurance training induces the formation of type 1 fibers, which is reflected by increased mitochondrial mass, while resistance training does not increase mitochondrial mass in newly formed type 2 fibers but improves mitochondrial ATP synthesis efficiency. Notably, resistance exercise amplifies the rise in mitochondrial oxidative capacity of sarcopenic skeletal muscle established by endurance exercise.[129,130] The ability of aged muscle to increase mitochondrial mass in response to endurance exercise[131] indicates that the mechanisms that regulate mitochondrial functional capacity remain intact in elderly individuals. Whether or not this is also the case for the secondary sarcopenia that develops in disease is less clear. For example, while the transcript level of peroxisome proliferator-activated receptor-γ coactivator-1α is increased in non-dialysed

individuals with chronic kidney disease following 12 weeks of aerobic physical activity, mitochondrial mass appears unaffected.[132]

3.2 | Nutrition

Appropriate nutrition is an essential aspect of current sarcopenia management.[17] Many dietary supplements have been explored, including both macro- and micronutrients such as protein,[133] unsaturated lipids[134] and vitamins,[135] as well as a range of polyphenols from natural sources,[136] but it should be emphasized that nutritional support is generally only effective in combination with exercise.[2,14,90] Benefit from polyphenols, vitamin D and polyunsaturated fatty acids may be related to the antioxidant properties of these nutrients,[137–139] but it is unclear to what extent their use as dietary supplements actually affects mitochondrial ROS production in sarcopenic muscle (Figure 3). The bioenergetic relation between dietary protein and mitochondrial activity is dual, since amino acids, specifically, leucine, are oxidative metabolic fuels,[140] allowing ATP synthesis when broken down through oxidative catabolism, as well as anabolic stimulants of protein synthesis,[69,141] provoking ATP consumption[142] (Figure 2).

Protein supplementation remains at the forefront of the nutritional management of primary and secondary sarcopenia, which is unsurprising as perturbed proteostasis is a key feature of this muscle disorder.[25,143] With age, muscle protein synthesis loses its sensitivity to anabolic stimuli such as essential dietary amino acids,[69] and, together with lost insulin inhibition of protein breakdown,[144] this anabolic resistance perturbs proteostasis.[69,141,145–147] Dietary protein supplements seek to overcome anabolic resistance but have limited benefit per se, as they appear most beneficial when administered together with exercise.[148] This observation suggests that both catabolic and anabolic stimuli are required to restore skeletal muscle mass and function in sarcopenia. Branched-chain amino acids—leucine in particular—have been recognized to add 'biological value' to essential amino acid and protein supplements,[149] as they appear able to stimulate both anabolic and catabolic processes.[150–153]

In healthy skeletal muscle, leucine acutely increases protein synthesis in the postprandial state through mTOR activation by various signals, including acetyl CoA, leucyl-tRNA and sestrin.[154] Perhaps to meet energy demand from this anabolic stimulation,[155] it is suggested by rodent pre-clinical studies that leucine also triggers an adaptive catabolic response that involves AMPK and that increases skeletal muscle mitochondrial biogenesis, mtDNA content, fatty acid oxidation and glucose uptake.[156] The apparently parallel occurrence of catabolic and anabolic stimulation is complex,[124,156] and indeed paradoxical, as AMPK is a well-established mTORC1 de-activator.[150,151] Leucine-induced catabolic and anabolic responses are thus likely separated temporally and spatially, through involvement of different fiber types.[157]

Protein contributes 10%–15% to total fuel oxidation in the postabsorptive state in resting skeletal muscle,[158] and catabolism of branched-chain amino acids accounts for about two-thirds of this contribution.[158] Insulin inhibition of protein breakdown is lost in sarcopenic muscle, which likely increases branched-chain-amino-acid-driven oxidative catabolism in older individuals.[159] The systemic oxidation of branched-chain amino acids occurs predominantly in skeletal muscle mitochondria[158,160] and oxidation rate is sensitive to nutrition-related changes in intramuscular branched-chain amino acid concentration.[160] The oxidation rate of branched-chain amino acids in elderly individuals is also increased by endurance[161–163] and resistance exercise,[164,165] as is the anabolic response to leucine, again suggesting that both anabolic and catabolic stimuli are necessary to obtain maximum benefit from nutrition in sarcopenia.

The notion that protein supplementation is most effective for management of sarcopenia when combined with physical activity,[148] suggests that bioenergetic processes triggered by energy demand may need to be active to obtain full benefit from anabolic stimuli. Supplemented amino acids may indeed only be usable as catabolic carbon fuel for ATP synthesis if demand for ATP is stimulated, for example, by exercise. It is worth emphasizing that increased intake of macronutrients without increasing energy expenditure may do more harm than good, as such intake is expected to create an overly reduced cellular environment that promotes ROS generation. Notably in this respect, obesity-related skeletal muscle insulin resistance arises at least in part because of imbalanced bioenergetics that increase ROS to pathological levels.[49] Moreover, loss of skeletal muscle insulin sensitivity is an early feature of uremic sarcopenia.[166] Nutrients with strong antioxidant properties may protect against excessively high ROS levels but may inadvertently attenuate any adaptive hormetic benefit from exercise that depends on an acute increase in ROS production.[167]

3.3 | Pharmacological intervention

Anti-sarcopenic drugs have not been approved to date,[2,14,168] as there is insufficient support from human trials to justify pharmacological interventions in clinical practice other than vitamin D in elderly women and testosterone in elderly men.[91] Vitamin D is thus an example of 'Foods for Special Medical Purposes' and, like

other nutrients discussed above, is sometimes referred to as a nutraceutical.[169] Despite lack of clinical trial evidence, numerous pharmacological approaches have been suggested. Drugs that have been investigated include testosterone, testosterone derivatives (melatonin), and selective androgen receptor modulators or SARMS,[170] which not only increase the number of skeletal muscle satellite cells,[171] but all also have beneficial effects on muscle fibers per se.[172,173] Inhibitory antibodies against proinflammatory cytokines[174] and myostatin inhibitors[175] are other examples of drugs that have been explored. Therapeutics that have been linked explicitly to mitochondrial function include growth hormone replacement,[176] which increases mitochondrial oxidative capacity, improves proteostasis, and has anti-sarcopenic benefit for elderly people,[177] ghrelin and ghrelin receptor agonists, which increase oxidative capacity in sarcopenia linked to chronic disease,[178–180] and 5-aminolevulinic acid, which improves muscle quality in mice while increasing mitochondrial content.[181]

The noticeable lack of drug approval is likely related to a limited number of randomized clinical trials, which are generally hampered by the range of sarcopenia definitions and by the difficulty of identifying primary endpoints.[168] Other therapeutic approaches are much sought after, and mitochondria have attracted much attention in this respect.[182–184]

Mitochondrial medicine is a rapidly developing field,[182–184] and approaches for delivering mitochondria-targeted drugs have been reviewed recently by others.[185,186] Exercise has been recognized as a 'natural medicine' for skeletal muscle mitochondria,[187] but it may well become possible in the foreseeable future to improve the activity of these organelles in sarcopenic muscle with targeted drugs. Drugs that are passively or actively delivered to skeletal muscle mitochondria hold promise to preserve mitochondrial quality and functionality by lowering oxidative stress.[188] Although in its infancy, several preclinical studies have offered proof-of-principle for this potential therapeutic approach. For instance, MitoQ and MitoTEMPOL, which are a mitochondria-targeted antioxidant and superoxide dismutase mimetic, respectively, have been shown to improve muscle strength and mass by altering bioenergetics in several disease mouse models,[189–191] while the mitochondria-targeted Szeto-Schiller peptide SS31 has been reported to increase exercise tolerance in aged mice.[192]

Mitochondrial transplantation is a therapeutic approach with much potential, but also very much in its infancy. The introduction of healthy mitochondria to dysfunctional cells or tissues has been trialed to increase oxidative capacity in various disease contexts,[193] while work with cell and animal models suggests the approach may help combat muscle atrophy.[194–197]

4 | CONCLUDING REMARKS

Imbalanced protein synthesis and breakdown in skeletal muscle accounts for muscle atrophy associated with old age and disease.[25,143] Decreased oxidative capacity is a central feature of both primary and secondary sarcopenia,[19,74–78] but the causal interrelation between altered bioenergetics and perturbed proteostasis remains unclear (Figure 2). It appears that mitochondrial bioenergetic changes in sarcopenia are broadly interpreted as an intrinsic dysfunction that renders skeletal muscle cells incapable of producing sufficient ATP to sustain protein synthesis. The general benefit of exercise for skeletal muscle mass and function in elderly and diseased individuals, however, demonstrates that this apparent insufficiency is readily overcome when energy expenditure is increased. This observation indicates that sarcopenic muscle has retained mechanisms to produce ATP when needed, and it suggests that the decreased oxidative capacity may be an adaptation to pathologically dampened energy demand. It is thus conceivable that impaired protein synthesis is one of the causes of lowered mitochondrial ATP synthesis in sarcopenic muscle, because this defect contributes to decreased total ATP consumption. Anabolic and insulin resistance that is responsible for the compromised balance between protein synthesis and breakdown is likely related to the inflammation and oxidative stress that typify sarcopenic conditions. The bioenergetic imbalance between nutrient supply and energy expenditure promotes oxidative stress, which may exacerbate mitochondrial and cellular defects. The observation that nutrition is only effective as an anti-sarcopenic intervention when applied with exercise, is consistent with this order of events. We emphasize that dietary supplements without increased physical activity may do more harm than good if compromised energy expenditure were at the root of muscle dysfunction, as they would distort the bioenergetic balance further and increase the risk of high ROS production. Notably, therapies based on mitochondrial transplantation would also be inconsequential if the bioenergetic changes seen in sarcopenia were secondary to pathologically diminished energy expenditure, i.e., if the oxidative capacity was increased without the need for such capacity. In conclusion, to achieve positive clinical outcomes it will be very important to obtain a more precise understanding of the causal interrelations between proteostasis, cellular bioenergetics and redox biology in both healthy and sarcopenic skeletal muscle.

AUTHOR CONTRIBUTIONS

Charles Affourtit: Conceptualization; Visualization; Writing – review & editing; Writing – original draft. **Jane E. Carré:** Conceptualization; Writing – original draft; Writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this review.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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