Summary Report

Duchenne Muscular Dystrophy as a mitochondrial myopathy: Why therapeutically targeting the mitochondria is a plausible treatment avenue

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DMD as a mitochondrial myopathy

Characterised as the most severe and aggressive form of all the muscular dystrophies, Duchenne Muscular Dystrophy (DMD) results from a gene mutation at position 21 on the X chromosome and consequently, absent expression of the cytoskeletal protein dystrophin [1]. The loss of dystrophin expression from skeletal muscle and neuronal tissue in which it is normally present as part of a transmembrane protein complex, induces chronic and progressive skeletal muscle wasting which is fatal in all cases. The accepted aetiology of the disease is intimately linked to the cytostructural role of dystrophin in providing stability to the sarcolemma, particularly during contraction; regulating the proper expression of components of the sarcolemmal Dystrophin Protein Complex (DPC); and, consequently, maintaining appropriate homeostatic transmembrane ion gradients and cell signalling functionality [2-4]. It is widely reported in the literature that the secondary molecular mechanisms ultimately leading to muscle degradation include abnormal calcium (Ca^{2+}) homeostasis [5,6]; [Ca^{2+}]-induced necrosis [7]; mitochondrial dysfunction and cellular energy perturbations [8-12]; and satellite cell (stem cells that repair damaged skeletal muscle) exhaustion [13,14]. As skeletal muscle regeneration fails to match degeneration rates and inflammatory activity persists, skeletal muscle becomes infiltrated with fat and connective tissue which limits function and leads to the loss of ambulation in the teenage years [15,16]. Ultimately fibrosis of the diaphragm and heart ensues causing respiratory dysfunction, cardiomyopathy and death by the third decade of life [17,18].

Both historically [19] and again more recently [20], DMD has been regarded as a disease of impaired myofibre energy homeostasis, which is at the very least a contributor to, if not an aetiological promoter of, dystrophinopathy. Cellular energy (ATP) homeostasis is rigorously maintained by a vast and intricate network of metabolic pathways within skeletal muscle, and dysregulation has a variety of detrimental consequences. These include: impaired force production leading to weakness and exercise tolerance; impaired intracellular Ca^{2+} buffering leading to loss of homeostasis and Ca^{2+}-induced degeneration, necrosis and apoptosis; reduced protein synthesis alongside increased macroautophagy leading to the loss of muscle mass; and reduced satellite cell activation, replication, migration and differentiation leading to a markedly decreased capacity for regeneration of damaged muscle fibres. In dystrophin-deficient skeletal muscle from human DMD patients as well as from the genetically homologous *mdx* mouse model of the disease [21,22], a myriad of metabolic deficits encompassing the enzymes of glycolysis [23-27], the purine nucleotide cycle (PNC) [28,29], and the mitochondrial Tricarboxylic Acid (TCA) cycle [27,30] and Electron Transport Chain (ETC) [10,12,31] have been consistently reported (see Table 1). These both individually and collectively, contribute to this loss of energy homeostasis.

During metabolic stress, a cell signalling cascade is initiated in skeletal muscle which inhibits protein synthesis and promotes muscle catabolism via autophagy. As such, ATP utilization is spared and metabolites stored within skeletal muscle tissue are made available to metabolism to increase ATP synthesis and restore energy homeostasis [32]. This is achieved predominantly through the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) which is

phosphorylated by rising AMP levels. AMPK activation also promotes mitochondrial biogenesis and targeted destruction of dysfunctional mitochondria (mitophagy), thereby increasing the viable mitochondrial pool and ATP synthesis [33]. It has been established that AMPK activation is increased in dystrophin-deficient skeletal muscle [34], highlighting in the first instance, that acute metabolic stress signals are switched on. However, *mdx* skeletal muscle seems to benefit from the additive effects of pharmacological AMPK activation [34], suggesting in the second instance that endogenous molecular adaptations to the AMPK-mediated metabolic stress response are insufficient and that therapeutically targeting metabolism amplification is beneficial. Importantly, while AMPK activation successfully induces beneficial adaptations in dystrophin-deficient muscle that are seemingly specific to utrophin upregulation and slow fibre type induction, it fails to appropriately increase oxidative ATP production at the mitochondrial level [34] and autophagic activity [34,35].

Due to the strong and multifaceted allosteric regulation of metabolism by associated up- and down-stream products and reactants, one broken link in the metabolic chain induces deleterious consequences at multiple levels spanning the entire metabolic system – thus pinpointing the precise defect becomes difficult. Indeed, the only established physical link between the dystrophin protein and the metabolic pathways is via neuronal nitric oxide synthase (nNOS). nNOS normally co-localises with dystrophin at the sub-sarcolemma [36,37] and dystrophin-deficiency results in the secondary loss of nNOS [38] and consequently, the capacity for endogenous skeletal muscle NO production. As both nNOS and nNOS-generated NO are strong regulators of glucose uptake and flux through the glycolytic enzyme cascade (particularly during muscle contraction) [39,40], it is logical that reduced substrate availability is a precursor to energy system de-regulation and non-responsiveness to metabolic stress signalling in dystrophin-deficient fibres. However, normal basal glucose uptake has been reported in human DMD muscle [41-43] and we have most recently demonstrated a higher contraction-induced glucose uptake in *mdx* muscle per unit of force produced [44]. This is despite glycolytic enzyme activities and intermediates being constitutively reduced, and glycogen content being higher in dystrophin-deficient muscle. Thus the metabolic deficit appears related to the utilisation of energy substrates rather than their availability. Since defects in fat oxidation have also been reported [41,45-50], the data strongly suggests a fundamental defect at the mitochondrial level that induces deregulation of all metabolic systems.

Mitochondrial dysfunction in dystrophic skeletal muscle is well documented and a key contributor to the reductions (up to 50%) in resting ATP content [8,12,51-61]. In addition to various functional and structural mitopathic features (summarised in Table 1), impaired handling of mitochondrial substrates including pyruvate [10-12,27,31,46,62-66], malate [10,12,31,63-65] and glutamate [10,12,66,67] have been consistently reported, and produce lower oxidation rates compared to healthy controls. Each of these substrates drives NADH production in the first instance, followed by NADH-mediated electron flow and proton flux at Complex I of the ETC. Addition of succinate, on the other hand, has been shown to either restore [27,31,68,69] or at least partially restore oxidation rates to near control levels [10,12,63,64]. Succinate drives Complex II metabolism via the $FADH_2$ that it generates, effectively bypassing Complex I. This is a widely reported feature of dystrophin-deficient muscle metabolism and as published by us recently, strongly indicates that the metabolic deficit may be located at Complex I of the ETC [12]. Depressed Complex I function [70] and concomitant reductions in ATP concentration [71] is also a feature of dystrophin-deficient human and *mdx* mouse brain – this is clinically important as Ca^{2+}-induced damage is not a feature of dystrophin-deficient neurons as per the skeletal musculature, suggesting that mitochondrial deficits are independent of the Ca^{2+}-related pathology.

Table 1. The metabolic deficits of dystrophin-deficient skeletal muscle.

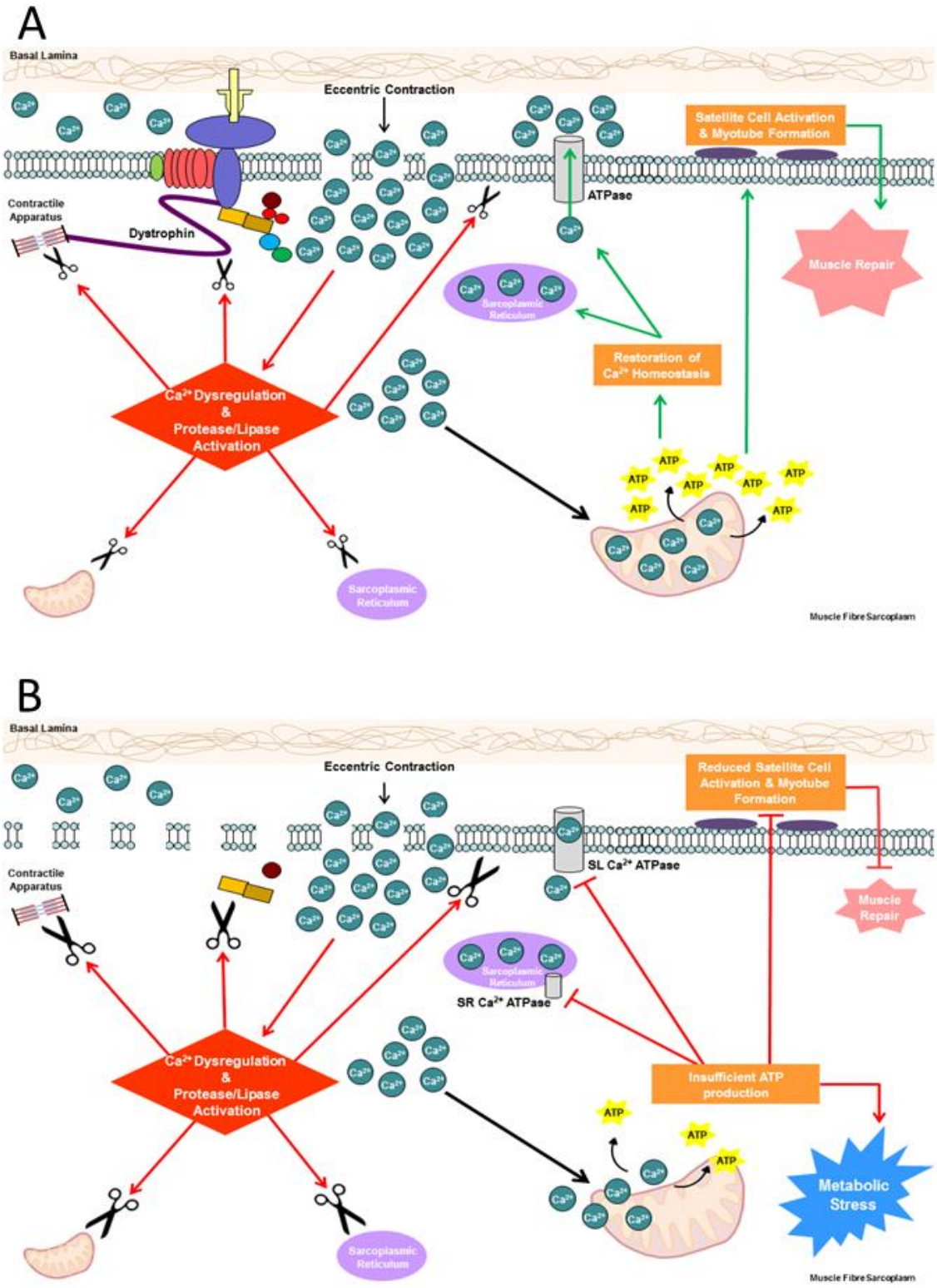
	Defect Description	DMD Model	References
Macronutrient uptake & availability	Normal basal glucose uptake (GLUT 1)	Human DMD & *mdx* mouse	[41-43]
	Reduced contraction-induced glucose uptake (GLUT 4)	*mdx* mouse	[44]
	Reduced glucose content	Human DMD & *mdx* mouse	[41-43]
Glycolysis	Reduction in glycolytic intermediates	Human DMD	[25]
	Reduced activity & sensitivity of glycolytic enzymes	Human DMD & *mdx* mouse	[23-26,55,72-74]
	Reduced allosteric modulation of regulatory PFK function	Human DMD & *mdx* mouse	[55,72]
	Reduced by-products of anaerobic metabolism & sarcoplasmic acidification	Human DMD & *mdx* mouse	[8,41,75]
Glycogen storage & utilisation	Increased glycogen content	Human DMD & *mdx* mouse	[76-78]
	Reduced glycogenolytic enzyme function	Human DMD & *mdx* mouse	[23-26,75,78-85]
Fat oxidation	Reduced substrate oxidation	Human DMD patients & carriers; *mdx* mouse	[41,45-50,86,87]
	Reduced total carnitine	Human DMD	[41,46,48-50,87]
	Reduced fatty acid transport into the mitochondria	Human DMD	[50]
Creatine phosphagen system	Reduced total creatine pool	Human DMD & *mdx* mouse	[41,42,51,56,57,59,88-93]
	Reduced PCr/Pi ratio	Human DMD	[57,88,94]
	Reduced PCr/ATP ratio	Human DMD	[57,88,95]
	Reduced urinary Cr excretion (due to reduced Cr phosphorylation)	Human DMD	[96]
Purine Nucleotide Cycle	Reduced enzyme activities and/or content Increased purine degradation & loss	Human DMD	[29,58,97,98]
Mitochondrial Function	Depressed TCA enzyme activity Reduced respiratory rate Reduced ETC Complex expression, activity & efficiency Reduced performance/flexibility and coupling efficiency	Isolated mitochondria, isolated fibres, whole muscle & cultured cells from human DMD patients & *mdx* mouse	[9-12,31,44,58,60,62-66,68,69,79-81,95,97-106]
Mitochondrial structure & locale	Reduced mass Reduced subsarcolemmal fraction Swollen morphology ETC Complex assembly	Human DMD patients & carriers; *mdx* mouse	[12,34,76,77,82,103,104,107-110]
Overall cellular energy homeostasis	50% reduction in resting ATP concentration	Human DMD & *mdx* mouse	[8,12,51-61]

Abbreviations: GLUT1 = glucose transporter sub-type 1; GLUT4 = glucose transporter sub-type 4; G-6-P = glucose-6-phosphate; PFK = phosphofructokinase; PCr = phosphocreatine; Pi = inorganic phosphate; ATP = adenosine triphosphate; Cr = creatine; ETC = electron transport chain; TCA = tricarboxylic acid (cycle).

It is the working hypothesis of our group, that mitochondrial pathology forms the basis of DMD aetiology alongside dystrophin-deficiency [20] (Figure 1), such that much like the damage following eccentric muscle injury (Figure 1A), dystrophin-deficiency-mediated damage could be regulated if ATP availability was sufficient. Teamed with mitochondrial pathology, however, a "two-hit" scenario exacerbates muscle degeneration and wasting (Figure 1B). Indeed, DMD shares common metabolic and mitopathological features with various mitochondrial diseases and with aged skeletal muscle, including often comparable symptomology. In addition a more recent study has shown that mitochondrial dysfunction exists in "pre" dystrophin-deficient myoblasts prior to the typical cascade of events that are commonly believed to cause the progressive muscle degeneration and wasting evident in DMD [11]. Because skeletal muscle accounts for ~40–50% of body weight and ~30% of oxygen consumption at rest, it is an important regulator of overall metabolism. As such, mitochondrial deficits manifest vastly in the skeletal musculature and myopathy is thus characteristic of many mitochondrial diseases. Mitochondrial disease can arise from mutations in the maternally inherited mitochondrial DNA (mtDNA), and less commonly in the nuclear DNA. mtDNA resides in the matrix and encodes for the hydrogen pumping regions of the ETC Complexes, highlighting its integral role in the regulation of metabolism [111]. However due to its proximity to the respiratory chain, mtDNA is extremely vulnerable to mutation, most commonly by reactive oxygen species (ROS) produced by the respiratory Complexes [112,113]. Initially, this has minimal effect on mitochondrial function, until the number of mutant mtDNA outnumbers wild-type mtDNA. As mutant mtDNA accumulates, the bioenergetical capacity of the cell diminishes. Various diseases result from mtDNA mutations and manifest themselves as multisystemic pathology. These mitochondrial diseases share common features with DMD including varying levels of mental impairment, skeletal muscle weakness, cardiomyopathy and multisystem metabolic dysfunction [111,114]. Reduced activities of Complex I, III, IV and V of the ETC, increased ROS production and decreased ATP synthesis are common nuances of both mitochondrial diseases and DMD [114]. The fact that dystrophin is encoded and expressed normally in these diseases, but that they share clinical features with dystrophinopathy indicates the potential for a common disease origin that is not linked to dystrophin-deficiency, but rather the mitochondria.

As the ETC complexes (excluding Complex II) are partially encoded by mtDNA and reports exist that describe mitochondrial dysfunction in DMD carriers that express dystrophin normally [115,116], maternal mtDNA mutations inheritance could be an origin of DMD-associated mitopathology. If not inherited, another likely origin is via the rapidly progressive accumulation of ROS-induced mutations similar to that which underscores senescence [117]. Aging muscle shares many symptomatic characteristics of dystrophic muscle including fatigability, muscular weakness and mitochondrial dysfunction. In aged muscle, it appears that accumulation of mutant mtDNA leads to mitochondria with decreased oxidative capacity and ATP synthesis and elevated oxidative stress [111,118] which impairs muscular function and viability. Notably, the co-occurrence of mtDNA mutation in patients from DMD family pedigrees and/or with dystrophin gene abnormalities but normal dystrophin expression is increasingly observed [119-121]. This highlights a propensity for dystrophin and mtDNA gene mutations to co-exist. Further, missense mutations at exon 15 of the dystrophin gene in which dystrophin protein expression is normal, induces clinical symptomologies in human patients that are characteristic of metabolic disease and which include mitochondrial cytopathy [120]. Isolated cases of DMD in a human patient [122] and in GRMD dogs [123-125], in which a mild disease phenotype leads to a normal lifespan, at the very least highlights that the loss of dystrophin expression is not the sole contributor to the pathological deterioration of skeletal muscle in DMD. It seems that while indeed promoting sarcolemmal leakiness and skeletal muscle damage, dystrophin-deficiency can be effectively buffered by adaptive mechanisms in some instances.

Figure 1. The physiology of skeletal muscle damage and repair in healthy (A) and DMD (B) skeletal muscle.



Schematic showing the normal physiological cascade induced by eccentric exercise-induced damage of healthy skeletal muscle (A). Eccentric damage causes membrane tears, Ca^{2+} influx from the extracellular space and increases in the intracellular Ca^{2+} concentration. Proteases and lipases activated by Ca^{2+}, cause damage to the contractile apparatus, mitochondria, sarcoplasmic reticulum and the muscle membrane. Ca^{2+} uptake into the mitochondria stimulates oxidative phosphorylation and ATP production is increased to support ATP-fuelled Ca^{2+} extrusion pumps in the muscle membrane, sarcoplasmic reticulum and mitochondria, thus restoring intracellular Ca^{2+} homeostasis. ATP also fuels satellite cell replication and skeletal muscle repair, which is activated by the inflammatory response. In dystrophin-deficient skeletal muscle (B), the increased propensity for membrane rupture during eccentric contraction causes the same (but amplified) degenerative cascade. Teamed with mitochondrial dysfunction, however, the muscle has no defence against Ca^{2+} influx and a limited capacity for skeletal muscle repair due to the high metabolic nature of cell proliferation. The consequence is metabolic stress, muscle degeneration, insufficient repair of degeneration and muscle wasting.

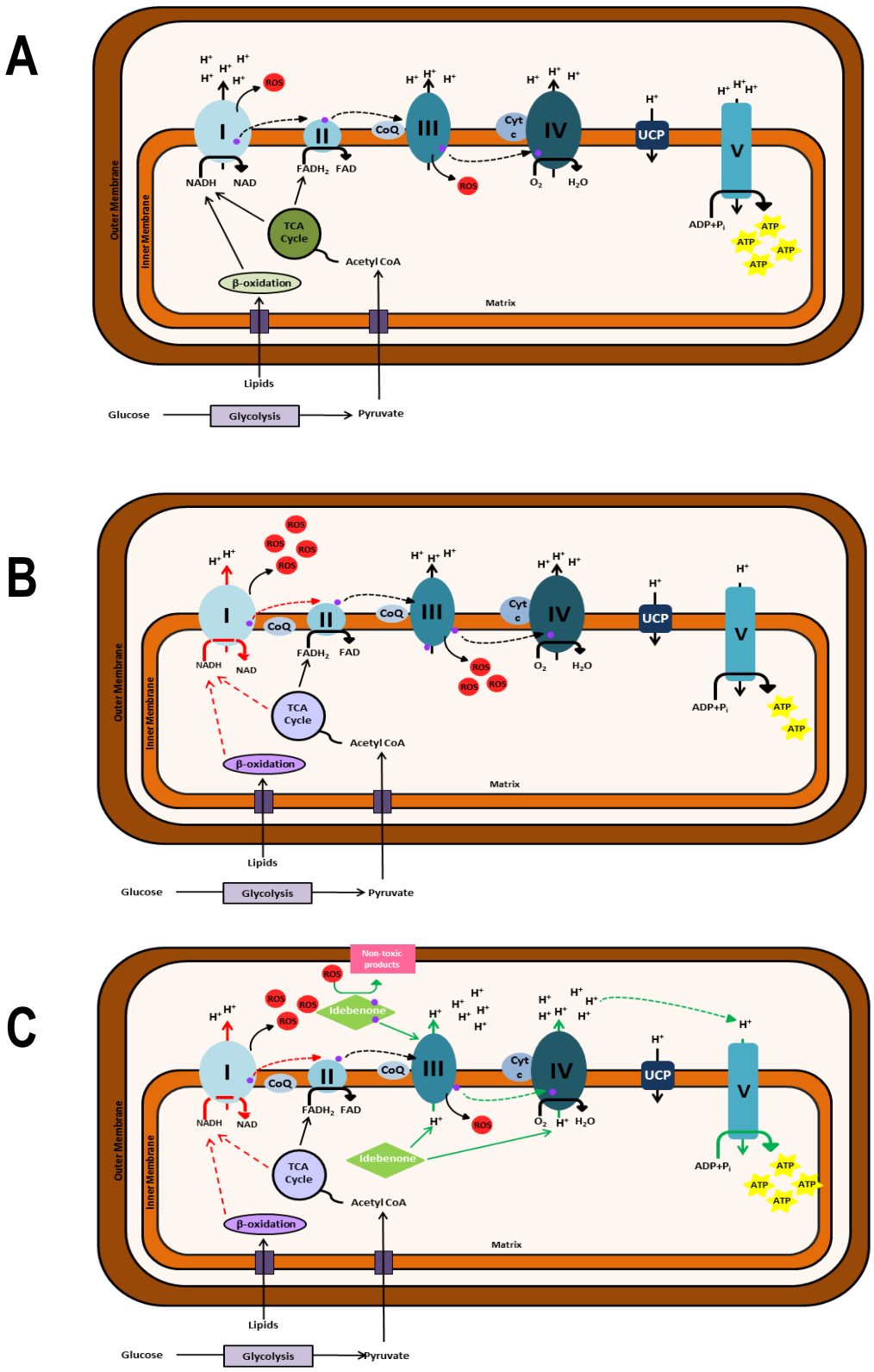
Therapeutically targeting the mitochondria for the treatment of DMD: Insights from Idebenone

Gene therapy represents the only potential cure for DMD. However, while exon skipping therapy has been successfully developed to restore dystrophin expression to ambulatory patients following missense mutation, appropriate curative therapies are not a mainstream treatment despite the dystrophin gene defect being identified some 20 years ago. Currently, DMD patients are treated somewhat successfully with corticosteroids, which while providing therapeutic value to the majority of sufferers, is not without serious side effects [126]. Thus, treatment protocols that reduce the severity and progression of muscle wasting must continue to be rigorously researched. Since dystrophin-deficient skeletal muscle is underscored by a reduced capacity for mitochondrial energy biosynthesis caused by an apparent deficit at Complex I, targeting the mitochondria for therapeutic intervention seems logical. Indeed, a solid body of literature has investigated the therapeutic potential of energy-promoting nutriceutical and metabogenic supplements for the treatment of DMD. Of these, the most promising is the synthetic Coenzyme Q10 (CoQ10) analogue, Idebenone, which has established therapeutic efficacy for the treatment of the Complex I-associated mitochondrial disease, Leber's hereditary optic neuropathy (LHON) [127].

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a short chain synthetic analogue of CoQ10 that has indications for the treatment of a variety of degenerative diseases associated with the vascular, central nervous and muscular systems. Like CoQ10, it has strong antioxidant properties and the capacity to improve mitochondrial respiratory chain function and cellular energy production [128]. However, Idebenone therapy has significant advantages over endogenous CoQ10 in that is has a lower molecular weight making it more readily incorporated into the mitochondrial membrane, as well as being able to positively compete with endogenous CoQ10 for protons and electrons [129]. Idebenone has been shown to facilitate the transfer of electrons in isolated mitochondria and avert electron leak from Complex I that would otherwise produce mitochondrial ROS [130], thus making it a strong regulator of mitochondrial ATP production capacity and oxidative stress buffering. In a recent study, Idebenone demonstrably restored electron transfer to Complex III in cells with genetically-induced Complex I dysfunction[131], highlighting that its primary benefit in DMD muscle could be to restore electron flow and ATP production by way of bypassing a defective Complex I (see Figure 2).

Indeed, Idebenone has emerged in clinical (and pre-clinical) safety and efficacy studies as a worthy therapeutic candidate for the treatment of DMD. Following promising pre-clinical data in the *mdx* mouse model in which protection from cardiomyopathy and improved voluntary running performance was a prominent feature of long-term treatment [143], Idebenone has been shown in clinical trials to improve respiratory function measures [132,133]. This suggests that Idebenone therapy affords benefit to core and limb skeletal musculature in addition to the respiratory and cardiac musculature, thus making it a promising therapeutic candidate for the treatment of DMD.

Figure 2. Schematic showing the potential of Idebenone to rescue abnormal energy production in mitochondria from dystrophin-deficient skeletal muscle.



In healthy mitochondria, glycolytic, TCA and fat (β-)oxidation pathways feed primarily NADH to Complex I and to a lesser extent $FADH_2$ to Complex II of the ETC. CoQ facilitates the transfer of electrons and proton pumping to establish the $\Delta\Psi$ and ATP production at Complex V (A). In DMD mitochondria, the delivery of reducing equivalents to the ETC is reduced (red dashed lines) and irrespective of this, Complex I dysfunction reduces ATP production at Complex V by up to 70% (B). Excessive mitochondrial ROS production is a consequence of this defect (B). Idebenone therapy rescues ATP production by effectively by-passing Complex I and facilitating electron exchange and proton pumping at Complex III. In the process of doing so, Idebenone elicits strong antioxidant potential by metabolising ROS to inert, non-reactive by-products.

Conclusions

More than 50 years of basic and clinical research (in addition to the earliest observations of Meryon [134] and Duchenne [135] who initially documented the disease) highlights that gross metabolic impairment is an important yet often ignored feature of DMD-associated dystrophinopathy. We believe that mitochondrial dysfunction (specifically Complex I) is an aetiological modifier and promoter of the clinical progression of DMD, and that the mitochondria is a worthy candidate for therapeutic target. There is strong evidence that by-passing the Complex I deficit and stimulating Complex II ($FADH_2$)-dependent energy production with oral Idebenone therapy is efficacious both in animal models and human DMD patients. There are other obvious benefits of Idebenone therapy that relate to its strong antioxidant potential and membrane protective effects. It is thus our opinion that Idebenone represents a novel and clinically relevant therapy for the treatment of a key aetiological modifier of DMD.

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