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A revised model for mitochondrial dysfunction in Duchenne muscular dystrophy

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Abstract

We recetly identified a signaling pathway that links the upregulation of miR-379 with a mitochondrial response in dystrophic muscle. In the present commentary, we explain the significance that this pathway may have in mitochondrial dysfunction in Duchenne muscular dystrophy (DMD). We identified the upregulation of miR-379 in the serum and muscles of DMD animal models and patients. We found that miR-379 is one of very few miRNAs whose expression was normalized in DMD patients treated with glucocorticoid. We identified EIF4G2 as an miR-379 target, which may promote mitochondrial oxidative phosphorylation (OxPhos) in the skeletal muscle. We found enriched EIF4G2 expression in oxidative fibers, and identified the mitochondrial ATP synthase subunit DAPIT as a translational target of EIF4G2. The identified signaling cascade, which comprises miR-379, EIF4G2 and DAPIT, may link the glucocorticoid treatment in DMD to a recovered mitochondrial ATP synthesis rate. We propose an updated model of mitochondrial dysfunction in DMD.

Key Words: Duchenne Muscular Dystrophy; DLK1-DIO3; miR-379, EIF4G2, Dapit, USMG5, mitochondria; oxidative phosphorylation.

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Duchenne Muscular Dystrophy (DMD) is an X-linked severe progressive muscle disease caused by mutations in the *DMD* gene, which encodes for the dystrophin protein. The disease affects the motor functions and leads to premature patients death, primarily due to respiratory and cardiac failures.[1] The consequence of the disrupted link between the ECM and the actin cytoskeleton is a process that involves sarcolemma destabilization, perturbation of Ca^{+2} homeostasis, activation of proteases, mitochondrial damage and tissue degeneration.[2]

Of particular interest for this commentary, initial and more recent studies highlighted over the years a critical role for mitochondrial dysfunction in the etiology of DMD.[3] However, the details of the molecular mechanisms of this dysfunction are not yet clear. We recently profiled miRNAs in the plasma and muscles of DMD animal models and patients, and found a large number of dysregulated miRNAs.[4-6] In agreement with other studies, we documented the dysregulation of the myomiRs, which are the skeletal muscle enriched miRNAs, and a few cardiac-muscle-enriched miRNAs. In addition, we identified the dysregulation of a large number of miRNAs which are clustered in the Dlk1-Dio3 genomic locus. The imprinted Dlk1-Dio3 locus hosts the largest miRNA mega-cluster in the human genome, plus other non-coding RNAs and three protein-coding genes (*DLK1*, *RTL1*, and *DIO3*) and is highly conserved in mammalian genomes.[7,8] Dlk1-Dio3 miRNAs (DD-miRNAs) have shown to play a critical role in fetal development and postnatal growth.[9-12] DD-miRNAs are also known to play important roles in embryonic and somatic stem cells.[13-16] Initial indications for Dlk1-Dio3 locus involvement in the muscular system came from the identification of the muscle hypertrophy Callipyge phenotype in the sheep.[17-19] Additionally, patients carrying genetic defects in Dlk1-Dio3 locus present hypotonia and muscle metabolic deficiencies.[20] In the cardiac muscle, DD-miRNAs were shown to regulate diverse functions.[21] In the developing muscle, DD-miRNAs were shown to control the metabolic maturation of muscle precursor cells.[16] However, the biological functions of DD-miRNAs in the context of muscular dystrophy remain relatively unexplored.

Of all dysregulated DD-miRNAs, we decided to focus on miR-379, which was found upregulated in many other muscular dystrophies in addition to DMD.[22] We found that miR-379 is among the most highly expressed and upregulated in DMD plasma. Importantly, it is one of the very few miRNAs whose expression is normalized by glucocorticoid treatment,[6] which is the standard pharmacological care for Duchenne Muscular

Dystrophy.[23] We then identified the translation factor *EIF4G2* as a potentially important target and mediator of miR-379 function in the muscle. *EIF4G2*, a member of the eIF4G translation initiation factors, mediates a cap-independent translation initiation through a mechanism involving the recruitment of the ribosome to specific mRNAs that contain an internal ribosome entry site (IRES) in their 5' untranslated region (UTR).[24] Our attention was drawn to *EIF4G2*, because it was shown recently to promote a mitochondrial shift of glycolytic to OxPhos metabolism, and subsequently of cellular differentiation.[24] Of interest, mitochondrial OxPhos activity was shown to promote myogenic differentiation,[25] suggesting that *EIF4G2* may promote myogenic differentiation by such mechanism. We then noticed that *EIF4G2* is a target gene for miR-139, which similarly to miR-379, belongs to the small group of glucocorticoid-responsive miRNAs in the plasma of DMD patients.[6] Thus, in the dystrophic muscle *EIF4G2* is under a tight regulation, independently by two distinct glucocorticoid-responsive miRNAs, which supported a particular importance of *EIF4G2* in the glucocorticoid response of the dystrophic muscle.

Because *EIF4G2* is a translation factor known to promote the mitochondrial OxPhos, we attempted to identify its putative translation target(s) in the context of mitochondrial activity. In a list of such targets, provided in supplemental information in,[24] we identified among the top hits the mitochondrial protein *DAPIT*, which is encoded by the Usmg5 gene. *DAPIT* struck our attention, because it has been shown previously to be expressed nearly 5-fold higher levels in DMD patients with loss of ambulation at late stage as opposed to early stage,[26] and more recently to be upregulated in the muscle of the neonatal DMD pig model.[27] *DAPIT* is a mitochondrial ATP synthase peripheral stalk subunit, which is required for the dimerization of the ATP Synthase,[28] the shaping of the mitochondrial cristae,[29] and a maximal ATP synthesis rate.[30] Indeed, mutation in Usmg5 gene was found recently in Leigh syndrome patients, characterized by mitochondrial perturbations.[31] We thus hypothesized that *EIF4G2* and *DAPIT* are of interest in DMD as targets of miR-379.

We validated in human myoblasts the targeting of *EIF4G2* by miR-379 and miR-139, and the subsequently downregulation of *DAPIT*, thus experimentally linking the upregulation of miR-379 to reduced *EIF4G2* expression and of *DAPIT* in the myogenic lineage. Immunofluorescence analysis of muscle transversal sections in the mouse confirmed the co-localization of both *EIF4G2* and *DAPIT* to oxidative myofibers. We then knocked down *DAPIT* expression, *in vitro,* in skeletal muscle myotubes, and identified reduced ATP production in the condition of reduced *DAPIT* expression.[32] Finally, treating mice with glucocorticoids increased *EIF4G2* and *DAPIT* expression in skeletal muscle via the reduction of miR-379 level, as seen in DMD patients. Taken together, these findings experimentally confirm a glucocorticoid-responsive signaling pathway in the myogenic lineage that links miR-379 upregulation with a reduced ATP synthesis rate.

In 1975 Mokri end Engel, who investigated muscle biopsies by electron microscopy, identified structural defects in the plasma membrane of DMD myofibers, which permitted the penetration of calcium-rich extracellular fluid.[33,34] Consistently, Wrogemann and Pena, proposed in 1976 the Ca^{+2} hypothesis for the mitochondrial dysfunction in muscular dystrophies.[35] Accordingly, the excessive entry of Ca^{2+} into the damaged myofiber initiates mitochondrial structural with subsequent functional defects reducing ATP production, and promoting a downstream cascade, leading to myofiber degeneration. Forty-five years later, through the discovery in the late eighties of the dystrophin gene and its role in DMD, the basic dogma of mitochondrial dysfunction has not much evolved,[36–38] assuming still that the mitochondria of the dystrophic muscle are merely passively exposed to the external insult of Ca^{+2} overload. Based on,[32] we are suggesting now a modified model for the explanation of mitochondrial dysfunction in DMD, which is presented in figure 1.

The results that were described above support that *EIF4G2* might be involved in the promotion of an oxidative phenotype in the differentiated muscle. As previously mentioned in embryonic stem cells, *EIF4G2* was proposed to modulate cellular differentiation through the promotion of mitochondrial oxidation.[24] Oxidative phosphorylation is also crucial for myogenic differentiation.[25] We identified the enriched expression of *EIF4G2* in oxidative myofibers, in the skeletal muscle.[32] It is possible that, by promoting the translation of *DAPIT* and other mitochondrial OxPhos proteins, *EIF4G2* is an important mediator of the oxidative phenotype in the skeletal muscle. A shift to oxidative phenotype was proposed to be beneficial in DMD,[39] and therefore it is tempting to speculate that overexpression of *EIF4G2* in the muscle may provide protection in DMD.

Another interesting question is concerning the expression pattern and biological functions of *DAPIT*. A number of studies reported *DAPIT*'s mitochondrial localization,[29-31] as a component of the OxPhos complex 5 ATP synthase.[28] In the skeletal muscle of the mouse, high-resolution confocal microscopy shown co-localization of *DAPIT* with *EIF4G2* into oxidative fibers, with however only partial overlap with the mitochondrial ATP synthase ATP5a subunit.[32] Interestingly, in C2C12 myoblast *DAPIT* expression was identified in the lysosome, in addition to the mitochondria, possibly as a component of the lysosomal V-ATPase complex,[40] which is structurally and mechanistically related to the mitochondrial ATP synthase. Thus, *DAPIT* may fulfill a (more than initially anticipated) complex role in the regulation of energy

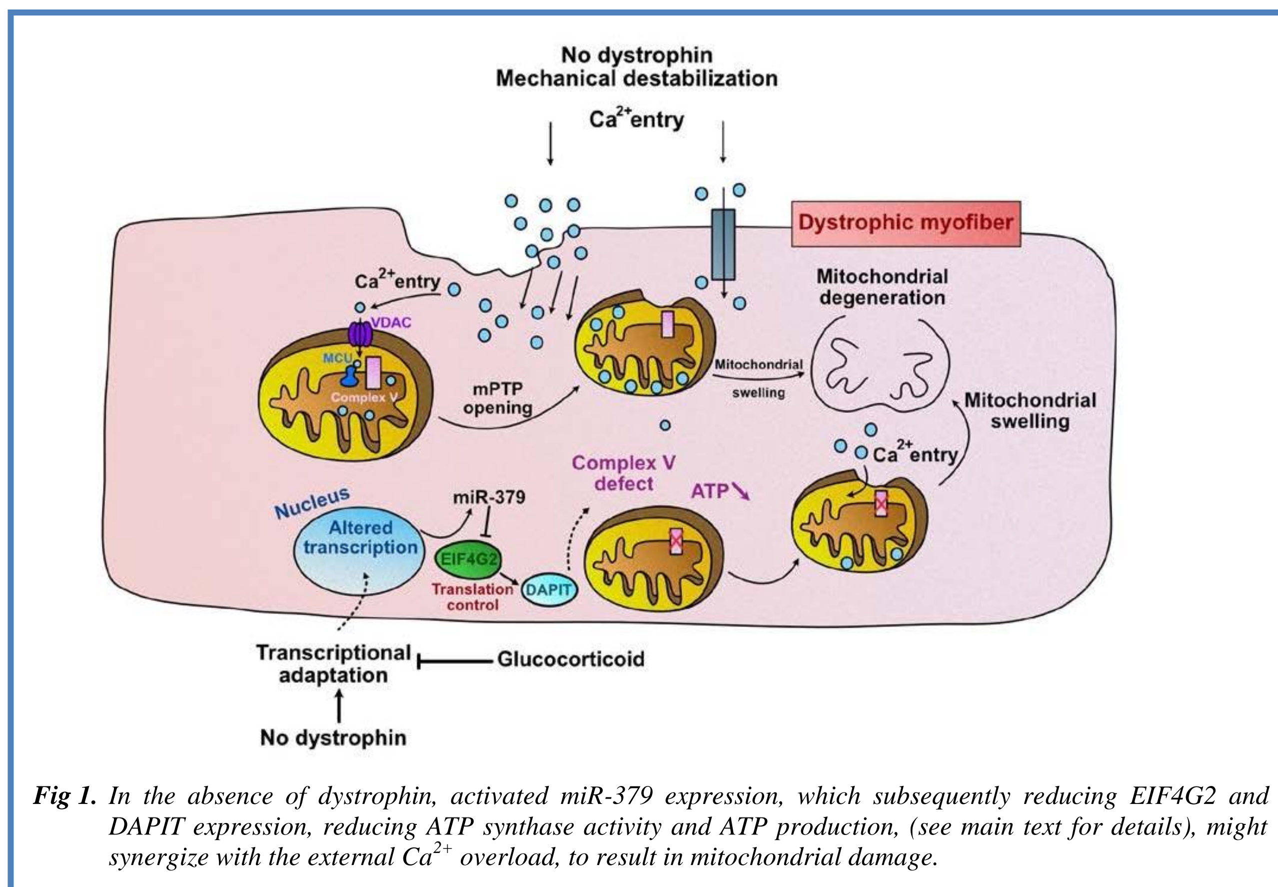

Fig 1. *In the absence of dystrophin, activated miR-379 expression, which subsequently reducing EIF4G2 and DAPIT expression, reducing ATP synthase activity and ATP production, (see main text for details), might synergize with the external Ca^{2+} overload, to result in mitochondrial damage.*

metabolism in the normal and dystrophic skeletal, and cardiac,[41] muscles, which is an interesting challenge for future investigations. Another hypothesis is that DD-miRNAs, other than miR-379, might regulate mitochondrial functions in DMD. Clustered miRNAs are thought to coordinately regulate a large number of target transcripts in given signaling pathways.[42,43] Of relevance and as mentioned above, we identified the coordinated upregulation of a large number of DD-miRNAs in the serum and muscles of DMD models and patients. A coordinated simultaneous activity of DD-miRNAs on mitochondrial functions were demonstrated in the hematopoietic system.[14] Moreover, the coordinated targeting of DD-miRNAs of mitochondrial functions was demonstrated in the metabolic regulation of muscle precursor cells.[16] It is therefore tempting to speculate that DD-miRNAs may simultaneously and coordinately regulate mitochondrial functions in myofibers of the regenerating muscle. An ongoing study in our group is toward these directions. In summary, our recent study,[32] exposed a new signaling pathway which is dysregulated in DMD, and contributes to a better understanding of mitochondrial perturbation in DMD.

List of acronyms

DMD - Duchenne Muscular Dystrophy
IRES - Internal Ribosome Entry Site
OxPhos - Oxidative Phosphorylation
UTR – Untranslated Region

Authors contributions

DI wrote the first draft. MS designed the figure. All authors reviewed, curated and approved the manuscript.

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Al authors declare no competing interests.

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