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New Roles of Mitochondrial Transcription Factor A in Cancer

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Abstract

Mitochondria are the main sites of energy production in almost all eukaryotic cells. Mitochondria use oxidative phosphorylation to convert redox energy of substrates into adenosine triphosphate (ATP). Mitochondrial transcription factor A (mtTFA; also known as TFAM) is necessary for both transcription and maintenance of mitochondrial DNA (mtDNA), and it is one of the high mobility group (HMG) proteins that preferentially recognizes cisplatin-damaged DNA and oxidized DNA. Loss of mtTFA causes depletion of mtDNA, loss of mitochondrial transcripts, loss of mtDNA-encoded polypeptides, and severe respiratory chain deficiency. Mitochondria play a critical role in cancer cell metabolism and are also essential for cell proliferation. It is well known that mitochondrial uncoupling mediates the metabolic shift to aerobic glycolysis in cancer cells. Thus, mitochondria control cell survival and growth. In addition, the number of mitochondria correlates with the growth rate of cancer cells. The information gleaned from this review may provide critical clues to novel therapeutic interventions aimed at overcoming cancer. More detailed functional analyses of mtTFA should further elucidate its role in mitochondrial genome instability and apoptosis.c

Keywords: mtTFA; Mitochondria; Cancer; Chemotherapy

Introduction

Mitochondria generate cellular energy in the form of adenosine triphosphate (ATP) by the process of oxidative phosphorylation. The organelle contains a small genome that, in animals, encodes 13 essential subunits of the respiratory chain complexes as well as all the rRNAs and tRNAs necessary for their translation [1]. The mitochondrial genome is more vulnerable to oxidative damage and undergoes a higher rate of mutation than the nuclear genome [2]. Otto Warburg observed that tumor slices have elevated levels of glucose consumption and lactate production in the presence of ample oxygen (termed the Warburg effect) [3]. He later postulated that cancer originates from irreversible injury to respiration followed by an increase in glycolysis to replace ATP loss due to defective oxidative phosphorylation [4]. According to Warburg, this metabolic shift from oxidative phosphorylation to glycolysis converts differentiated cells into undifferentiated cells that proliferate as cancer cells. Although the observation that tumor cells exhibit high levels of aerobic glycolysis has been corroborated, the role of mitochondria in tumor cells has been contentious [5]. While multiple investigators have demonstrated that mitochondria are indeed functional in most tumor cells, some argue that decreases in mitochondrial metabolism and respiratory rate are essential for tumor cell proliferation [6]. However, the only tumor cells shown to exhibit mitochondrial dysfunction are those that have mutations in the tricarboxylic acid cycle enzymes succinate dehydrogenase or fumarate hydratase [7]. Furthermore, oncogene activation increases mitochondrial metabolism [8], correlating with metastatic potential [9].

Mutations of mitochondrial DNA (mtDNA) cause several genetic syndromes in humans [10] and have also been implicated, through circumstantial evidence, in common age-associated diseases such as diabetes mellitus and Parkinson's disease and in aging [11-13]. Tumor formation is often associated with mtDNA mutations and alterations in mitochondrial genome function. Mitochondrial aberrations have been identified in cancer of the bladder, breast, colon, head and neck, kidney, liver, lung, stomach and in the hematologic malignancies of leukemia and lymphoma [14-21].

Mitochondrial transcription factor A (mtTFA) was first purified and cloned as a transcription factor for mtDNA [22]. mtTFA is essential not only for mitochondrial gene expression but also for mtDNA maintenance and repair [23]. In addition, increased apoptosis has been observed in cells lacking mtDNA gene expression, suggesting that mtTFA is involved in apoptosis [24]. Mitochondria act as a pivotal decision center in many types of apoptotic responses [25,26]. These mitochondrial functions depend on mitochondrial DNA and proteins with the cooperation of some cellular proteins. During mitochondrial oxidative phosphorylation, large amounts of ROS are generated, which can cause mitochondrial and nuclear DNA damage [27-29]. Since mtDNA lacks protection by histones and because the mtDNA repair system is insufficient, the mutation frequency of mtDNA is 10- to 1000-fold higher than that of nuclear DNA [30]. All genes in the mtDNA are essential for the biogenesis and energic function of mitochondria, and therefore mutations of mtDNA may result in malfunction of the altered gene products. Mitochondrial proteins are likely to be involved in apoptosis, and the search for proteins that can specifically bind to damaged DNA is crucial for understanding mtDNA instability and apoptosis.

Structure of mtTFA

mtTFA, which is a nucleus-encoded DNA binding protein of 246 amino acids, is a member of high mobility group (HMG) proteins and contains 2 HMG-box domains. The involvement of HMG1 in cancer is complex, and intracellular/nuclear and extracellular forms of HMG1 have been implicated in tumor formation, progression, and metastasis and in the response to chemotherapeutics. Elevated expression of

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HMG1 occurs in several solid tumors, including melanoma, colon cancer, prostate cancer, pancreatic cancer, and breast cancer [31-33]. In general, HMG proteins are able to recognize structurally altered DNA. Both HMG1 and HMG2 could not bind to oxidized DNA indicating that mtTFA is functionally different from nuclear HMG proteins, HMG1 and HMG2. The homology between mtTFA and other nuclear HMG proteins show low homology. However, it is unclear which amino acid sequence may involve generating the oxidized DNA recognition activity of mtTFA. The initial 42 amino acids presumably encode a mitochondrial targeting signal (MTS) that would be cleaved within the mitochondrial matrix [34]. mtTFA has putative nuclear localization signals in each HMG-box [35]. The HMG box is an L-shaped three-helix domain that binds to DNA in the minor groove and dramatically bends and unwinds DNA with the help of DNA intercalating residues. One group of HMG proteins is associated with the maintenance and architecture of DNA in nuclear chromatin through nonsequence-specific DNA binding, and another is involved in the transcriptional activation of specific genes through site-specific DNA binding in gene promoter regions [36-38]. The sequence-specific HMG proteins typically contain one HMG domain, whereas the nonsequence-specific HMG proteins usually have two HMG domains. mtTFA is unique in that it is site-specific, but contains tandem HMG-box DNA-binding domains. A 27 amino acid residue linker connects the HMG boxes, which are followed by a 25 residue carboxyl-terminal tail that is rich in basic amino acid residues. The C-terminal tail is essential for specific DNA recognition as well as transcription initiation and activation [39,40]. mtTFA activates transcription by binding upstream of transcriptional start sites and induces conformational changes in the DNA such as bending and DNA unwinding [41]. In contrast to other HMG proteins, there is evidence that mtTFA can oligomerize. A dimer of mtTFA is needed to drive mtDNA into a compacted nucleoid structure [42]. The structure of mtTFA is shown in Figure 1. Using an alignment program, we compared the mtTFA to HMG1 and HMG2 (Figure 1). Examination of residues likely to be strongly conserved revealed that mtTFA appears to contain 2 HMG boxes at amino acid positions 50 to 122 and 152 to 223; these boxes have 26% identity and 36% overall similarity with each other. The HMG boxes of mtTFA and HMG1 have 25% identity and 48% overall similarity.

mtDNA and Transcription

Mitochondrial genomes are short circular molecules that represent the most economically packed forms of DNA in the whole biosphere. The human mitochondrial genome is composed of only 16,569 base pairs [43] and codes for 7 subunits of the NADH-ubiquinone oxidoreductase (complex I), a ubiquinol cytochrome c oxidoreductase (complex III), 3 subunits of the cytochrome c oxidase complex (complex IV), 2 subunits of the ATP synthase, 2 mitochondrial rRNAs, and 22 mitochondria-specific tRNAs. The regulation of respiratory chain capacity is unique in that it exhibits dual dependence on both the nuclear and mitochondrial genomes [10]. The oxidative phosphorylation system consists of 5 multi-subunit enzymatic complexes formed from the gene products of approximately 74 nuclear genes and the 13 mitochondrial genes [11,44] (Table 1).

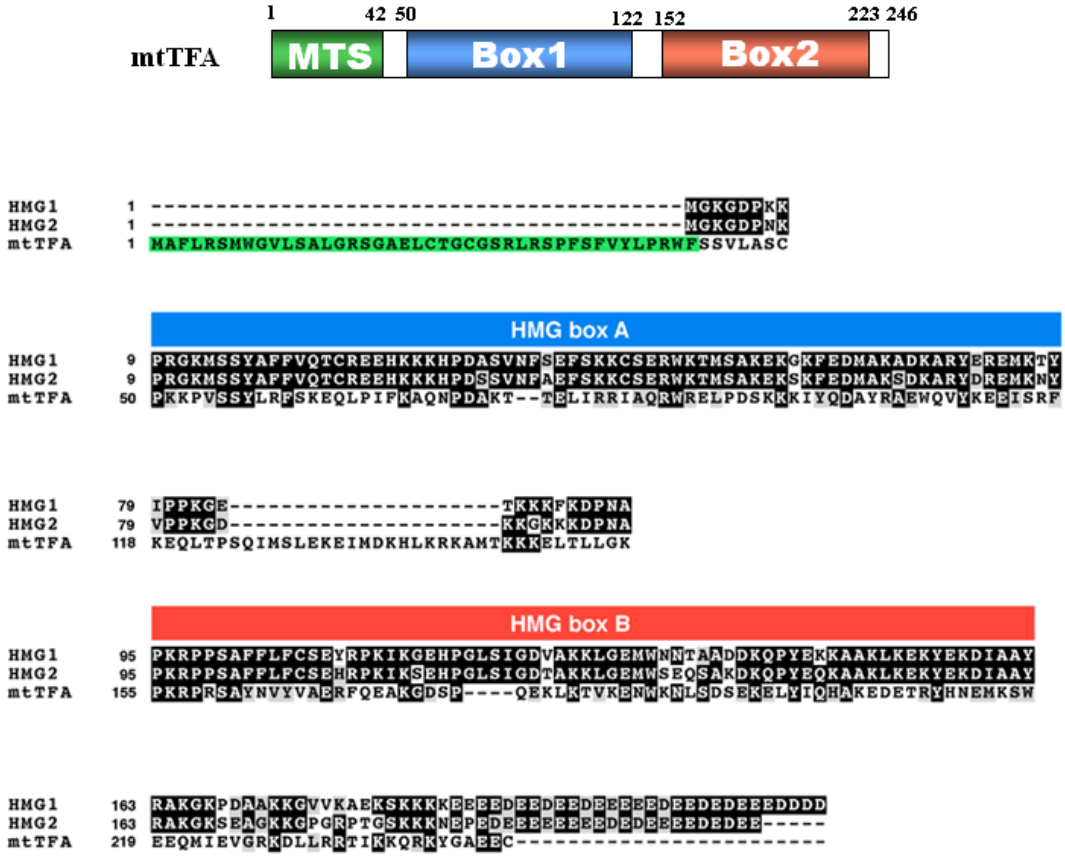

Figure 1: Structure of mtTFA and alignment of mtTFA amino acid sequence with those of other members of the HMG-box family. The sequence of MTS is marked in green on the sequence. The amino acids marked in black is the identity of HMG box. MTS: mitochondrial targeting signal.

complex	Name of mtDNA gene products	Number of mtDNA gene products	Number of nDNA gene products	total
I	ND1 ND2 ND3 ND4 ND4L ND5 ND6	7	36	43
II	-	0	4	4
III	Cytochrome b	1	10	11
IV	Cytochrome c oxidase I - III	3	10	13
V	ATPase 6, ATPase 8	2	14	16
total		13	74	87

Table 1: Number of mitochondrial and nuclear DNA-encoded gene.

mtTFA recognizes the mitochondrial light strand promoter and heavy strand promoter regions of mtDNA [22]. The binding is absolutely required to activate the transcription. mtTFA indeed enhances mtDNA transcription by mitochondrial RNA polymerase in a promoter-specific manner in the presence of a mitochondrial transcription factor B [45,46]. In mammalian mitochondria, the replication of mtDNA is coupled with the transcription from the light strand promoter. Thus, mammalian mtTFA is also essential for initiation of the mtDNA replication [47].

Recognition of Damaged DNA

Nuclear HMG-box proteins, such as HMG1/HMG2, are ubiquitous in higher eukaryotic cells and bind preferentially to cisplatin-damaged DNA [48,49]. HMG-box A of mtTFA binds to cisplatin-modified DNA but HMG-box B does not [50]. Proteins in the family can contain multiple HMG domains and specifically recognize either DNA structures or sequences. They bind in the minor groove and bend DNA upon binding. The ability of HMG domain proteins to recognize distorted structures explains their binding to cisplatin-modified DNA. HMG1 and mtTFA bend the DNA by 86° and 87° to 90°, respectively [51]. The bend locus in all of these protein-DNA complexes was centered near the platinum adduct. Several mechanisms have been considered for how HMG-domain proteins might modulate the sensitivity of cells to cisplatin [52]. One hypothesis is that cisplatin-DNA adducts hijack proteins away from their normal binding sites, thereby disrupting cellular function. Since many HMG-domain proteins function as transcription factors, their removal from promoter or suppressor sequences by binding to cisplatin-DNA adducts could severely alter cancer cell biology. The other hypothesis suggests that HMG-domain proteins could block cisplatin-DNA adducts from damage recognition that is needed for repair.

An oxidized form of the guanine base, namely, 8-oxo-7, 8-dihydroguanine (8-oxoG), is one of the most abundant form of DNA alterations resulting from exposure to reactive oxygen species (ROS) [53]. Binding of mtTFA to DNA containing mismatches attributable to the presence of 8-oxoG has been observed [50]. 8-oxoG is considered to be pertinent to mutagenesis and carcinogenesis [54] because it can pair with adenine as well as cytosine with almost equal efficiency during DNA replication; therefore, 8-oxoG has the potential to cause a high frequency of mutation [55,56]. These transversions are the second most common somatic mutations found in human cancers and are especially prevalent in the mutational spectrum of the tumor suppressor gene p53 [57]. mtDNA is more susceptible to DNA damage than genomic DNA because mtDNA lacks nucleosome structures like chromatin and since mitochondria produce a large amount of ROS. Hence, DNA repair activity in mitochondria may be more effective than DNA repair activity in the nucleus. However, it was reported that mtTFA is abundant enough to wrap entire mtDNA [58]. In that study, most mtTFA is indeed associated with mtDNA and thus organizes a protein-DNA complex. Therefore, mtTFA may function as a main constitutive factor of nucleoid structure (The portion within a prokaryotic cell where the genetic material is to be found) in mammals.

Interaction Between mtTFA and p53

The tumor suppressor p53 has documented roles in the response to DNA damage and cellular stress. In addition, p53 also triggers pro-oxidant genes and cell death pathways, presumably as a means to remove extensively damaged or genetically unstable cells that can contribute to cancer or other diseases. As a transcription factor, many of its effects are mediated through expression of target nuclear genes involved in the various processes it controls. However, effects of p53 that are independent of it transcription factor function have been uncovered, as have novel functions beyond its stereotypical safeguarding role [59]. For example, p53 has been implicated in regulating glucose metabolism and mitochondria respiration through expression of nuclear genes involved in glycolysis and cytochrome oxidase assembly [60]. Although the mechanism of p53-mediated apoptosis after cellular stress remains unclear, mitochondrial localization of p53 protein has been observed [61-66]. The mitochondrial localization of p53 was correlated with early changes leading to p53-mediated apoptosis in diversified cell types stimulated by a range of stressors, including DNA damage and hypoxia [63,64]. These studies showed that redirecting the wild-type p53 protein to the mitochondrion provides an enhancer pathway for stress-induced apoptosis, involving the direct action of p53 on the organelle. The expression levels of several genes encoded by mtDNA are affected by the activity of p53 [67-69]. p53 interacts with Pol γ [70] and mtTFA [66,71], proteins with documented roles in mtDNA replication/repair and mtDNA transcription/packaging, respectively.. This suggests that interaction between mtTFA and p53 may be involved in transcriptional regulation, because both proteins exhibit DNA binding activity as transcription factors. Interestingly, the interaction with p53 enhances mtTFA binding of cisplatin-damaged DNA but inhibits its binding to oxidatively damaged DNA. mtDNA is physiologically more vulnerable compared with nuclear DNA, in view of its close proximity to oxidative phosphorylation sites. It is considered that ~1–5% of mitochondrially consumed oxygen is converted to reactive oxygen species due to electron leaks from respiratory chain. In addition, mtDNA is more prone to chemical damage since lipophilic cations tend to accumulate in mitochondrial matrix, facilitated by negative membrane potential at matrix-side. mtTFA has been reported to protect mtDNA from these oxidative and chemical attacks. Moreover, mtTFA displayed higher affinity to branched DNA structure (e.g. 4-way junction) and might affect DNA recombination events. Our findings suggest that the interaction of p53 with mtTFA may play an important role in apoptosis.

Apoptosis

The mitochondrial respiratory chain is the main source of cellular energy. Respiratory chain dysfunction can be pathological since it affects cellular energy production and can produce symptoms in almost any organ at almost any age of onset. Loss of mtTFA causes depletion of mtDNA, loss of mitochondrial transcripts, loss of mtDNA-encoded polypeptides, and severe respiratory chain deficiency [23,72-75]. Human cells lacking mtDNA (ρ^0 cells) are resistant to *in vitro* apoptosis induced by staurosporine, suggesting that respiratory chain function is required for apoptosis [76]. Impaired mitochondrial translation or disruption of mtTFA causes a global deficiency of all mtDNA-encoded respiratory chain subunits, indicating that the same type of respiratory chain deficiency affects complexes I, III, IV, and V. However, the nucleus-encoded complex II was not affected in mtTFA knockout hearts [24]. The finding that respiratory chain deficiency

is associated with increased *in vivo* apoptosis may have important therapeutic implications for human disease. Apoptosis resistance is suggested to be of importance for the development of malignant tumors. Furthermore, chemotherapy and radiation treatment of cancer are intended to induce apoptosis in cancer cells. Manipulation of respiratory chain function may be used to enhance or inhibit apoptosis in a wide variety of conditions.

mtTFA in Cancer

Mitochondria play a critical role in cancer cell metabolism, which is also essential for cell proliferation [77]. It is well known that mitochondrial uncoupling mediates the metabolic shift to aerobic glycolysis in cancer cells [77,78]. Thus, mitochondria control cell survival and growth. In addition, the number of mitochondria correlates with the growth rate of cancer cells [79,80]. We previously found that mtTFA is overexpressed in cisplatin-resistant human cancer cells [81]. mtTFA may function to protect mtDNA from oxidative stress.

Some mtTFA binds tightly to the nuclear chromatin [35]. DNA microarray and chromatin immunoprecipitation assays showed that mtTFA can regulate the expression of nuclear genes. Overexpression of mtTFA enhanced the growth of cancer cell lines, whereas downregulation of mtTFA inhibited their growth by regulating mtTFA target genes such as baculoviral IAP repeat-containing 5 (BIRC5; also known as survivin). Knockdown of mtTFA expression induced p21-dependent G1 cell cycle arrest.

We have recently reported that mtTFA expression may be useful for predicting the clinical outcome of metastatic colorectal cancer patients treated with FOLFOX (chemotherapy protocol consisting of oxaliplatin, 5-fluorouracil and folinic acid) [82]. We also reported the relationship between mtTFA expression and clinicopathological variables in endometrial carcinomas [83]. mtTFA mutations induce mtDNA depletion and result in decreased tumor sensitivity to cisplatin in most colorectal cancer (CRC) with microsatellite instability (MSI) [84]. The presence of these alterations suggests the potential importance of mtTFA in tumorigenesis of CRC with MSI and implicates mtTFA-dependent mitochondrial instability as the unique pathogenetic factor for CRC with MSI. mtTFA mutation may be potentially useful in predicting outcomes and selecting chemotherapy for patients with microsatellite-unstable CRC. The involvement of mtTFA in apoptosis is probably temporally regulated and/or may be tissue specific. It is necessary to identify CRC cell lines with MSI, which do not carry mtTFA truncating mutations, to test whether the overexpression of mtTFA truncating mutation or knockdown of mtTFA in these cells induces apoptosis. Although the detailed mechanism by which Mut-mtTFA promotes tumor cell growth remains to be elucidated, the data indicate that loss of the ability to induce Cyt *b* expression and thus the inability to induce Cyt *b*-dependent apoptosis is probably one of the mechanisms by which Mut-mtTFA induces tumor progression in most microsatellite-unstable CRC [84]. CRC cells carrying mtTFA truncating mutations were more resistant to cisplatin-induced apoptosis than the same kind of cells overexpressing Wt-mtTFA. These data thus provide evidence that mtTFA is required for the induction of cisplatin-dependent apoptosis in CRC with MSI. It is critical to initiate an investigation of the responsiveness of CRC patients who carry or who do not carry mtTFA truncating mutations to cisplatin-based chemotherapy. Such data may help to improve therapeutic intervention protocols for patients with or without mtTFA truncating mutations.

In summary, it has been shown that the presence of high frequency of mtTFA truncating mutations in human microsatellite-unstable CRC cell lines and primary tumors. The CRC with MSI harboring the mtTFA truncating mutation displayed impaired mitochondrial stability, dysregulated cell proliferation, mitigated Cyt *b*-dependent apoptosis, and enhanced cisplatin-dependent apoptotic resistance. The preliminary data also indicate a potential mechanism by which mtTFA truncating mutation is involved in apoptosis through downregulation of Cyt *b* transcription due to reduced interaction with mitochondrial HSP. These findings support the role of mtTFA and mitochondrial stability in CRC tumorigenesis. This result may have potential relevance in the pharmacogenetic selection of CRC patients for treatment with cisplatin or other drugs. Furthermore, disruption of mitochondrial function by loss of mtTFA gene reduced tumorigenesis in an oncogenic Kras-driven mouse model of lung cancer [85]. These results indicate that mitochondrial metabolism and mitochondrial ROS generation are essential for Kras-induced cell proliferation and tumorigenesis.

Summary and Future Perspectives

This review has focused on the recent evidence for new roles of mtTFA in cancer. mtTFA mutations induce mtDNA depletion and result in decreased tumor sensitivity to cisplatin in most CRC with MSI. The presence of these alterations suggests the potential importance of mtTFA in tumorigenesis of CRC with MSI and implicates mtTFA-dependent mitochondrial instability as a unique pathogenetic factor for CRC with MSI. mtTFA mutation may be potentially useful in predicting outcomes and selecting chemotherapy for patients with microsatellite-unstable CRC.The information gleaned from this review may provide critical clues to novel therapeutic interventions aimed at overcoming cancer. More detailed functional analyses of mtTFA should further elucidate its role in mitochondrial genome instability and apoptosis.

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