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Review

Mitochondrial proteases and cancer☆

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ABSTRACT

Mitochondria are a major source of intracellular reactive oxygen species, the production of which increases with cancer. The deleterious effects of reactive oxygen species may be responsible for the impairment of mitochondrial function observed during various pathophysiological states associated with oxidative stress and cancer. These organelles are also targets of oxidative damage (oxidation of mitochondrial DNA, lipids, protein). An important factor for protein maintenance in the presence of oxidative stress is enzymatic reversal of oxidative modifications and/or protein degradation. Failure of these processes is likely a critical component of the cancer process. Mitochondrial proteases degrade misfolded and non-assemble polypeptides, thus performing quality control surveillance in the organelle. Mitochondrial proteases may be directly involved in cancer development as recently shown for HtrA2/Omi or may regulate crucial mitochondrial molecule such as cytochrome c oxidase 4 a subunit of the cytochrome *c* oxidase complex degraded by the Lon protease. Thus, the role of mitochondrial proteases is further addressed in the context of oxidative stress and cancer. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. Introduction

Functional integrity and rapid and appropriate responses to physiological and pathophysiological stimuli are required for mitochondria to meet cellular energy demands. In addition, mitochondria participate in cellular Ca^{2+} homeostasis, signaling cascades [1]. Mitochondria are cell organelles involved in the processes of cell life and death and therefore also in tumoral transformation [2,3]. Indeed, mitochondria dysfunction is a prominent feature of cancer cells. The mitochondrial respiratory chain is one of the main sources of endogenous reactive oxygen species and mitochondrial proteins represent targets for oxidative modification and loss in function [4,5]. More recent evidence indicates the importance of hypoxia and stressful conditions of nutrient (lack of glucose) in cell proliferation [6]. These two factors can promote the process of malignant transformation. It is apparent that hypoxia can cause the progressive elevation in mitochondrial ROS production that can target mt DNA and drive the malignant transformation process. Mitochondrial proteins and DNA have also been previously studied as markers of tumorigenesis [2,3]. Old or damaged mitochondria that produce high levels of ROS are normally degraded by mitophagy [7,8]. Degradation of oxidized protein in the mitochondria can prevent the induction of tumorigenesis [9]. In the cytosol, the proteasome constitutes the main proteolytic machinery involved in the elimination of oxidized protein [10]. However, this proteolytic complex is not present in the mitochondria. Pioneering studies have shown that mitochondrial matrix from liver and heart contains proteolytic activity that degrades oxidized, dysfunctional, and misfolded protein [11]. More recent work supports a role for the mitochondrial matrix Lon protease in eliminating oxidatively modified mitochondrial proteins [12], similar to the role of the proteasome in the cytosol (Table 1). We review here the current evidence that Lon protease can directly or indirectly be involved in tumorigenesis. Two other mitochondrial proteases have received great attention in the last few years for their potential in cell proliferation, the HtrA2/Omi and prohibitin complexes. They will be discussed here because of some similarities in the way they affect cell apoptosis.

2. Emerging role of the mitochondrial Lon protease in cancer

2.1. The Lon protease: from protein control to regulatory function

Mammalian mitochondria contain four major ATP-dependent proteases, Lon, Clp-like, and AAA proteases. Clp-like and AAA proteases are hetero-oligomeric complexes located in the matrix and inner mitochondrial membrane, respectively [13]. As evidenced by various mutational studies, these proteases contribute to the

Abbreviations: COX, cytochrome c oxidase; HIF, hypoxia inducible factor; IM, inner mitochondrial membrane; IMS, intermembrane space; mtDNA, mitochondrial DNA; OM, outer mitochondrial membrane; PHB, prohibitn complex; PDZ, PDZ domain; PHD, prolyl hydroxylase domain enzyme; PMSF, phenyl methyl sulfonyl fluoride; Pol γ, polymerase Gamma; ROS, reactive oxygen species; TFAM, transcription factor A mitochondrial; WT1, Wilm's tumor suppressor gene

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Table 1
Physiological substrates of mitochondrial proteases.

Lon protease	Degradation of oxidatively modified or misfolded proteins	Aconitase [16], Atp1, Atp2, Atp7, Rip1, Qcr2, Pdb1, Lat1, Lpd1, Kgd2, Ilv5 [81]
	mt DNA replication, transcription, maintenance	[46,89,90]
	Composant of the mitochondrial nucleoid	Selective degradation of TFAM [91].
	Hypoxia	Degradation of cytochrome C oxidase COX4-1 subunit [37,92].
	Cholesterol metabolism	Star protein [93].
HtrA2/Omi	Induction of apoptosis	XIAP [94], Apollon/BRUCE [101], WT1 [55,56]
	Induction of apoptosis	Ped/Pea-15 [95]
	Cytoskeleton protein	Actin, Tubulin-α, β-vimentin [96]
	Translation machinery	EF1-α [96]
Prohibitin (PHB complex)	Assembly/stabilization of OXPHOS complex	OXPHOS complex [97], F1/F0 ATPase [98]
	Component of mt DNA nucleoid	[84]
	Protein degradation/associationwith m-AAA protease	[15]
m-AAA protease	Respiratory complex components	[97,98]
	Ribosome assembly	Mrlp32 [99]
	Mitochondrial dynamic	Opa1 [100]

degradation of misfolded and damaged proteins and/or the maintenance of mitochondrial genome stability. In addition, both proteolytic systems appear to exert chaperone activity. The physiological function of Clp-like protease, however, is yet to be determined. Currently, information regarding the regulation of each of the ATP-dependent proteases and/or the identities of specific protein substrates is limited. Nevertheless, exposure of hydrophobic residues is likely a common recognition element and both chaperone and proteolytic functions participate in prevention of the accumulation of aggregated material [14,15]. The Lon protease plays a critical role in the removal of oxidized protein and damage (Fig. 1). Aconitase, a Krebs cycle enzyme known to be susceptible to oxidative inactivation, has been shown to be a substrate of the Lon protease when the enzyme is inactivated upon treatment with oxygen radicals [12]. Indeed, the matrix proteolytic activity responsible for the selective degradation of oxidatively modified aconitase was strongly stimulated by ATP and inhibited by the serine protease inhibitor PMSF. In addition, the same proteolytic activity co-purified with the Lon protease after size exclusion chromatography and affinity chromatography of the mitochondrial matrix fraction. Moreover, both purified Lon protease and mitochondrial matrix extracts exhibited similar activation and inhibition profiles. Treatment with anti-sense oligonucleotides in WI-38 human lung fibroblasts resulted in decreased Lon protease content and activity while causing an accumulation of oxidatively modified aconitase [16]. More recently, it has been shown that downregulation of the human Lon protease results in disruption of mitochondrial structure, loss in function, and cell death, with the majority of cells undergoing caspase 3 activation and apoptosis within four days [17]. Electron microscopy performed on Lon-deficient cells revealed aberrant mitochondrial morphology and the presence of electron

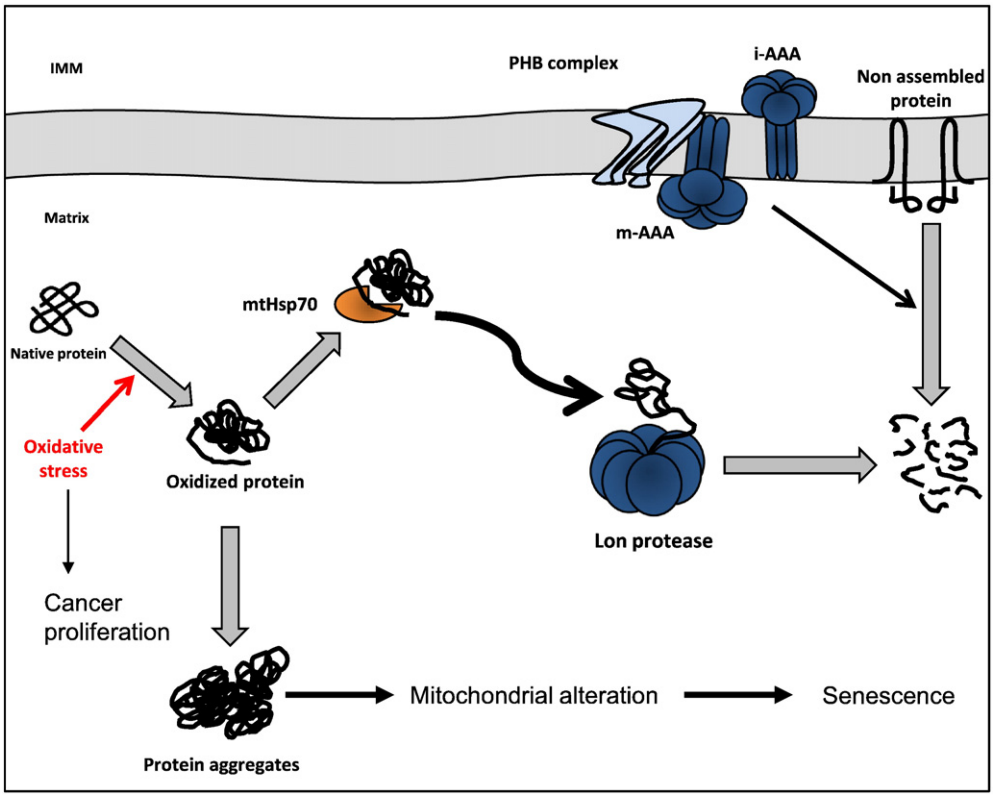

Fig. 1. Mitochondrial protein quality control in the matrix compartment. In the early stages of tumorigenesis hypoxia and glucose deprivation alter mitochondrial function by promoting ROS production. Protein become misfolded due to oxidative stress conditions and tend to aggregate. By degrading oxidized protein, Lon protease prevents their accumulation and mitochondria injury. In conditions of excessive damage, oxidative modification of mitochondrial protein can trigger senescence. Mitochondrial dysfunction would favor carcinogenesis only when senescence program is inactivated.

dense inclusion bodies in the mitochondrial matrix thought to represent oxidatively modified and aggregated protein [17]. Taken together, these findings argue for an important role of the Lon proteolytic system for the degradation of oxidized protein within the mitochondrial matrix and for the maintenance of mitochondrial structural and functional integrity (Fig. 1).

2.2. Structure and functions of the Lon mitochondrial protease

As are numerous mitochondrial proteins, the Lon protease is encoded by the nuclear genome (Fig. 2). The lon gene encodes a 963 amino acid protein [18] homologous to the bacterial protease La. This protease is active as an homo-oligomeric complex composed of 6 monomers in *Escherichia coli* and 7 monomers in eukaryotes such as yeast with a molecular weight of approximately 106 kDa. The Lon protease is composed of three domains that are conserved within the different species [19]. The N-terminal domain (domain N) is capable of interacting with protein substrates in concert with the second domain, also termed the AAA+ module. The AAA+ module is composed of two segments, one involved in ATP binding (α/β domain) and the other in ATP hydrolysis (α domain). A third domain (P domain) carries the Serine and Lysine active site residues that form the catalytic dyad for proteolytic activity [20]. The identity of these active site residues was first evidenced by a comparison of the different Lon protease protein sequences and further confirmed by a site directed mutagenesis analysis and elucidation of the three dimensional structure of the *E. coli* Lon protease P domain [21–23]. Interestingly, the isolated P domain does not exhibit any proteolytic activity towards protein substrates such as casein but is capable of degrading small peptides such as melittin [24]. The three dimensional structure of both the N and AAA+ domains of the *E. coli* Lon protease has also been recently solved [23]. While the manner by which protein substrates bind to the Lon protease remains to be elucidated, it has been proposed that exposed loops at the surface of substrate proteins are essential features for recognition [19]. The Lon protease acts as a serine protease that undergoes the formation of an acyl-enzyme intermediate with a cleavage specificity that would be similar to that of chymotrypsin, allowing proteolysis at the C-terminus of hydrophobic amino acids such as methionine, tyrosine, and tryptophan [25]. An important feature of the proteolytic activity of Lon is its stimulation by ATP. In contrast, ADP acts as an inhibitor of the protease indicating regulation in response to changes in energy charge [26]. In addition to its proteolytic activity, mammalian Lon has also been shown to display chaperone properties and to specifically bind sequences of human mitochondrial DNA and RNA, as well as to interact with mitochondrial DNA polymerase γ and the twinkle helicase [27]. It has been shown that Lon downregulation in WI-38 human lung fibroblasts elicits two temporally and mechanistically distinctive patterns. Initially, loss of Lon activity causes massive apoptosis, with the classic hallmark of caspase-3 activation. At this early stage cell survival can only be improved by addition of caspase-3 inhibitor. Two Lon functions seem to be mostly involved in this early apoptosis: the proteolytic defect causes accumulation of aggregated proteins inside mitochondria, while loss of chaperone function severely affects mitochondrial respiration and membrane potential, rendering cells extremely susceptible to apoptotic stimuli. At a later stage, the surviving cells lose their ability to undergo apoptosis and are respiratory deficient and unable to divide due to defects in uridine synthesis [17].

2.3. Suppression of mitochondrial activity in cancer cell: regulation of cytochrome c oxidase activity by HIF-1 and Lon protease

In some forms of cancer, analysis of possible alterations in the oxidative phosphorylation machinery revealed downregulation of the catalytic subunit of the mitochondrial ATP synthase. It was found to inversely correlate with the rate of aerobic glycolysis [6].

Fast proliferation is one of the main characteristics of cancer cells. This leads to hypoxia in tumors due to inability to provide adequate oxygenation. Hypoxic conditions are usually lethal to non malignant cells due to hypoxia-mediated P53 dependent cell death [28]. Due to the inability of the mitochondria to provide enough ATP for cell survival under hypoxic conditions tumor cells must upregulate the glycolitic pathway. This occurs via induction of HIF-1 factor (hypoxia-inducible factor). HIF plays an important role in the metazoan response to low oxygen levels (hypoxia) [29]. HIF is a heterodimeric transcription factor; in human cells, levels of the HIF-α domain are regulated in an oxygen-dependent manner by four enzymes, known as the HIF hydroxylases [30–33]. Under normal oxygen conditions, these enzymes catalyze hydroxylation of two prolyl residues in HIF-α (Pro^{402} and Pro^{564}) targeting them for ubiquitination and degradation by the proteasome [34]. HIF induces genes that control crucial features of cancer biology.

HIF can modulate mitochondrial functioning by its involvement in the regulation of cytochrome oxidase (COX) expression. COX is a dimer composed of 13 subunits. Mammalian cells express a predominant COX4-1 isoform [35] (Fig. 3). Another isoform COX4-2 is also expressed but only in some tissues such as lung [36]. Under hypoxia, its expression is increased whereas the other isoform expression is decreased. Degradation of COX4-1 isoform occurs via activation of the Lon protease [37]. This switch between the two isoforms provides a mechanism to maintain the efficiency of

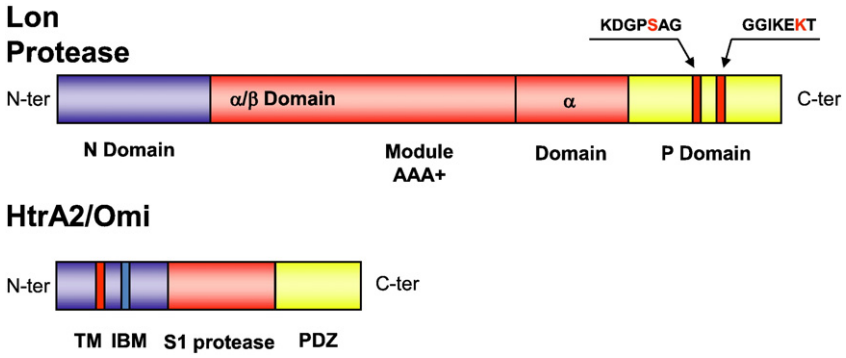

Fig. 2. Schematic representation of domain organization of human Lon protease and Htra2/Omi. Abbreviations: N, N-terminal domain (interaction with substrates); AAA, ATPase associated with various cellular activities; α/β domain, ATP binding site; α domain, ATP hydrolysis domain; P domain, proteolytic domain; TM, transmembrane domain; IBM domain, inhibitor of apoptosis (IAP-binding motif); S1 protease, trypsin-like protease domain; PDZ, PDZ domain.

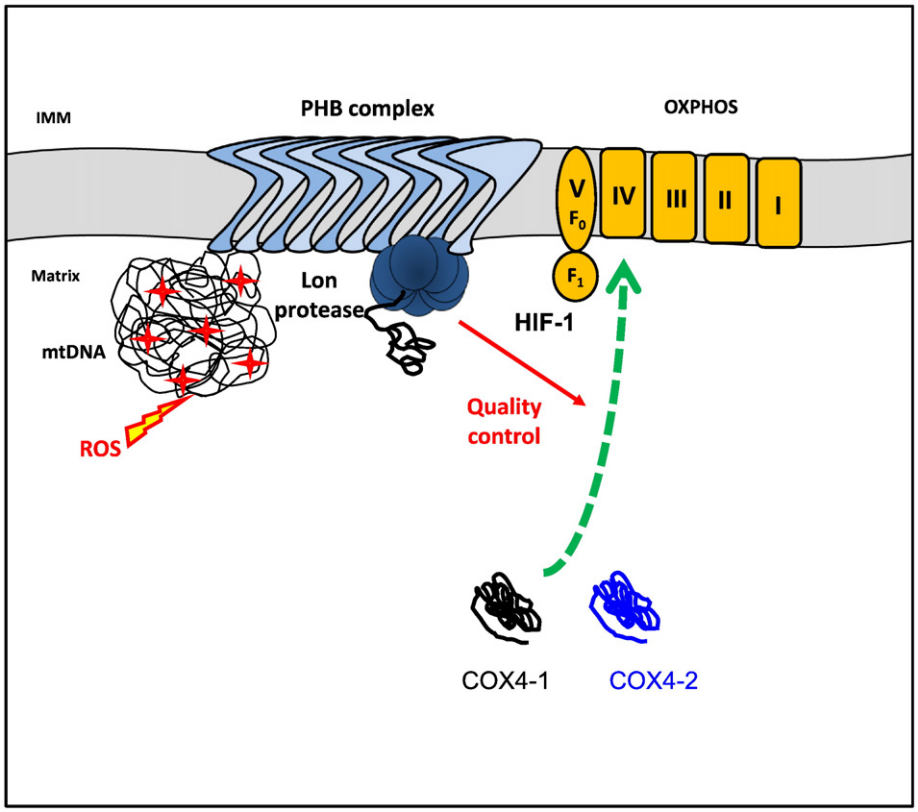

Fig. 3. Implication of Lon protease and prohibitin in cancer. Prohibitin form a complex in the mitochondrial inner membrane. They may assist with protein folding and assembly. The association of prohibitin with mitochondrial nucleoid and Lon protease may assure protection and regulation of mt DNA. Under aerobic conditions, mammalian cells express COX4-1 subunits whereas under hypoxic conditions, they express COX4-2, respectively. The change in subunit composition provides a mechanism by which mitochondrial respiration is optimized according to O_2 concentration. Degradation of COX4-1 subunits via activation of the Lon protease provides a mechanism to maintain the efficiency of respiration in tumor cells.

respiration under conditions of reduced O_2 availability and may be involved in the adaptive response to hypoxia. Remarkably, Lon gene expression is induced in response to hypoxia and multiple HIF-1 binding sites were identified in the 5-flanking region of the human gene LON gene by chromatin immunoprecipitation and reporter-gene transcriptional assays [37]. Thus HIF-1 mediates co-ordinate regulation of COX4-1 and COX4-2 subunit expression in response to changes in O_2 availability. The regulated expression of these subunits results in a significant decreases in O_2 consumption.

2.4. Mitochondrial genome changes in cancer and involvement of Lon protease

The mitochondrial genome in human cell is extremely small (16,569 bp) compared to the nuclear DNA although every mitochondria contains between 2 and 20 copies of mt DNA and the copy number of mitochondrial genome per cell ranges from several hundreds to more than 10,000 depending on the cell type. The identification of increased or reduced mt DNA content has been reported in cancer cells [38]. Mt DNA is located in close proximity to the respiratory chain and exposed to ROS-induced oxidative damage [39]. Mt DNA includes a short segment of three strands called D loop. This loop is the control region where replication and transcription occur. Replication involves DNA polymerase γ as well as TFAM, one of the three transcription factors [40]. In the past decade, many groups have demonstrated that mt DNA mutations occur in a variety of cancers and sequences of the D loop where Lon protease and TFAM are binding are hot spot [41]. This is reflected in the higher frequency of mt DNA mutations in somatic cells and significantly correlates with the development of cancer [42]. Mutations in the Pol γ exonuclease activity domain are known to promote large deletion in mt DNA. The concomitant presence of somatic alterations in mt DNA and mutation of the DNA binding domain of p53 in cancers have been noted and proposed to facilitate cell survival and tumorigenesis [43]. This also supports that dysfunction of mitochondrial respiration in patients with cancers facilitates tumor growth through ROS production.

Alongside protease activity Lon regulates the replication of mitochondrial DNA. Mammalian Lon binds single strands DNA with specificity for a G-rich consensus sequence. Previous studies show that ATP blocks Lon binding to mtDNA [27,44–46]. Investigating the role of Lon in the protection of mt DNA is challenging and needs further research. Stimulation of its binding activity to mt DNA should prevent initiation of tumorigenesis (Fig. 3).

3. HtrA2/Omi, a new target in cancer therapy

The members of the HtrA family of proteases play important role in cell physiology and are involved in several pathological processes including cancer and neurodegenerative diseases [47]. Members of the HtrA family are present in nearly all bacterial and eukaryotic genomes. Whereas HtrA2/Omi resides in the mitochondrial intermembrane space, its paralogs HTRA1, 3, and 4 are mostly targeted to the secretory pathway. There are several indications of HtrA2 involvement in oncogenesis. It is widely expressed in a variety of cancer cell lines [48–51]. Analysis of biopsy samples showed changes in expression of HtrA2 in cancer tissues compared with normal tissues. The serine protease HtrA2/Omi is involved in the regulation of apoptosis and is principally found in the mitochondria, although a fraction is also located in the nucleus [47]. HtrA2 serves as a protein quality control and increase of its proteolytic activity via allosteric ligands mimicking peptides could improve effects of

chemotherapy [52]. HtrA2 is expressed as a 49 kDa proenzyme and consists of a chymotrypsin-like proteolytic domain with catalytic triad Ser-His-Asp and one PDZ domain. PDZ domains have been shown to act as regulatory elements and as specificity determinants [53,54] (Fig. 2). The proteolytic activity of HtrA2 can be stimulated by several apoptotic stimuli, and substrates include members of the inhibitors of apoptosis family (IAPs) (reviewed in reference 47). In a recent study, Hartkamp et al. [55] identify the serine protease HtrA2 as a WT1-interacting protein and demonstrate that it can degrade WT1. They showed that endogenous WT1 in tumor cells is cleaved following cytotoxic drug treatment and demonstrate that this cleavage is HtrA2 dependent. These findings suggest that HtrA2 is a critical regulator of WT1 under proapoptotic conditions [55,56].

4. Role of prohibitin in cell proliferation

4.1. The mitochondrial prohibitin complex (PHB)

PHB are considered to be involved in regulation of the cell cycle [57,58], apoptosis [59,60], and senescence [61,62] and are chaperones to mitochondrial proteins [63]. Prohibitins primary function is to stabilize new synthesized polypeptides in mitochondria, as they serve as foldase unfoldase molecular chaperones [63]. Phb1p and Phb2p localize in the inner mitochondrial membrane (IM) forming a 1MD complex, composed of 14 subunits (hPhb1p, 32 kDa; hPhb2p, 34 kDa) in a 1:1 ratio [64] (Fig. 3). The substrates of the PHB complex are not known in details yet, but the most important seem to be electron chain transport subunits [65]. It seems that PHBs are negative regulators of m-AAA-proteases and PHBs stabilize m-AAA proteases in low activity conformation [63]. PHBs are also able to modulate accessibility and conformation potential substrates of proteases [66]. PHBp have also been recognized as negative regulators of cell cycle. It was established that PHBs are overexpressed in metabolic stress, when the mtDNA/nDNA balance is altered, after heat shock or oxidative stress [67,68].

4.2. Prohibitin 1 as a tumor suppressor

The eukaryotic mitochondrial PHB comprises two highly homologous subunits, PHB1 and PHB2 (around 50% amino acid sequence identity and 60% similarity). The first mammalian prohibitin PHB1 was identified as a potential tumor suppressor with antiproliferative activity and hence was named prohibitin [69]. Extensive and rapidly accumulating evidence suggests that both prohibitins function within mitochondria [70,71]. Cell fractionation of rat liver showed almost all of the prohibitin proteins to be localized in mitochondria, with some protein in the lysosomal and ribosomal fractions and none in the cytoplasm. Observed nuclear localization was traced back to contaminations during preparation [69]. Nevertheless, Fusaro et al. [59] appear to have identified a nuclear localization for prohibitin 1 in two breast cancer cell lines—MCF-7 and T47D cells. Upon camptothecin induced apoptosis prohibitin 1 translocates from the nucleus to the mitochondria [60]. While overexpressed but not mutated prohibitin 1 is found in a relevant percentage of cancers [72], the human prohibitin 1 gene is a candidate tumor suppressor locus that maps to a region of chromosome 17 (17q21) commonly deleted or mutated in breast tumors [73]. Research on prohibitin started out in the early nineties with the discovery of its anti-proliferating function when microinjected into fibroblasts [74]. This attribute was later ascribed to its 3′ UTR, thus assigning it to the novel class of non coding RNAs. The importance of the 3′UTR for regulating proliferation was demonstrated when point mutations in this region were found in a relevant number of cancers [74]. However, numerous studies contradicted these findings, showing no relevance of prohibitin polymorphisms to breast cancer risks [75,76]. At the same time, the protein itself is still the subject of intensive research, which attempts to clarify its function as a tumor suppressor. Wang et al. [58] report that prohibitin 1 interacts with pRb and regulates E2F function.

4.3. Prohibitins function as mitochondrial chaperones of m-AAA proteases and interaction with Lon protease

As already indicated, prohibitins perform a role as mitochondrial chaperones. Furthermore, mitochondria occupy the central focus in apoptotic signaling processes, therefore potentially providing the stage for the apoptotic function of prohibitins [67]. As for most mitochondrial proteins, such as members of the mitochondrial import machinery, research to identify the role of prohibitins in mitochondria was mainly performed in yeast. Nijtmans et al. [77] were the first to show that prohibitins form a complex in the mitochondrial inner membrane. Multimeres, consisting of 16–20 prohibitin molecules and presumably linked by their C-terminal coiled coil domains, act as chaperones to stabilize mitochondrial proteins and facilitate respiratory complex assembly [77]. Additional work by Tatsuta et al. [64] showed that this complex was circularly arranged around the m-AAA protease (Figs. 1 and 3). The AAA proteases are ATP dependent proteases (ATP-associated with diverse cellular activity) of the inner mitochondrial membrane. Their proteolytic domains have metal-dependent peptidase activity [78]. While the active site of the i-AAA protease reaches into the intermembrane space, m-AAA exposes its catalytic site towards the matrix (Figs. 1 and 3). In yeast, on which most of the studies were done, the m-AAA protease consists of two subunits, Yta10p and Yta12p, and regulates the turnover of non-assembled inner membrane proteins [15]. Their homologues in vertebrates are paraplegin and AFG3L2, respectively [79]. This complex stabilizes newly synthesized mitochondrial translation products [64,65]. While the deletion of one of the m-AAA subunits leads to an impaired degradation of non-assembled inner membrane proteins and an impaired assembly of respiratory chain complexes, the deletion of either Phb1p or Phb2p leads to an accelerated turnover of these proteins [63]. Our results show that Lon protease could be recruited to the inner membrane of mitochondria and interact with the prohibitins [80,81]. These findings indicate that prohibitins interact with Lon protease, could serve as a recruiter complex in the inner membrane to assist the quality control of membrane proteins by Lon protease, and maintain of mtDNA metabolism. Prohibitin has been reported to be involved in the mitochondrial nucleoid complex [82,83]. In a recent study, prohibitin 1 has been shown to be involved in the maintenance of the mitochondrial nucleoid organization by TFAM-independent pathway and regulation of mtDNA copy number by TFAM-dependent pathway [84]. It is possible that prohibitin 1 directly maintains the mitochondrial nucleoid organization by its interaction with the Lon protease which binds mt DNA and regulate TFAM expression. Protection of mitochondrial DNA from oxidative damage can therefore prevent cellular transformation and accelerated proliferation.

5. Conclusions and future directions

In conclusion, Lon protease emerges as a major controller of multiple human mitochondrial functions, including the assembly of respiratory chain protein complexes, the degradation of damaged proteins, the interaction with prohibitin, and the maintenance of mitochondrial DNA integrity.

Only a few specific substrates of Lon protease have been identified in mammalian systems [15,85]. Lon homeostasis is crucial to mammalian cell fate, as Lon upregulation is associated with tumorigenic transformation [86,87] and its downregulation leads to apoptosis [17]. Thus, further studies in animal systems are needed to explain the specific pathways controlled by Lon and to develop an advanced understanding of Lon involvement in apoptosis and cancer.

In summary the importance of Lon protease in cancer is due to increasing the rates of biogenesis of mammalian mitochondria either by neoplastic transformation or rapid cell growth. The rapid growth and division of cancer cells induce a disproportionate expression of some unassembled subunits that are subjected to degradation by the Lon protease. This scenario fits with the enhanced expression of the mitochondrial genome observed in rapidly growing neoplastic cells and with the increased turnover of mitochondrial protein in rapidly growing cells [2]. Taken together, these data underscore the important role of mitochondrial proteases in both mitochondrial protein maintenance and cellular redox homeostasis through regulated degradation of oxidatively modified proteins. It is increasingly apparent that pro-oxidants do not simply cause damage but can regulate protein function in a reversible fashion [85]. Future studies must explore the delicate balance between these two opposing effects. The specific role of Lon in these processes, physiological substrates, and mechanisms of pro-oxidant induced activation must be established [88]. Development of specific inhibitors and substrates of the various mitochondrial proteases will hasten these discoveries [80]. In addition, conditions that adversely affect the removal of oxidatively modified protein must be defined. Thus, critical risk factors that shift the balance from reversible to irreversible loss in mitochondrial and cellular function may be identified.

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