Journal of Medicine and Therapeutics

Review Article

ISSN: 2399-9799

ATAD3 and endoplasmic reticulum to mitochondria connection: A main actor and interaction regarding pathogenesis

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Abstract

Metabolic fluxes between mitochondria and endoplasmic reticulum appear today of first importance in normal and pathologic cellular physiology sustaining important regulation processes involved in mitochondrial biogenesis, homeostasis and stress responses. The basis of these interrelations is well described in yeast, the mechanism involved in higher eukaryotes and mammals is unknown. Here will be to present and emphasize on the role of a newly discovered protein, ATAD3, that may represent a molecular bridge between these compartments and essential link for associated exchanging processes.

Introduction

Mitochondria appeared in early eukaryotes, allowing thus a great multiplication of the cellular energetic power and opening gates to higher eukaryotes evolution [1].

Until human, mitochondria improved in their architecture, specificity (associated to cell differentiation), regulation pathways, biogenesis, renewal and elimination processes (mitophagy). All these progresses have allowed, step by step, a much better and sophisticated production and use of this main cellular energy source. To improve cellular efficiency, which depends on energy supply, it was needed to ameliorate mitochondria functioning and specification, as good examples with neurones (and synaptic mitochondria), muscles, spermatozoids or oocytes. More in details, mitochondria are responsible, in addition to their main ATP-producing function, of several other processes involved in diverse cellular functions. Mitochondria are thus essential for (i) lipogenesis, and reversely for beta-oxidation, (ii) membrane biogenesis and plasticity (like in producing phosphatidyl-choline for plasma membrane, or sphingosine for myelinisation), (iii) steroids synthesis (especially in gonads or cortico-surrenal glands) and of course in (iiii) apoptosis processes, calcium homeostasis and signalization. Therefore, all the different mitochondrial activities are fully integrated to the whole cellular metabolism. This integration takes place especially through functional interactions with the main mitochondria partner which is the endoplasmic reticulum (ER) [2-5]. Indeed, mitochondrial biogenesis regulation is essentially supported by to the tight metabolic relations with the ER compartment, as well as their morphology, the produced reactive oxygen species, autophagy, apoptotic processes and calcium homeostasis [6,7]. These tight molecular connections between ER and mitochondria involve the MAM (Mitochondrial Associated Membranes) from one side and specific anchoring systems from mitochondrial side. Mitochondrial functions are therefore closely linked to their intercommunication with the ER, in both senses, showing how ER and mitochondria depend of each other and how a miss connection will impact both mitochondria and ER physiology [8-11]. These interactions are therefore involved in mitochondrial biogenesis and mitochondrial mass regulation according to the cell physiology and fate, like along tissue regeneration and aging processes.

Because of the main roles of mitochondria in cellular metabolism, mitochondrial dysfunctions can be responsible of very diverse diseases, severe and even rare, that can affect all organs. Therefore, it comes easy to understand how Endoplasmic Reticulum (ER)-mitochondria interactions can be potentially involved in certain pathologies. As central actors of cellular metabolism, the deficient physiology of mitochondria consecutively initiates various and numerous pathologies including neuropathies, myopathies like cardiopathies and ataxia, diabetes and cancers. Involved also in steroidogenesis, mitochondrial miss of function can also cause hormonal disorders and sterility. Then, any disorders in ER-M interactions may cause mitochondrial defects and related pathologies.

Neuropathies and ER-M contact sites

Mitochondria are of course the main cellular source of ATP, produced by the coupled activities of the Krebs cycle, the respiration chain and the F1F0 ATP synthase. Also, mitochondria are the site for *de novo* lipid synthesis, from Krebs cycle's citrate and Acetyl CoA "leakage" and lipid storage, as for lipid consumption by the β-oxidation. Mitochondria are therefore the crosstalk centre for bioenergetic regulations. For this reason, and because of their role in lipid metabolism, any mitochondrial miss function may have a direct impact on cell capacity to ensure their functions. Then it is not surprising to discover that many pathologies like myo- and neuro-

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Received: February 25, 2019; **Accepted:** March 11, 2019; **Published:** March 18, 2019

pathies are mitochondria-linked and involve ER-M interaction defects [7,12].

A significant disease, of modern times, Alzeimer disease, involves demyelination and degeneration of hippocampal and cortical neurons associated with intracellular accumulation of phosphorylated Tau and extracellular accumulation of β-amyloid peptides. The genetic causes can be either mutations of the precursor protein or of Presenilin which is involved in the processing of amyloid peptides and is enriched at ER-M contact sites [13]. In both patients and animal models, an increase of ER-M contacts was observed, associated with increase calcium flux and phospholipid biosynthesis [14,15]. Among the several hypothesis attempting to explain the pathogenesis, mitochondria dysfunctions have been shown recently to induce activation of sphingomyelinase, by oxidative stress and H_2O_2 over-production, provoking there and consecutively a demyelination process [16]. However, other hypothesis also exists to explain how and why ER-M contact sites and mitochondrial activities can be involved in the disease, but defective or abnormal ER-M interrelations can be clearly a cause for the disease [12].

Similarly, Parkinson disease, which is characterized by the degeneration of dopaminergic neurons, involves modifications of ER-M contact sites, implicating α-synuclein, DJ-1, Parkin, Mfn2 and PINK [17-20], and implying also BECN1 during mitophagy [21]. α-synuclein is found abundant at ER-M contact sites and its mutation induces a parkinsonism associated to decreased ER-M contact sites and of phospholipid synthesis. Parkin mutations are the main cause for Parkinson disease as Parkin, as PINK and BECN1 which are involved in mitophagy as well as in mitochondrial biogenesis, fission and transport. All these processes occur at ER-M contact sites. Indeed, increased contacts were observed in fibroblasts from patient with Parkin mutations so we can guess how much the disturbance of these sites could be linked to Parkinson disease [22,23].

Similarly, ER-M dysfunctions are also revealed in Amyotrophic lateral schlerosis and Huntington disease as in neuroinflammation [7,12]. As another example of ER-M dysfunction in neuropathies is a more recent case report on SERAC1 mutation related to MEGDEL syndrome [24,25]. This lipase-domain containing protein localizes at ER-M contact sites and may act by remodelling phosphatidylglycerol.

Finally, the best-case study to point again the importance of ER-M contacts in neuronal pathophysiology is MFN2 (Mitofusine 2). This mitochondrial protein involved in ER-M tethering is, under mutated form, responsible of the Charcot-Marie-Tooth neuropathic disease type 2A [26]. MFN2 contributes mainly in ER-M contact sites by creating a GTPase-dependent structure involving coiled-coil domain and supra-structure oligomerization that are implicated in mitochondrial fusion and ER-M interaction. Mutations in the GTPase, coiled-coil or conserved R3 domains induce severe neuropathies.

Mitochondria are also organelles involved in lipid and phospholipid synthesis like for cardiolipin, phosphatidyl Ethanolamine, phosphatidyl Serine, phosphatidyl Choline as for sphingomyelin synthesis, and for that, the ER is providing the required lipid precursors to the mitochondria [27-29]. The ER provides also mitochondria with glycosphingolipids for which the transfer may occurs also at MAM [30]. Therefore, any disturbance in the lipid fluxes between ER and mitochondria may have an important effect on lipid constitution/equilibrium within the cell and the mitochondria and may impact drastically mitochondrial and cell activities. Concerning glial cells, a deficient lipid metabolism of mitochondria may contribute also in demyelination diseases or other unclassified neuropathies like in disease involving membrane dysfunction.

Myopathies and ER-M contact sites

As other high energy consuming organs, the muscles, heart and skeletal muscles, can also suffer intensively from mitochondrial miss-functions. Therefore, improper ER-M contact sites in muscles could be the cause of certain myopathies.

During muscle contraction, the ryanodine receptor permits the transfer of calcium from the ER (sarcoplasmic reticulum) to the mitochondria, to increase ATP production. The ryanodine receptor is also involved during muscle differentiation. Therefore, it is not surprising that disturbed ryanodine receptor functioning is related to myopathies. Indeed, ryanodine receptor mutation were observed in patients with central core disease and malignant hyperthermia [31,32]. Theses mutations induce alteration of calcium signalling and damaged mitochondria.

Calcium regulation is also modified in many muscular dystrophies [33]. As mitochondria play a significant role in calcium signalling and balancing, by an interplay with the endoplasmic reticulum involving the MAM [34], it is not so surprising to observe that a mutation of a regulator for the mitochondrial calcium uniporter induces pathological features like mitochondrial myopathies [35]. Then, targeting ER-M contact sites related to calcium balancing may be a solution to improve muscle function of patients [33,36].

We guess that other muscular diseases will be found to reside in a miss functioning of ER-M contact sites but since this research area is still new, cause-effect relations between ER-M dysfunction and myopathies are still under investigations.

If we do not know today if these regulations are the cause or the consequence of the associated diseases, ER-M contact sites seem however to be of first importance in different and various neurological and muscle disorders.

Obesity, diabetes, hepatic diseases and ER-M contact sites

ER-M contact sites have been shown to be modulated by diets or nutritional transitions [37], and especially in the liver [38], and they are considered today as metabolic sensor site. Adaptations may occur during the switch between glucose oxidation and lipid oxidation, which depends of nutrition. Therefore, it is not surprising to observe that ER-M sites react to nutrition signals by the action of ER-stress system [39].

Therefore, metabolic diseases are also linked to mitochondrial activities and therefore to ER-M contact sites status. Obesity and diabetes have been also shown to involve ER-M contact sites regulations [40-42], and ER-stress activations were observed in several models for obesity and diabetes as well as in humans, and in different organs like the liver, the adipose tissue and skeletal muscle [43-45]. Reorganization of ER-M contact sites was correlated there with mitochondrial calcium overload, reduced oxidative capacities and increased oxidative stress. Also, molecules reducing ER-stress ameliorate the physiology of obese mice and humans [46,47]. The same observations were made in liver, in alcoholic and non-alcoholic diseases where ER-M contact sites are regulated and where active molecules can also modulate ER-M contact sites and produce beneficial effects [38].

Sterility and ER-M contact sites

Mitochondria are also main actors in steroidogenesis [48,49]. This role is first based on ER-M contact sites that promotes a cholesterol

flux between ER and mitochondria where steroidogenesis takes place [50]. The transport of cholesterol is the rate-limiting step of steroidogenesis. It was demonstrated that the cholesterol transport activity, which depends of protein synthesis, is ensured by the protein StAR (steroidogenic acute regulatory protein), at ER-M contact sites, and that hormonal stimulation promotes both the cholesterol transport and the number of contacts [51]. StAR localizes in mitochondria, at the outer mitochondrial membrane and is associated to partner in the inner mitochondrial membrane and matrix protein [50]. Mutation in StAR gene cause congenital lipoid adrenal hyperplasia [52], a disease characterized by defective steroidogenesis. Mutations in any of the proteins involved in the cholesterol transport process may have a strong impact in steroid production, like for testosterone production and might induce therefore reduced fertility.

Cancer and ER-M contact sites

Many cancers are associated with increased cholesterol flux and ER-M contact sites. A one marker of breast cancer is TSPO (Translocator Protein), which belong to the cholesterol transport complex [53]. In other cancers, involving PML-driven malignant transformation, it has been observed that PML (promyelocytic leukaemia) partially localizes to ER-M contact site [54] and modulates Akt-dependent IP3R phosphorylation by the action of phosphatase 2A. The phosphorylation state of IP3R determines the amount of calcium driven from ER to mitochondria and is involved in apoptotic processes.

PTEN is another oncogene that can modulate Akt/IP3R signalling at the ER-M contact sites and that links cancer development and ER-M status [55]. Indeed, mTORC2 can localize to ER-M contact sites in growth factor stimulated cells in order to sense nutrient availability and metabolism. There, mTOTRC2 promotes the interaction between Grp75 and IP3R, regulates ATP production and is associated with increased phosphorylation of IP3R by Akt.

The famous tumour-suppressor protein p^{53} has also been reported to localize at ER-M contact sites and influence calcium signalling during cell stress [56]. Since most cancers have one or two mutated p^{53}, which induce resistance to treatments, overexpression of SERCA or MCU can overcome this phenotype and sensitize the tumour cells to treatments [57].

Another example of improper ER-M contact sites involvement in cancer is the case study of Bcl-2. It has been shown recently that Bcl-2 inhibitor (ABT737) reverses cisplatin resistance by regulating ER-M calcium signalling [58]. Indeed, ABT737 treatment of ovarian cancer cells increases ER-M contact sites and increases cisplatin induced apoptosis. ER-M contact sites appears therefore as targets for anti-cancer therapy.

Mfn2 is also a cancer-associated gene. If overexpression of Mfn2 have been related to poor prognostic in gastric cancer [59], experiments have proved that Mfn2 presents tumour suppressor activity [60]. Both results are not contradictive, as Mfn2 overexpression in cancer can be of a mutated form, like for p53 in many tumour types.

Finally, TpM (trichioplein/mitostatin), a cytoskeleton binding protein under expressed in breast, prostate and bladder cancers was shown to play a role at ER-M contact sites and calcium signalling by interacting with MFN2 [61].

To conclude about ER-M contact sites and pathogenesis is to add finally that Ischemy-reperfusion contexts also implicate ER-M contact sites regulation, and molecules that can decrease ER-M contacts at reperfusion can protect cardiomyocytes against injuries and improve the success of heart vessels surgeries [62].

In yeast, the molecular organization of ER-M contact sites are today well described and called ERMES [5,9]. They involve Mdm1 Mdm10 Mdm12 Mdm34 and Mdm32.

However, in higher eukaryotes, where cholesterol takes place rather than ergosterol in yeast, and where mitochondrial mobility becomes tubulin-based, the protein complex involved in contact sites is still not known precisely but may involve a recently discovered protein, ATAD3 (ATPase family AAA Domain-containing protein 3).

ATAD3 and ER-M contact sites

The "mitochondrial mass" and its regulation is today a new concept in Cell Biology, Physiology and Medicine, and we are now considering that the mitochondrial "patrimoine" is a highly dynamic system that evolve all lifelong. Also, these regulations involve necessarily ER-M contact sites.

In higher eukaryotes, mitochondria can adapt, or not, at short, mid and long terms. Short terms adaptations are linked to short term signalizations, like post-translational regulations, while mid and long terms regulations concern translational and transcriptional levels. Increased feeding for example, or increased brain and muscular activities will induce mitochondrial biogenesis, mitochondrial mass increase, and this occurs at different regulation level and all along cell and body lives. At birth for example, the mitochondrial mass is developing a lot with breathing start, and thereafter at all phases and places involving cellular proliferation and differentiation (as the specific mitochondrial proteomic "editing" that occurs upon differentiation).

At the opposite, pathologies, aging, inactivity or nutritional starvation involved a general stress-response process that will lead to mitochondrial mass reduction and mitophagy.

The endoplasmic reticulum is in fact the first and major "associate" for the mitochondrial biogenesis. The ER provides mitochondria with several essential biomolecules like phosphatidyl-serine, cholesterol, phosphatidic acid, calcium, iron, zinc, amino-acids and probably nuclear tRNA and neo-synthesised, nuclear-encoded proteins [8,29,63]. Today we believe therefore that ER-M contact sites, via cholesterol raft and imported proteins system are crucial for mitochondrial biogenesis/renewal [27].

The newly identified ATAD3 might be a mark of this steps for mitochondrial mass adaptation and ER-M interactions improvements along evolution.

ATAD3 is encoded by an immediate vital gene, necessary for development as soon as embryonic implantation stage [64], when the embryo starts to produce its "own", zygotic, mitochondria for first time. Along evolution, ATAD3 appears after yeast, in higher and pluricellular eukaryotic organisms, notably when cholesterol starts to take a place in membrane constitution and metabolism.

ATAD3 is an ATPase located in the inner mitochondrial membrane and is fully ubiquitous [65-67]. Then, its role can be important, essential, in all organs. Even if inserted through the inner mitochondrial membrane, ATAD3 is however suspected to interact with the outer membrane too, as even with endoplasmic reticulum-located partners. In more details ATAD3 has been shown to interact molecularly with Mfn2 and Drp1 [68], and functionally, as Drp1 and ATAD3 work in concert to drive mitochondrial biogenesis and fragmentation [69,70].

Also, ATAD3 interacts with WASF3 and GRP78 and this interaction may be involved during cancerogenesis [71]. Having its ATPase domain in the matrix [72], ATAD3 can constitute a bioenergetic sensor able to create a physical link-docking with the ER depending of ATP synthesis [65,69]. ATAD3 is also involved in stress-responses [71] and since ATAD3 interacts with S100B in a calcium-dependent manner, ATAD3 is also concerned by calcium signalling and regulation [69].

ATAD3 gene appeared as a single gene in pluricellular organisms, until rodents. In primates surprisingly, two others homologous genes appeared, probably by duplication. The three *ATAD3* genes, called therefore *ATAD3A*, *B* and *C* (where *ATAD3A* is the ancestral form of *ATAD3* gene), present significant molecular differences (especially ATAD3C that does not possess large N- and C-terminal part) [73]. ATAD3A and ATAD3B were only studied yet, and the functional and molecular differences between both is especially the relative abundance and the tissue-specific expression differences. ATAD3A is expressed in all organs studied until now, and is expressed all life long, in embryo and adult. ATAD3B itself is expressed specifically in embryonic cells, in adult pituitary gland, and notably in tumours [74,67,73]. These differences are related to gene promoter particularities. Also, other shorter isoforms, produced by alternative splicing and translation, present specific patterns of expression [73].

Other differences between ATAD3A and ATAD3B are related to their phosphorylation sites and membrane structural insertion, but none of these particularities have today been explained [75].

If the precise function of ATAD3 is still not known today, the sure is that its expression level monitors mitochondrial biogenesis, as to be vital at very early stages of animal development. The first work concluding this is the ATAD3 Knock Down in D. melanogaster and C. elegans [76,77] and the ATAD3 Knock Out in mouse [64].

In C. elegans, ATAD3-siRNA-based K.D. induces an arrest in the development, at L1 larvae stage. Indeed, the ATAD3 K.D. larva fed themselves normally but failed to accumulate lipids in their adipocyte-like intestinal tissue. The authors showed indeed that the pre-required mitochondrial biogenesis does not occur efficiently in these cells, avoiding proper lipids storage [77].

In mouse, more recently, it has been shown that ATAD3 K.O. induces an early arrest of embryo development, at day 4 [64]. ATAD3-/- early embryos appeared unable to develop their trophoblast and to implant onto the uterine mucosa. This phase corresponds to the first zygotic mitochondrial biogenesis. Even if ATAD3 is vital, the ATAD3+/- mice are viable under conventional breeding and did not show evident signs for any deficiencies. However, we may believe that allelic compensation may not function in all the situations and that haplo-insufficiencies could be revealed.

The most recent studies have lightened up a new and very interesting hypothesis developed by Papadopoulos and colleagues and deeply analysed [78-80]. They observed that ATAD3 may function as a part of a cholesterol-transporter, transferring cholesterol from the endoplasmic reticulum into the mitochondria, especially to provide lipids for mitochondrial-based steroids synthesis. We hypothesize ourselves that ATAD3 can contribute to drive the import of some nuclear-encoded mitochondrial proteins [70]. In fact, both hypotheses can fit and be joined together since we believe that RE exports (lipids and proteins), which support mitochondrial biogenesis, could occur as lipid-raft systems [81,27,80].

Whatever hypothesis, we are today at a time to be certain that ATAD3 insures a major function in mitochondrial biogenesis like in correct proliferation and differentiation, by its contribution to ER-M contact sites and related transfers.

As a strong demonstration for this, recent studies have highlighted the major role of ATAD3 and the impact of its miss of function. Indeed, single or bi-allelic ATAD3 mutation or deletion have been reported this and last years to induce dramatic neuro- and myopathies.

ATAD3 and myopathies/neuropathies

As expected, researches from the last two years highlighted this important role of ATAD3 in mitochondrial status and pathogenesis. Three important studies have described that ATAD3A/B mutations are associated with severe neuro-myopathies in humans [82-84]. Lupski's team identified a recurrent de novo *ATAD3A* mutation in few unrelated individuals with a phenotype of developmental delay, hypotonia, optic atrophy, axonal neuropathy, and hypertrophic cardiomyopathy, as seen with *MFN2, OPA1, DNM1L* and *STAT2* mutations [84]. They described two families with biallelic mutations of *ATAD3A* and biallelic deletions issued from a nonallelic homologous recombination between *ATAD3A* and *ATAD3B and ATAD3C.* They found that these mutations induce in drosophila a dramatic decrease of mitochondrial mass, a modified mitochondrial morphology and an increased autophagy. Fibroblasts from patient exhibited also increased mitophagy. The same team reported these years a new set of pathological cases that links again *ATAD3* mutations and other diseases for which no molecular diagnosis has been yet achieved as a clinical genomic diagnosis [82]. The team of H. Tyynismaa also described and linked *ATAD3* mutations to myopathies as spastic paraplegia [83]. They identified a dominantly inherited heterozygous mutation in *ATAD3A* in an individual with hereditary spastic paraplegia and axonal neuropathy and his children with dyskinetic cerebral palsy, both diseases installed in childhood. They also showed that overexpression of the mutant ATAD3A induces fragmentation of the mitochondrial network in patient fibroblasts and neurons derived from their pluripotent stem cells. Mutations in *ATAD3A* is observed here also to be dominantly inherited. Also, more recently, a third study elucidated the genetic basis of cerebellar atrophy linked to ATAD3A/B deletion [85], stressing how much ATAD3 mutation can be deleterious.

In all case studies, the mutation affects the Walker A motif, responsible for ATP binding in the AAA module of ATAD3A. This mutation is believed to act as a dominant-negative because ATAD3 proteins may function as hexamers and mutant can compete negatively in the constitution of fully active polymers.

ATAD3A variations/mutations represent therefore an additional link between mitochondrial dynamics and recognizable neurological and muscular syndromes, as expected. This finding extends therefore the group of mitochondrial inner membrane AAA proteins associated with spasticity.

ATAD3 and Sterility

Since ATAD3 is involved in ER-M contact sites and cholesterol transport, it is not surprising to find that ATAD3 controls steroids production in adrenocortical and Leydig cells [79,78]. Therefore, is to hypothesize that ATAD3 miss function/mutation can be the cause of certain infertility in males and females. Investigation of ATAD3 status in patient suffering of infecundity could be an interesting program of research.

ATAD3 and cancer

More importantly is the involvement of ATAD3 in cancer occurrence and development. Indeed, ATAD3 studies started with the

observation of its overexpression in cancer [86] and that ATAD3 gene is a target gene of c-MYC [87]. This observation has been made in head and neck cancers, as in lung, uterine, glial, prostate and breast cancers [74,88-90]. Furthermore, ATAD3A/B expression correlates with chemoresistance and radioresistance of the tumours [74,91,92] as well as in metastasis activities through molecular interaction with GRP78 and modulation of WASF3 function [71]. Moreover, diminishing ATAD3A/B expression levels induces reversion of the transformed phenotype of glioma *in vitro* [74]. Therefore, decreasing ATAD3 activity is definitively a pertinent target for reversion of transformed phenotypes and limitation of tumour growth and invasion. Also, ATAD3 expression level detection on biopsies is a potential indicator for tumour classification and prognosis at hospital [75].

Before to conclude is to add, as we have seen before, that ER-M miss-regulations are involved in metabolic diseases like obesity, diabetes, or in fertility. It is therefore very attractive to see if any of these diseases can be cause by ATAD3 miss of function.

Conclusion

Along evolution, mitochondria physiology improved, and especially regarding the tight and important relation with the ER that became more and more complex and regulated.

Indeed, ER-M contact sites may support a coupled functioning between mtDNA control (replication/transcription/translation), translation and import of nuclear-encoded mitochondrial proteins, lipid fluxes and bioenergetic level. Therefore, an involvement of ATAD3 as a new importing raft system might be a good hypothetical model that could explain and support all these mechanisms.

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