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Modulating mitophagy in mitochondrial disease

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Abstract: Mitochondrial diseases may result from mutations in the maternally-inherited mitochondrial DNA (mtDNA) or from mutations in nuclear genes encoding mitochondrial proteins. Their bi-genomic nature makes mitochondrial diseases a very heterogeneous group of disorders that can present at any age and can affect any type of tissue.

The autophagic-lysosomal degradation pathway plays an important role in clearing dysfunctional and redundant mitochondria through a specific quality control mechanism termed mitophagy. Mitochondria could be targeted for autophagic degradation for a variety of reasons including basal turnover for recycling, starvation induced degradation, and degradation due to damage. While the core autophagic machinery is highly conserved and common to most pathways, the signaling pathways leading to the selective degradation of damaged mitochondria are still not completely understood. Type 1 mitophagy due to nutrient starvation is dependent on PI3K (phosphoinositide 3-kinase) for autophagosome formation but independent of mitophagy proteins, PINK1 (PTEN-induced putative kinase 1) and Parkin. Whereas type 2 mitophagy that occurs due to damage is dependent on PINK1 and Parkin but does not require PI3K.

Autophagy and mitophagy play an important role in human disease and hence could serve as therapeutic targets for the treatment of mitochondrial as well as neurodegenerative disorders. Therefore, we reviewed drugs that are known modulators of autophagy (AICAR and metformin) and may effect this by activating the AMP-activated protein kinase signaling pathways. Furthermore, we reviewed data available on supplements, such as Coenzyme Q and the quinone idebenone, that we assert rescue increased mitophagy in mitochondrial disease by benefiting mitochondrial function.

Keywords: Mitophagy, AICAR, metformin, Coenzyme Q10, idebenone, phenanthroline

1. INTRODUCTION

Mitochondrial disease comprises a group of disorders ultimately caused by dysfunctional mitochondria. Mitochondria are cellular organelles of bacterial origin [1] that are often referred to as the 'power house' of the cell. However, in addition to generating energy mitochondria fulfil a number of roles in order to maintain cellular homeostasis, such as participating in calcium storage [2], iron metabolism and haem synthesis [3, 4], apoptosis [5, 6] and thermogenesis [7].

Mitochondria have their own genome, transmitted maternally, comprising 37 genes in total, all essential for its function. Human mitochondrial DNA (mtDNA) encodes 13 proteins (7 subunits of Complex I, 1 subunit of Complex III, 3 subunits of Complex IV, and 2 subunits of the F1F0-ATPase) along with the 22tRNAs and 2 rRNAs necessary for their translation [1]. Mitochondrial disease may result from mutations in the mitochondrial genome as well as from mutations in nuclear genes encoding proteins required for mitochondrial function. As a result of this bi-genomic nature mitochondrial disease can have recessive, dominant, X-linked or maternal inheritance.

Disorders of mitochondrial oxidative phosphorylation (OXPHOS) are common inborn errors of metabolism. While 1 individual in 400 carries a common mtDNA mutation that causes presbycusis [8], the incidence of clinically diagnosed mitochondrial disease is nearer 1 in 4300 in adults, making it one of the commonest adult forms of inherited neurological disorders [9].

Mutations in mtDNA cause a number of diseases, which primarily affect tissues with high energy demand such as muscle and neural tissue. In many of these, mutant and normal mtDNA co-exist in the same individual (heteroplasmy). Clinical severity is often influenced by the proportion of mutant mtDNA present within cells. Many of these diseases are progressive, presumably because the mutant load increases with time. However, homoplasmic mtDNA mutations also exist when the entire mitochondrial pool harbours mutant mtDNA. Symptoms tend to present as a single acute episode rather than as progressive disease. Mitochondrial diseases are not just genetically but also a

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clinically heterogeneous group of disorders that can present at any age and can affect any type of tissue.

Dysfunctional or redundant mitochondria are selectively degraded by a specialized form of macro-autophagy, termed mitophagy [10-12]. Mitochondrial quality control is an important aspect of cellular homeostasis, especially in post-mitotic tissues as mitophagy protects against the release of pro-apoptotic proteins, production of reactive oxygen species and ineffective generation of ATP by damaged or aged mitochondria. Regulation of the mitochondrial life cycle and the maintenance of a robust functional population within cells are achieved by a fine balance between mitochondrial turnover and biogenesis [13, 14].

2. MITOPHAGY

2.1. Mitophagy in outline

Mitophagy is one of the major mechanisms of mitochondrial quality control and the only known pathway to turn over whole mitochondrial genomes. Mitochondria could be targeted for autophagic degradation for a variety of reasons including basal turnover for recycling, starvation induced degradation, and degradation due to damage. The core autophagic machinery is evolutionarily highly conserved and the signaling cascades mediate both bulk and selective autophagic processes [12, 15]. Damaged or depolarized mitochondrial fragments are engulfed by the autophagosome, an organelle that is central to macro-autophagy. Key features of this stage are recruitment and lipidation of LC3 (microtubule-associated protein-1 light chain-3) to the autophagosome, and recognition of cargo by adapter molecules then interaction with LC3-ll (the lipidated form of LC3). Acidification and degradation of the cargo follow formation of an autolysosome by fusion with a lysosome.

2.2. The mammalian target of rapamycin

The mammalian target of rapamycin (mTOR) is a key regulator of autophagy dependent of the cell's metabolic status (Fig. 1). Under nutrient rich conditions mTOR inhibits autophagy. Association of mTOR with Raptor forms the mTORC1 complex [16]. Phosphorylation of Atg13 by mTOR prevents the assembly of the ULK1 (uncoordinated 51-like kinase 1)- Atg13-FIP200 complex [17, 18] that would activate autophagic signaling downstream of mTORC1[18, 19]. AMP-activated protein kinase (AMPK) is a component of an evolutionary conserved kinase cascade. AMPK is a sensor of cellular energy regulated by upstream kinases such as the tumor suppressor, LKB1[20]. An increase in AMP: ATP ratio triggers the AMPK signaling cascade which results in the downregulation of anabolic pathways and any non-essential ATP consuming operations while activating catabolic processes that generate ATP [21, 22]. Activation of AMPK also results in the downregulation of mTOR activity and therefore induction of autophagy [23] through the phosphorylation of ULK1 at Ser 317 and Ser 777 [11]. Egan et al. showed that the loss of AMPK or ULK1 in mammals leads to defective mitophagy and that phosphorylation of ULK1 by AMPK is an essential step [24].

2.3. Elongation of the isolation membrane and closure of the autophagosome

The class III phosphoinositide 3-kinase (PI3K) complex composed of Atg14, the class III PI3K Vps (vacuolar protein sorting) 34 and Beclin-1, is required for early steps of autophagosome nucleation and expansion of autophagosome formation [25, 26] (Fig. 2). However, it was shown that Beclin-1 independent pathways exist. Chu et al., demonstrated that 3-methyladenine (3MA) and wortmannin (PI3K inhibitors), as well as the knock-down of Beclin-1 in SH-SY5Y neuroblastoma cells, failed to decrease MPP+ (1-methyl-4-phenylpyridinium, the active metabolite of parkinsonian neurotoxin MPTP and Complex I inhibitor) induced mitophagy [27]. Two ubiquitin-like modifications, the Atg (autophagy-associated protein) 12 and LC3 (microtubule-associated protein-1 light chain-3) conjugations, are essential for membrane elongation and autophagosome formation respectively [17, 25] (Fig. 2). The C-terminal glycine of Atg12 is conjugated to an Atg5 lysine residue mediated by Atg7, an ubiquitin-activating enzyme (E1)-like enzyme [17]. LC3 is the mammalian orthologue of the yeast Atg8 protein. Upon activation of autophagy cytosolic LC3 (LC3-I) becomes conjugated to phosphatidylethanolamine via Atg7 (E1-like enzyme) and Atg3 (E2-like enzyme) [28] generating LC3-II. LC3-II can then be recruited to autophagosomes forming punctate structures. LC3-II positive autophagosomes are often used as markers to characterize autophagy [29].

2.4 Selective degradation of damaged mitochondria

The signaling pathways leading to the selective degradation of damaged mitochondria are still not completely understood. The nature of the specific molecules involved seems to be dependent on the trigger and therefore there are multiple mechanisms by which mitochondria can be targeted for degradation.

Parkin, an E3 ubiquitin ligase [30], is recruited to depolarized mitochondria by PINK1 (PTEN-induced putative kinase 1) [31]. Parkin promotes mitophagy by the ubiquitination of mitochondrial outer membrane proteins and the recruitment of ubiquitin binding autophagic components like HDAC6 and p62 [32]. Lazarou et al. investigated the involvement of autophagy receptors in mitophagy and found that NDP52 (nuclear dot protein 52 kDa) and OPTN (optineurin) are recruited to mitochondria by PINK1 where they redundantly mediate mitophagy. They are also involved in the recruitment of the upstream autophagic machinery [33].The authors also confirm previous findings that p62 is essential for the formation of perinuclear clusters of damaged mitochondria, however, dispensable for mitophagy [34, 35]. In mammals the mitophagy pathway that is essential for programmed clearance of mitochondria during erythrocyte maturation is mediated by ???? [36, 37]. Nix acts as an adaptor protein by directly binding to LC3 through its amino-terminal LC3-interacting region (LIR) [38]. Nix was also shown to contribute to mitochondrial

priming, following CCCP-induced depolarization, by controlling the mitochondrial translocation of Parkin. It is also involved in the recruitment of the autophagic machinery. Ding et al. reported that under conditions of CCCP-induced stress GFP-LC3 punctae formation required Nix and the presence of ROS in HeLa cells [39].

Mitochondrial morphology also plays an important role in the clearance of unwanted mitochondria as fragmentation is believed to be a pre-requisite for mitophagy to occur [40]. On the other hand, stress-induced mitochondrial hyperfusion, a response to selective stresses such as starvation, spares mitochondria from autophagic degradation, increases mitochondrial ATP production and promotes cell survival [41, 42]. Human sirtuins (SIRTs) target a variety of molecules in order to coordinate certain aspects of cellular metabolism [43, 44]. SIRT3 localizes to mitochondria and in addition to stimulating the transcription factor FOXO3 (forkhead box O3) [45] it also regulates mitochondrial dynamics by targeting the outer membrane fusion protein OPA1 (optic atrophy 1) [46], this provides an additional "druggable" target for modulating mitophagy.

2.5. Type 1 and type 2 mitophagy

Recently, mitophagy was classified into different categories by Lemasters based on the involvement of the PI3K complex in the formation of autophagosomes and of Pink1 and Parkin. This contrasts with the myriad of reports claiming that each of these is indispensable for autophagosome formation. Mitophagy induced by nutrient deprivation was designated as type 1 mitophagy and this is independent of PINK1 and Parkin. Autophagosome formation during type 1 mitophagy is inhibited by 3-MA and wortmannin, inhibitors of PI3K. Mitophagy induced by photodamage was referred to as type 2 mitophagy and involves PINK1 and Parkin. This was not inhibited by the above mentioned PI3K inhibitors [47].

3. AUTOPHAGY AND HUMAN DISEASE

Autophagy is essential for normal development both in humans [48] and other species [49] defects resulting in severe malformation syndromes. Further, autophagic dysfunction is associated with a number of conditions such as neurodegeneration, cancer and ageing. Monoallelic deletion of Beclin1 is a common feature of human breast, ovarian and prostate cancer [50].

Impaired mitochondrial quality control via autophagy appears to play a key role in many types of Parkinson's disease [32, 51], suggesting that mitophagy is particularly important for the affected tissue, substantia nigra. Hence mtDNA mutations accumulate in substantia nigra in many different types of Parkinson's disease [add reference Bender et al 2006 and 2008]. However, in vivo experiments have not greatly supported its importance, largely because of technical difficulties. Mitophagy is increased in cell cultures from various mitochondrial disorders such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) [52-54], complex I deficiency [55], and even in Alzheimer's. It appears to be protective in heteroplasmic disease [52] but is potentially harmful in disorders that cause excessive mitochondrial fragmentation [56]. Hence, drugs that modulate mitophagy hold promise as therapies for these diseases. Indeed, heteroplasmic cybrid cells harbouring deleterious COXI mutations underwent a shift towards wild-type mtDNA when exposed to long-term overexpression of Parkin. In parallel cytochrome c oxidase activity was also restored [57]. Indeed overexpression of Parkin is protective in many forms of Parkinson's, which could be due to its mitophagy effects [58]. It is reasonable to assume that autophagy and mitophagy could be a therapeutic target for the treatment of not just mitochondrial disease but neurodegenerative disorders and cancer as well.

4. DRUG MODULATORS OF MITOPHAGY

While there have been several scholarly reviews of drug modulators of autophagy [59], much less comparable information is available specifically targeting mitophagy. Park et al. developed a cell line in which LC3 was tagged with GFP and mitochondria with YFP and screened the LOPAC1250^{TM} Chemical Library of 1200 pharmacologically active compounds and the Prestwick Chemical library (1200 FDA approved medicines) for drugs that fragmented mitochondria and increased the number of autophagosomes [60]. These investigators identified phenanthroline, an extremely useful laboratory tool, as a candidate activator of mitophagy. However there is a large area of uncertainty regarding the use of drugs for modulating mitophagy in patients.

As mitophagy is a specific subtype of macro-autophagy that depends on the availability of autophagosomes and most of the proteins in that pathway, the autophagy findings are largely applicable. Several stages of the autophagy process are "druggable". Activation of AMPK and/or inhibition of mTORC1 by various stress signals induces activation of the ATG1–ULK1 complex and this increases autophagy. The best known such agent is probably rapamycin which stabilizes the raptor-mTOR association by forming a complex with the immunophilin FK506–binding protein of 12 kDa (FKBP12) and thereby inhibits the kinase activity of mTOR [61]. Amiodarone is another mTORC1 inhibitor that also affects calcium channels [62]. An important signaling cascade that controls mTORC1 is the PI3 kinase pathway. Class I and III PI3 kinases have opposite effects on autophagy; their activity either inhibiting (class I) or accelerating (class III) the process [59]. Autophagy can be attenuated by inhibiting class III PI3K activity with 3-methyladenine (3-MA), wortmannin and 2-(4-morpholinyl)-8-phenylchromone (LY294002). Upstream of these, AMPK activation downregulates mTOR and hence activates autophagy [23]. For example, the sugar trehalose, whose mechanism is usually held to be rescue of protein misfolding, is now known to inhibit glucose transporters in the GLUT class [63] and hence activate AMPK.

A significant group of drugs modulate mitophagy via the phosphoinositol signaling pathway, a pathway that is independent of mTORC1. For example, lithium, carbamazepine and valproic acid reduce the intracellular

inositol level and hence activate autophagy [59]. Of these lithium is known to be an inhibitor of mitophagy [64]. Lysosomal inhibitors also slow autophagy and mitophagy, the antimalarial drug, chloroquine, being a well-known example that prevents lysosomal acidification and proteolysis [65].

The specific triggers for mitophagy include impaired mitochondrial function and/or mitochondrial depolarization and mitochondrial fragmentation. These processes are closely interlinked and all are partially rescued by mitochondrial stress responses associated with mitochondrial elongation [41, 42]. For instance, impaired mitochondrial function inhibits mitochondrial fusion, and hence is frequently associated with mitochondrial fragmentation [66]. The drug, mitochondrial division inhibitor 1 (Mdivi-1) specifically inhibits the pro-fission mitochondrial protein, dynamin related protein-1 (Drp-1) [67] and this lengthens mitochondria. This drug is being investigated as a possible therapy in heart failure from multiple causes [68] its mode of action potentially involving inhibition of mitophagy.

We [56] and others [69] showed that excessive mitochondrial fragmentation associated with profound knockdown of the pro-fusion protein, OPA1, is associated with loss of mtDNA and loss of mitochondrial membrane potential. Phenanthroline activates mitophagy by impairing OPA1 processing and hence function [60]. It results in excessive fragmentation that drives mitophagy, but this is non-selective [53]. Furthermore, reduced OPA1 activity is associated with impaired activation of its GTPase domain, modulated by acetylation and rescued by the mitochondrial deacetylase SIRT3 [46]. In addition, respiratory chain inhibitors are likely to increase mitophagy by inhibiting mitochondrial fusion [66], including those that do not depolarize mitochondria, such as oligomycin. We have previously identified drugs which increase mitochondrial function in Parkin mutant cells; it will be interesting to assess the effects of these compounds on mitophagy rates in these cells [70]. In particular ursodeoxycholic acid (UDCA) which was identified in this screen and is used in the treatment of biliary cirrhosis has been shown to stop increases in LC3-II formation in the rat intestine [71].

A recent study investigates Urolithin A [72] a component of pomegranate juice, that is able to increase mitophagy in c. elegans, mice and rats. As little as 6 weeks treatment is able to improve motor performance in elderly rodents. While this is extremely promising, the increase in mitophagy is accompanied by decreased complex 1 activity and presumably compensatory increase in complex ll. The increase in mitophagy might thus be an appropriate response driven by impaired mitochondrial function, a characteristic that is likely to limit its clinical usefulness.

Given that there are no established treatments for mitochondrial disease involving drug modulators of mitophagy, despite their likely usefulness in heteroplasmic mtDNA disease, we will focus the remainder of this review on specific drugs for which clinical data are available.

5. INCREASED MITOPHAGY IN MITOCHONDRIAL DISEASE CAN BE RESCUED BY SPECIFIC THERAPIES

5.1. Coenzyme Q10

Coenzyme Q10 (CoQ10) is an essential electron and proton carrier in the mitochondrial respiratory chain (MRC), transferring electrons from complexes I and II to complex III [73]. Primary deficiencies of CoQ are rare. However, many patients undergo a therapeutic trial and anecdotally report benefit. Furthermore, an increasing number of disorders involving the mitochondrial electron transport chain (ETC) are associated with secondary CoQ10 deficiency [52, 74]. Investigation of MELAS fibroblasts from two patients harboring the m.3243G>A mtDNA mutation revealed a significant reduction in the activity of all of the mitochondrial respiratory chain complexes and additionally an over 40% reduction in CoQ10 levels when compared to controls. This secondary CoQ10 deficiency was associated with an increased degradation of mitochondria via mitophagy [52].

In a screen for effective pharmacological treatments for MELAS syndrome CoQ10 was identified as one of top candidates [75]. Furthermore, CoQ10 was able to rescue respiratory defects in yeast A14G, harbouring a mutation equivalent to the homoplasmic human m.3243A > G mutation. The effect of CoQ10 was further investigated in fibroblasts derived from a MELAS patient. CoQ10 supplementation significantly increased the proliferation rate of MELAS fibroblasts along with cellular ATP levels without any effect on control cells. Additionally, CoQ10 treatment rescued the decreased MRC activity of patient cells. Increased autophagic activity was shown in MELAS fibroblasts (using lysotracker and LC3-II western). CoQ10 treatment attenuated this increase [75].

The etiology of numerous other neurodegenerative disorders is believed to involve dysfunctional mitochondria potentially because of oxidative stress. CoQ10 has shown beneficial effects in several animal models of neurodegenerative diseases including amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease [76]. While data from clinical trials has failed to show any effect of the oxidised form of CoQ10 [77], the reduced form has shown some benefit in a small clinical trial [78]. Exogenous administration of CoQ10 was shown to be neuroprotective during iron induced mitochondrial damage and apoptosis in human dopaminergic neurons (SK-N-SH) [79].

5.2. Idebenone

Idebenone [2,3-dimethoxy- 5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone] is a synthetic analogue of coenzyme Q [80] able to scavenge a variety of free radical species as well as prevent lipid peroxidation [81]. Idebenone, along with other short-chain quinones, has a certain energy rescue capacity in case of complex I dysfunction. These compounds are able bypass complex I and by shuttling electrons directly from the cytoplasm to complex III of the mitochondrial respiratory chain to produce ATP [82].

Idebenone was reported to benefit patients with Leber's hereditary optic neuropathy (or LHON, a nonsyndromic mitochondrial optic neuropathy) [83]. In a small study it also improved respiratory function in patients with Leigh syndrome [84]. We showed that mitophagy is increased in fibroblasts from two independent families who were homoplasmic for the m.13051G>A pathogenic mtDNA mutation, in association with a Leigh –LHON phenotype with increased ROS production [55]. This missense mutation causes a Ser for Gly substitution in ND5, but without measurable complex 1 deficiency. When one patient harboring the m.13051G>A mtDNA mutation was given idebenone her vision improved. Treatment of patient derived fibroblasts harboring this mutation with idebenone increased cell viability and attenuated the previously observed increased mitophagy [55]. This reduced mitophagy suggests that the idebenone directly benefited mitochondrial function, potentially by rescuing the increased ROS production.

6. MODULATORS OF AMPK AND MITOPHAGY

6.1. Metformin

One of the most widely used orally administered treatment for type 2 diabetes is metformin. Metformin decreases hyperglycemia and has beneficial effects on circulating lipids, without affecting insulin secretion [68, 69]. It also has neuro-protective [70], cardio protective [71] and tumour-suppressive potential [85]. Metformin is a known activator of AMPK [72, 73], an effect that is required for metformin's inhibitory effect on glucose production by hepatocytes [74]. It activates autophagy by both AMPK-dependent [75] and –independent pathways [76]. As discussed above, AMPK phosphorylates ULK1 [11] thus inducing autophagy by downregulating mTOR activity [20]. This contrasts with metformin's AMPK-independent pathway for increasing autophagy by activating the sirtuin class of histone/protein deacetylases (SIRT1)- FOXO pathway, activated by increased NAD+ [76]. The same group also showed that metformin treatment facilitates Parkin-mediated type 2 mitophagy by decreasing the expression of cytosolic p53 and increasing degradation of mitofusins [77]. However, in our quantitative assay of mitophagy, combining high content fluorescence microscopy and mitochondrial DNA load, we showed that metformin strongly inhibits mitophagy under energetic stress [53]. When patient derived fibroblasts harboring the common m.3243G>A mtDNA mutation are forced to use their mitochondria by growing on glucose-free galactose-based media, the mutant mtDNA is progressively cleared by type 1 mitophagy. Treatment of these cells with metformin for 7 days decreased the clearance of mutant mtDNA compared to untreated cells [53]. This suggests that while metformin activates type 2 mitophagy and macro-autophagy, it inhibits type 1 mitophagy. It is unlikely that this inhibition of type 1 mitophagy reflects an unexpected beneficial effect of metformin on mitochondrial function that enables the cells to tolerate a higher mutant load than untreated cells, which would parallel that of idebenone (above). This is because the m.13051G>A mutant cells grew better in idebenone and we did not see a robust growth advantage to m.3243G>A in metformin under energetic stress up to 72 hours. On the other hand, metformin treatment of cells over expressing alpha synuclein (a major component in many forms of Parkinson's) has proved effective in increasing cell viability and abolished the toxic effects of alpha synucelin [86]. In addition metformin has shown to be protective in other models of Parkinson's [87, 88] and Alzheimer's [89].

6.2. AICAR

5-aminoimidazole-4-carboxamide riboside (AICAR) is transported into cells by adenosine transporters and converted by adenosine kinase into monophosphorylated nucleotide 5-aminoimidazole-4-carboxamide-1-dribofuranosyl-5-monophosphate (ZMP), an intermediate product that mimics the activating effect of AMP on the AMPK system [90]. Golubitzky et al. investigated the effect of active small molecules in patient derived fibroblasts with Complex I deficiency. Three parameters; growth, ROS production and ATP production; were measured after 72 hours treatment. The effect of small molecules was assessed in galactose media as it is void of substrates for glycolysis and cell growth is dependent on OXPHOS. The screen identified AICAR as the most favorable compound with positive effects on multiple parameters in five out of six patient derived fibroblasts. Further investigation of AICAR in a representative cell line (NDUFS2) revealed increased cell growth and mitochondrial content upon treatment [91]. While these investigators did not investigate mitochondrial morphology, mitophagy or direct phosphorylation of PGC-1α (proliferator-activated receptor gamma coactivator 1alpha) [92], any of these could contribute to the changes seen.

Indeed, increased mitochondrial content could be the result of AMPK acting via the direct phosphorylation of PGC-1α [92], a well-established regulator of mitochondrial biogenesis [93, 94]. Activation of the AMPK signalling cascade by AICAR treatment induces PGC-1α expression demonstrated by increased mRNA levels [58, 92].

AICAR treatment was also deemed beneficial to fibroblasts derived from MELAS patients with increased autophagosome accumulation. Treatment with this AMPK-activator increased cell proliferation rates, decreased ROS levels and alleviated the accumulation of autophagosomes, and the authors attributed this to increasing autophagosome turnover [95]. In neither of these studies was the effect of AICAR on mitochondrial morphology considered. Other authors showed that AICAR fragments mitochondria in glucose media [96]. We confirmed this and found that it increases the lengthening of mitochondria under energetic stress (unpublished data). As elongated mitochondria generally have increased mass and cellular ATP content with reduced mitophagy, this could be the mechanism underlying Golubitzky's findings. Neither does it directly conflict with the findings of Garrido-Maraver, who cultured their cells in much higher glucose concentrations

Duchenne muscular dystrophy (DMD) is characterized by myofiber death from apoptosis or necrosis and DMD muscles often harbor dysfunctional mitochondria [97]. Activation of the autophagy-mitophagy cascade via AICAR treatment was shown to alleviate the phenotype of the mdx mice [98] the current animal model for Duchenne muscular dystrophy (DMD) [99]. AICAR was also shown to have a strong and cancer-specific anti-growth effect which could be attributed to its affects in mitochondrial apoptotic signaling [100].

AICAR treatment of alpha synuclein over-expressing cells reduced the increase in LC3 II conversion caused by alpha synuclein toxicity and increased cell viability, having a similar effect to metformin (discussed above, [86]).

7. USING MEASUREMENTS OF MITOPHAGY AS OBJECTIVE SUPPORT FOR CLINICAL BENEFIT

Because there are no treatments for the vast majority of patients with mitochondrial disease, clinicians are frequently asked to prescribe co-factors and supplements that are unlikely to significantly benefit their patients. It is difficult to confirm improvement objectively as there are no good biomarkers and clinical scales can only confirm substantial changes. Measuring changes in physical activity requires a high level of patient compliance that may be too great for these often severely disabled patients. Hence a means of demonstrating pharmacological benefit to individual patients at the cellular level would be clinically useful. Having developed high throughput methods for measuring mitophagy in fibroblast cultures [53], our clinical experience provisionally suggests that we can use a combination of improved cell growth and reduction in mitophagy in tissue culture to support our clinical findings.

CONCLUSIONS

Even though mitophagy studies have not yet identified drugs that can be used to treat mitochondrial specific by targeting mitophagy specifically, we anticipate they will do so in the medium term. Such processes are likely to be important in drugs commonly used to treat mitochondrial patients and may well underlie the unexplained effects of small molecules such as AICAR. In the interim, mitophagy assays can be used as functional studies of cell cultures from individual patients who feel their disease is helped by specific drugs, as a supplement to clinical observation.

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