Chapter 14
ATAD3A on the Path to Cancer

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Abstract The ATPase family AAA-domain containing protein 3A (ATAD3A), a nuclear-encoded mitochondrial enzyme, is involved in diverse cellular processes, including mitochondrial dynamics, cell death and cholesterol metabolism. Overexpression and/or mutation of the ATAD3A gene have been observed in different types of cancer, associated with cancer development and progression. The dysregulated ATAD3A acts as a broker of a mitochondria-endoplasmic reticulum connection in cancer cells, and inhibition of this enzyme leads to tumor repression and enhanced sensitivity to chemotherapy and radiation. As such, ATAD3A is a promising drug target in cancer treatment.

Keywords ATAD3A · Mitochondria · Oncogene · Drug target · Cancer treatment

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14.1 Introduction

The AAA ATPase is a large and functionally diverse superfamily of NTPases that are characterized by a conserved AAA+ module [1, 2]. More than 53 members have been identified in this superfamily, and these proteins mainly localize to mitochondria and play diverse roles in cellular processes, including protein degradation, membrane fusion, peroxisome biogenesis, cytochrome assembly, regulation of enzymatic activity microtubule severing, helicase activity and gene expression [3]. ATPase family AAA domain-containing protein 3 (ATAD3), an ATPase localized in the mitochondrial inner membrane (MIM), was discovered as a novel molecular target of c-Myc [4, 5]. In primates and humans, ATAD3A, ATAD3B and ATAD3C are three tandemly repeated genes of ATAD3, essential for the development several kinds of organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster* and *Mus musculu*s [6–8]. ATAD3A functions as a critical regulator of lipid and fatty acid metabolism, contributing to metabolic diseases (e.g. cancer) involving disturbances in energy production and anabolism tightly related with mitochondria [6, 9, 10]. Here we summarize the biologic role of ATAD3A in the regulation of mitochondria-related metabolism, autophagy and apoptosis, communication between the endoplasmic reticulum (ER) and mitochondria in cancer development and treatments. Specific challenges in current research and future prospects are also discussed.

14.2 The Structural Characteristics and Modifications of ATAD3A

Compared with other types of organisms, primates including humans have three tandemly-repeated genes of ATAD3, ATATD3A, ATAD3B and ATAD3C, which are located in chromosome 1 at locus p36.33. ATAD3A is believed to be the ancestral gene, which was duplicated and mutated to generate the other two paralogs, ATAD3B and ATAD3C [11]. ATAD3A has three predicated transcript variants. Isoform 2 of ATAD3A acts as the main one being 586 amino acids (aa) in length, shorter than isoform 1, which is 634 aas and longer than isoform 3 at 507 aas [12]. The genetic structure and protein sequence of the ATAD3B is similar to ATAD3A [11]. Compared with its ancestor, ATAD3C is mutated on the translation initiation site. There is 87% identity in the similar region of the ATAD3C transcript and ATAD3A transcript 2 [11].

The putative promoter of ATAD3A contains numerous regulatory elements linked to cell growth, including CCAAT/enhancer binding protein (C/EBP), core binding factor (CBF), iron regulatory protein (IRP), cAMP response element binding protein (CREB), erythroid transcription factor (GATA-1), OCTAM-binding protein (Oct-1) and transcription factor II D (TFIID) [11]. The expression of ATAD3A is ubiquitous and has been detected in all tissues and cell lines tested, with

higher expression in the brain/cerebellum, heart, liver and kidney [12]. ATAD3B is expressed in human astrocytoma cell lines, in embryonic tissues and in the pituitary gland and heart [13, 14]. However, there is no available study regardingt ATAD3C expression.

ATAD3A can be divided into two parts, the N and C terminals. The N-terminal portion constitutes the specific domain of ATAD3A. It contains a flexible region rich in proline residues (aas 18–27), transmembrane domain 1 (TM1, aas 225–242), transmembrane domain 2 (TM2, aas 247–264), and two coiled-coil regions (CC1, aas 85–115; CC2, aas 180–220), offering an interaction zone which could be important for the oligomerization of ATAD3A monomers and/or for interaction with partners [15–17] (Fig. 14.1). The C-terminal part of the protein constitutes the ATPase domain, which is involved in the binding and hydrolysis of ATP, a second region of homology (SRH) motif, sensor I, sensor II, arginine (Arg) finger, and Walker A (WA) and Walker B (WB) sites [11, 16]. The N-terminal domain (aas 1–245) is positioned in the MIM and interacts with the mitochondrial outer membrane (MOM). The first 50 aas of the N-terminus are located close the mitochondrial surface. The topology of ATAD3 was analyzed and confirmed by trypsin digestion, which showed that the C-terminal domain is localized in matrix compartment [15, 18].

ATAD3A has been reported as a specific binding target of S100B, one member of the S100 family of EF-hand calcium binding proteins. S100B could assist the newly synthesized ATAD3A protein to fold and locate in the mitochondria [19]. ATAD3A contains many putative phosphorylation sites, including those for PKC, PKA, GSK3, CDC2, CKI, CKII, DNAPK, RSK, Cdk5, PKG and p38MAPK and INSR [11]. The most probable kinase for ATAD3A is protein kinase C at the possible phosphorylation sites Thr335, Thr338, Thr359 [18] (Fig. 14.1). The regulation of ATAD3A after phosphorylation and stabilization by PKC has been confirmed [20]. The expression of ATAD3A was found to be decreased by the pan-PKC inhibitor Calphostin C, and increased by ectopic expression of PKC isozymes [20].

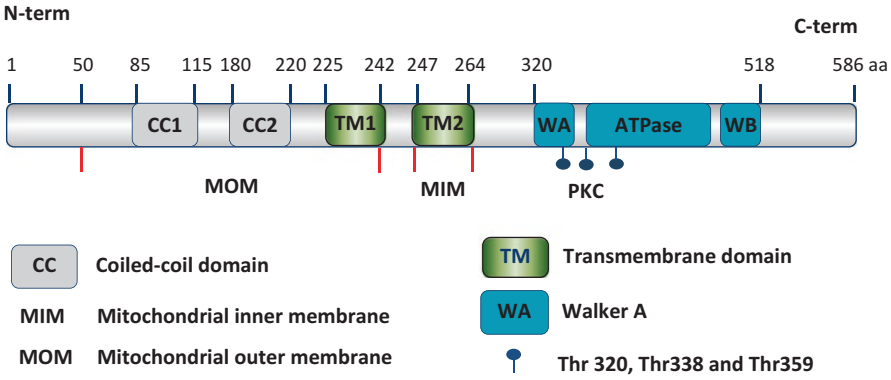

Fig. 14.1 The molecular ATAD3A structure with the main domains. The main domains and PKC phosphorylation sites of ATAD3A (isoform 2 for example) are exhibited

14.3 ATAD3A Functions as a Mitochondria Protein

It has been showed that ATAD3 plays an important role in mitochondrial dynamics that is mediated by fission and fusion of these organelles [15]. Knockdown of ATAD3A by RNAi in HeLa and lung cancer cells showed increased mitochondrial fragmentation and a decreased co-localization of mitochondria and the ER [15, 20]. The interactions of ATAD3A with mitochondrial fission (Drp1) and fusion (mitofusins, OPA1) proteins have been identified [6, 15, 18]. Mitochondrial fragmentation was also observed following over-expression of a deficient Walker A or mutant ATAD3A [15, 21]. Knockdown of Drp1 by siRNA in U373 cells inhibited mitochondrial fragmentation induced by mutant ATAD3A over-expression. As such, ATAD3A is required for the maintenance of mitochondrial integrity in mammalian cells. Mitochondrial DNA (mtDNA) molecules are usually clustered and attached on the inner mitochondrial membrane in nucleoprotein complexes called nucleoids [22]. The nucleoproteins mediating the interaction with MIM are important in mtDNA organization and distribution. ATAD3 appeared in HeLa cell mitochondrial nucleopro the possible binding to the D-loop of mtDNA [23, 24]. Gene silencing of ATAD3 by RNAi altered the structure of mitochondrial nucleoids and induced the dissociation of mitochondrial DNA fragments [25]. The nucleoid size is inversely correlated with ATAD3A/ATAD3B expression, although nucleoid number is tightly related with ATAD3 expression. Fibroblasts from human individuals with an ATAD3 deletion (chimeric ATAD3A/ATAD3B fusion gene) display mtDNA abnormalities [10].

14.4 The Role of ATAD3A in Lipogenesis

Mitochondria are important organelles for lipid metabolism. Knockdown of ATAD3 in *Caenorhabditis elegans* affects the intestinal fat tissue and the gonads at a time when these cells initiate mitochondrial biogenesis and lipogenesis [6]. ATAD3 is also a limiting factor for the processes of adipogenesis and lipogenesis in mouse adipocyte model 3T3-L1 cells [9]. Downregulation of ATAD3 inhibited adipogenesis, lipogenesis and impeded over-expression of many mitochondrial proteins. These phenotypes were rescued after ATAD3 re-expression. Lipogenesis was increased by over-expression of ATAD3 and inhibited by a dominant-negative mutant. Moreover, downregulation of lipogenesis by knockdown of ATAD3 was not related with insulin signaling, but linked to another mitochondrial protein, Drp1 [9]. ATAD3 has also been found to enhance hormonal-induced steroidogenesis in MA-10 mouse tumor Leydig cells [26]. Interestingly, ATAD3A has been identified in the mitochondrial-ER contact site formation, where it was found to transfer and metabolize cholesterol from the ER into mitochondria for steroidogenesis [15, 26, 27] (Fig. 14.2). Cholesterol can bind the translocator protein (TSPO) monomer, and with hormone stimulation, polymerized TSPO associates with the protein complex

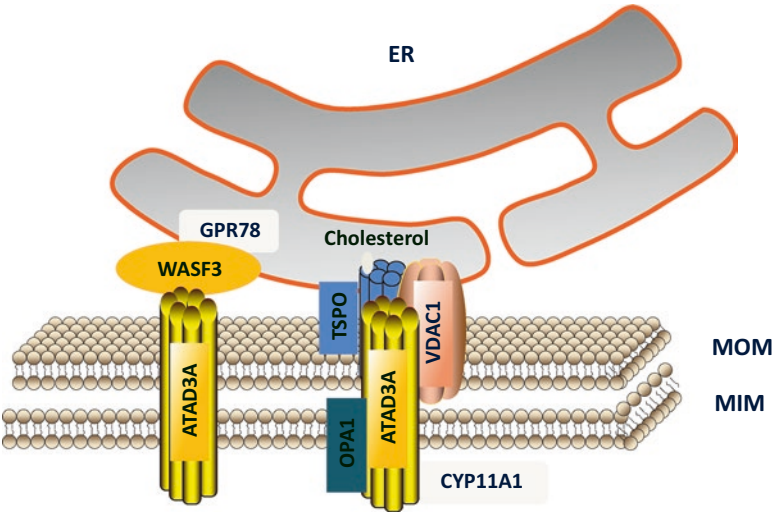

Fig. 14.2 ATAD3A interacts with WASF3 and other proteins for cholesterol import at the ER-mitochondria contacts. ATAD3A/WASF3/GPR78 protein complex and ATAD3A/TSPO/VDAC1 are the two main protein complexes are currently found at the contact sites of the mitochondria and ER

and voltage-dependent anion channel (VDAC1). Cholesterol bound to TSPO is translocated to the MIM through the formation of a contact site by VDAC1 and ATAD3A. Then, cholesterol is metabolized by CYP11A1 in the protein complex [27] (Fig. 14.2). The N-terminus of ATAD3A containing 50 aas in the MOM is associated with ER. Deletion of the ATAD3A N-terminus resulted in the reduction of hormone-stimulated progesterone biosynthesis [26]. The important role of ATAD3A in cholesterol metabolism has been linked to human disease recently. Deletion in the ATAD3 locus that generates the chimeric ATAD3A/ATAD3B fusion gene causes fatal congenital pontocerebellar hypoplasia in humans [10]. Fibroblasts from these individuals display altered cholesterol metabolism and mtDNA abnormalities. Moreover, cholesterol homeostasis disturbed by drugs can cause mitochondrial DNA disorganization in control cells [10].

14.5 The Role of ATAD3A in Development

ATAD3A is essential for the development of multicellular organism. Silenced ATAD3A by RNAi can cause severe defects in the worm *Caenorhabditis elegans*, including early larval arrest, gonadal dysfunction and embryonic lethality [6]. The indispensable role of ATAD3A in the development *Drosophila melanogaster* has also been confirmed. There is a high degree of similarity (70%) between the *Drosophila melanogaster* ATAD3A (dATAD3A) ortholog and human ATAD3A

[15]. Homozygous mutants of dATAD3A showed growth arrest during larval development [15]. Functional genomic studies identified the dATAD3A ortholog as a major gene positively regulated by the target of rapamycin (TOR) signaling pathway involved in cell growth and division [28]. ATAD3 deficient mouse embryos died around embryonic day 7.5 (E7.5) due to growth retardation and defective development of the trophoblast lineage immediately after implantation into the uterus [8]. This was caused by disrupting mitochondrial biogenesis and ATP production in mouse embryo. Fatal congenital pontocerebellar hypoplasia has been observed in humans with the deletion in ATAD3 locus that generates chimeric ATAD3A/ATAD3B fusion genes. In addition, rearrangements of the ATAD3 family genes can lead to late-onset encephalopathy [10].

14.6 The Role of ATAD3A in Human Diseases

14.6.1 ATAD3A in Cancer

Over-expressed ATAD3A has been found in different kinds of cancer, including head and neck cancer, gliomas, uterine cervical cancer, lung adenocarcinomas, prostate cancer and breast cancer [13, 18, 20, 29–32]. The gene alterations of ATAD3A, including those caused by mutation and amplification, are rare in different types of cancer. Elevated ATAD3A seems not to be directly related to gene alteration but rather to transcription and modification. ATAD3A was identified as one of the tumor antigens with strong overexpression in head and neck cancer [32]. It was also identified as one of cell surface antigens in acute myeloid leukemia (AML) [33]. Elevated ATAD3A expression increases glioma cell proliferation, and is tightly related with the growth and invasive potential of prostate cancer cells [13, 30]. ATAD3A was detected with a high expression rate in prostate cancer tissue compared with normal to non-tumor prostate epithelium (NTPE) or benign hypertrophic prostate epithelia (BHPE). Moreover, the ATAD3A expression levels were associated with disease status, tumor grade, serum prostate-specific antigen (PSA) level, lymphovascular infiltration as well as expression of the androgen receptor (AR) in prostate cancer [30]. ATAD3A overexpression was also detected in uterine cervical cancer patients [29]. A significant correlation has been found between ATAD3A expression and the presence of hrHPV (high-risk human papillomavirus), disease stage, lymph node involvement, and patient survival in uterine cervical cancer [29]. Additionally, silencing of the hrHPV E6/E7 expression decreased ATAD3A expression and uterine cervical cancer cell survival, which may be associated with p53 and pRB [34]. Mechanistic studies showed that HPV infection may stabilize ATAD3A expression to inhibit cell autophagy and apoptosis as well as increase chemotherapy drug resistance in uterine cervical cancer [29]. Elevated ATAD3A has been found in lung adenocarcinoma (LADC) cell lines and patient samples, and metastatic lymph nodes [18]. Moreover, LADC patients with over-expressed

ATAD3A have a high risk of recurrence and short time of survival [18]. Our previous study revealed that ATAD3A increased breast cancer metastasis, accompanied with GPR78 through the metastasis promoter WASF3 [31]. WASF3 is a member of the Wiskott-Aldridge family of proteins that are involved in actin polymerization tightly related with cell movement and invasion [31, 35]. ATAD3A interacts with WASF3/GPR78 at the ER-mitochondrial contact site (Fig. 14.2). Knockdown of ATAD3A showed reduction of cancer cell anchorage-independent growth and invasion in breast cancer MDA-MB-231 and colon cancer SW620 cells [31]. Silencing ATAD3A also suppressed breast tumor growth and metastasis in an orthotopic mouse model. Compared with the tumors derived by knockdown control breast cancer cells, the tumors generated by ATAD3A knockdown breast cancer cells were markedly smaller and showed significantly reduced expression of CD31, the marker for the tumor vasculature. Reduced metastases were also observed in lungs of the mice receiving ATAD3A knockdown breast cancer cells [31].

ATAD3A was identified as the most sensitive gene related with growth in the inhibition of the TOR pathway by rapamycin in *Drosophila melanogaster* [28]. The potential of a hyperactive mammalian TOR-ATAD3A axis needs to be confirmed and elucidated in cancer cells. Recently, a cell adhesion molecule, tumor suppressor Fat 1 protein (FAT1) was found to control cell growth and mitochondria function. ATAD3A is one of the interactors between FAT1 and mitochondria [36]. The mechanisms involved in ATAD3A-mediated cancer cell proliferation and survival are still unclear.

The mostly common types of cancer treatment are surgery, chemotherapy and radiotherapy. The resistance to chemotherapy and radiotherapy is a major cause of recurrence and mortality in cancer patients [37]. As a mitochondrial protein, ATAD3A has been identified as an anti-apoptotic factor in prostate cancer. Silencing ATAD3A expression in LNCaP cells markedly decreased the resistance to cisplatin treatment [30]. ATAD3A and ATAD3B are located on chromosome 1 (1p36-33) and usually lose their heterozygosity in the large distal regions of chromosome 1 in human oligodendrogliomas. Compared with the oligodendroglimas, astrocytomas are chemoresistant with an intact ATAD3A/ATAD3B gene on chromosome 1 [13]. It has been found that human glioma cell lines with over-expressed ATAD3A showed chemo-resistance to doxorubicin and temozolomide (TMZ) [20]. Moreover, high ATAD3A-expressing T98G cells exhibited higher resistance to radiotherapy compared with low ATAD3A-expressing U87MG cells. Knockdown of ATAD3A in T98 cells impaired the colony-formation ability. On the other hand, ectopic ove-expression of ATAD3A increased the radiation resistance [20]. Knockdown of ATAD3A using siRNA in uterine cervical cancer cells increases cell autophagy and apoptosis, and decreases resistance to anticancer drugs [29]. In lung cancer, knockdown of ATAD3A increased mitochondrial fragmentation and cisplatin sensitivity [18]. Serum starvation increases ATAD3A expression in lung cancer cells in a dose- and time-dependent manner [18]. The increase of ATAD3A expression is not caused by transcription but occurs more likely at the translational level. The cisplatin resistance is also associated with the increase in ATAD3A expression in response to serum starvation [18].

14.6.2 ATAD3A in Other Diseases

Dysfunctional central nervous system and neurological disorders are common clinical features of mitochondrial disorders. As a vital mitochondrial protein, ATAD3A gene alterations, including deletions and mutations, has been identified recently as a cause to these central nervous system dysfunctions [10, 21, 38]. 1p36 deletion syndrome is a congenital genetic disorder characterized by intellectual disability, delayed growth, hypotonia, seizures and other features [39]. The recent studies showed the potential role of ATAD3A located in 1p36 with this deletion syndrome. This has been observed in the fatal congenital pontocerebellar hypoplasia in humans with the biallelic deletion in ATAD3 locus that generates chimeric ATAD3A/ATAD3B fusion genes. The rearrangements in the ATAD3 genes, affecting the ATAD3B/ATAD3C genes on one allele and ATAD3A/ATAD3B genes on the other, manifest as later-onset encephalopathy with cerebellar atrophy, ataxia and dystonia [10]. The impaired mtDNA organization and cholesterol metabolism related with deletion of ATAD3A offers a pathogenetic explanation for these disorders. De novo mutations in ATAD3A c.1582C-T (p.Arg528Trp) has been found to result in global delayed development, hypotonia, spasticity, optic atrophy, axonal neuropathy and hypertrophic cardiomyopathy [38]. Tissue-specific overexpression of dATAD3AR534W, the Drosophila mutation homologous to the human c.1582C-T (p.Arg528Trp) variant, leads to a dramatic decrease in mitochondrial content, aberrant mitochondrial morphology and increased autophagy. Homozygous null dATAD3A larvae showed a significant decrease of mitochondria. ATAD3A variations represent an additional link between mitochondrial dynamics and recognizable neurological syndromes. Another dominantly inherited heterozygous variant c.1064G -A (p.G355D) in ATAD3A has been identified in two patients presented with hereditary spastic paraplegia (HSP) and dyskinetic cerebral palsy [21]. The dominant-negative patient mutation affects the Walker A motif, which is responsible for ATP binding in the AAA module of ATAD3A. The recombinant mutant ATAD3A protein has markedly reduced ATPase activity. Overexpression of the mutant ATAD3A fragments the mitochondrial network and induces lysosome mass [21].

14.7 Targeting ATAD3A for Novel Anticancer Therapy

ATAD3A overexpression has been confirmed to relate with cancer growth, metastasis and resistance to chemotherapy and radiotherapy. As a potential oncogene, ATAD3A represents a good candidate to develop novel therapy to combat cancer. However, there are no specific inhibitors of ATAD3A available. Two chemicals have been identified to decrease the ATAD3A expression. Calphostin C, the inhibitor of PKC, destabilizes ATAD3A through blocking its phosphorylation by PKC [18]. The other chemical drug is resveratrol, which provides a number of anti-aging health

benefits including improved metabolism, cardioprotection, and cancer prevention [40]. Resveratrol can reduce ATAD3A expression with increased cellular autophagy and apoptosis [29].

14.8 Conclusions and Future Prospects

ATAD3A, as a vital mitochondrial AAA-ATPase family member, shows essential roles in the lipid metabolism and ER-mitochondria communication. Mutation and deletion of ATAD3A is related with neurological disorders, while overexpression of ATAD3A tightly linked with cancer growth and metastasis. Cancer is mainly believed to be a disease with disrupt energy production and nutrient metabolism [41]. Elevated ATAD3A increases cancer cell anabolism especially for steroid synthesis and resistance to chemotherapy and radiotherapy at least in part through inhibition of autophagy and mitophagy. Several molecular mechanisms have been demonstrated recently to regulate ATAD3A in the control of mitochondrial functions, including the mTOR-ATAD3A functional axis and the ATAD3A-FAT1 interaction. Moreover, ATAD3A is involved in cancer metastasis through interacting with WASF3 and GRP78 at ER-mitochondria contacts. These findings support the critical role of ATAD3A in cancer development and progression. However, more regulations between ATAD3A and oncoproteins or tumor suppressors need to be elucidated.

Ion radiation affects various aspects of mitochondrial physiology, including mitochondrial respiration, ATP production and mitochondrial dynamics [42, 43]. Thus, investigating whether or not ATAD3A increases resistance to radiotherapy through modulating mitochondrial functions is an emerging research direction. Elevated ATAD3A has been shown to protect cancer cells from cytotoxic chemotherapy. Undoubtedly, novel therapies targeting ATAD3A will be investigating in the clinic as a potential single or combined anticancer agents in the future.

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