Mitochondrial LONP1: Linking structure and function to context-dependent roles in disease (Review)

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Abstract. Mitochondrial proteostasis is essential for maintaining organellar integrity, metabolic adaptation and cellular survival under physiological and stress conditions. Among mitochondrial quality control mechanisms, Lon peptidase 1 (LONP1) is an ATP-dependent AAA+ serine protease localized predominantly in the mitochondrial matrix and plays a central role in the recognition and degradation of damaged or misfolded proteins. Recent structural, molecular and multi-omics studies have expanded our understanding of LONP1 beyond proteolysis, implicating it in protein quality control, mitochondrial DNA maintenance, metabolic regulation and responses to oxidative and cellular stress. Increasing evidence also indicates that LONP1 functions are highly dependent on cellular and disease context, with both loss and gain of LONP1 activity associated with distinct pathological outcomes. The present review integrated recent structural and functional advances to establish a structure-function framework for understanding how LONP1 coordinates proteolytic and chaperone-like activities and how these functions are shaped by cellular and disease context. The present review further examined its roles in metabolic, neurodegenerative, reproductive, cardiovascular and malignant diseases, with particular emphasis on the context-dependent consequences of LONP1 dysregulation and its emerging therapeutic potential. Finally, the present review highlighted unresolved questions concerning substrate recognition and specificity, the relative contributions of protease and chaperone-like functions, disease-specific directionality and the safety and feasibility of therapeutic modulation. These challenges need to be addressed to establish the functional and translational boundaries of LONP1.

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Abbreviations: LONP1, Lon peptidase 1; AAA+, ATPases associated with diverse cellular activities; ROS, reactive oxygen species; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; mtHSP70, mitochondrial heat shock protein 70; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; CYP11A1, cytochrome P450 family 11 subfamily A member 1; ER, endoplasmic reticulum; EMT, epithelial-mesenchymal transition; HIF-1α, hypoxia-inducible factor 1 alpha; ATF5, activating transcription factor 5

Key words: Lon peptidase 1, proteostasis, mitochondrial quality control, oxidative stress, diseases

Contents

1. Introduction
2. Structural basis and biological functions of LONP1
3. LONP1 and disease
4. Regulatory mechanisms of LONP1
5. LONP1 as a potential therapeutic target
6. Conclusion

1. Introduction

Mitochondria are central hubs of cellular metabolism and energy production and play essential roles in maintaining cellular homeostasis. However, mitochondrial oxidative phosphorylation inevitably generates reactive oxygen species (ROS), which can damage mitochondrial proteins, lipids and DNA (1). To preserve mitochondrial integrity and function, mitochondria have evolved a complex mitochondrial quality control (MQC) system involving mitochondrial biogenesis, dynamics, proteostasis and mitophagy (2,3). Mitochondrial proteostasis specifically maintains the integrity of the mitochondrial proteome through coordinated protein synthesis, import, folding, assembly and degradation (4), whereas mitochondrial dynamics and mitophagy primarily regulate organelle remodeling and elimination. The stability of proteins is also influenced by their biochemical environment

and susceptibility to denaturation and degradation (5). Thus, mitochondrial proteostasis represents an important component of the broader MQC network.

Mitochondrial proteases constitute an essential component of mitochondrial proteostasis and regulate the turnover of damaged, misfolded and selected functional proteins (6). Among these proteases, LONP1 and CLPP are primarily localized in the mitochondrial matrix, whereas AFG3L2 and YME1L are associated with the mitochondrial inner membrane (7-9). CLPP contributes to mitochondrial protein quality control, while AFG3L2 regulates mitochondrial protein stability and YME1L contributes to mitochondrial functional and metabolic homeostasis. These proteases therefore constitute complementary components of mitochondrial quality control but differ in their localization and functional properties. Among them, LONP1 is a major ATP-dependent serine protease in the mitochondrial matrix with both proteolytic and chaperone-like activities. Its combination of proteolytic and chaperone-like functions, together with its involvement in mitochondrial homeostasis and disease, makes LONP1 an important focus for understanding mitochondrial proteostasis (10-14).

The present study summarized recent advances in the structural organization and functional mechanisms of LONP1, with particular emphasis on its proteolytic and chaperone-like activities in mitochondrial proteostasis. The present study further discussed its roles in metabolic, neurodegenerative, cardiovascular, cancer-related and genetic diseases and highlight current challenges and potential therapeutic implications.

2. Structural basis and biological functions of LONP1

Molecular structure of LONP1. LONP1 is a highly conserved ATP-dependent mitochondrial protease that assembles into an asymmetric hexameric complex within the mitochondrial matrix. Each monomer consists of an N-terminal domain (NTD), a central AAA+ ATPase domain and a C-terminal proteolytic domain, which together coordinate substrate recognition, ATP-dependent substrate processing and proteolytic cleavage (15,16). The NTD contributes to substrate recognition and initial substrate engagement, whereas the AAA+ ATPase domain provides the energy required for substrate unfolding and translocation through the central channel. The C-terminal proteolytic domain contains the conserved Ser855-Lys898 catalytic dyad responsible for peptide bond hydrolysis (17,18). Unlike a static oligomeric assembly, structural studies of human LONP1 reveal that the hexamer undergoes conformational transitions associated with different functional states, highlighting the importance of structural flexibility in regulating substrate processing (11).

Recent cryo-electron microscopy studies have provided mechanistic insights into how structural transitions regulate LONP1 activity. Substrate engagement induces rearrangement of the AAA+ ATPase domains, in which conserved pore-loop elements interact with substrate polypeptides and facilitate ATP-dependent translocation toward the proteolytic chamber (11,18,19). The AAA+ domain adopts spiral staircase-like conformations during substrate processing, supporting a model in which ATP hydrolysis-driven conformational changes promote directional substrate movement. However, substrate binding within the ATPase channel alone is insufficient to fully activate the proteolytic domains in human LONP1. Instead, substrate interaction with the protease active site promotes rearrangement of the catalytic region, enabling formation of a catalytically competent Ser855-Lys898 configuration (11). These findings indicate that substrate recognition, mechanical translocation and proteolytic activation are structurally coupled processes rather than independent events.

Beyond its proteolytic activity, LONP1 has also been reported to possess chaperone-like functions (20). However, these two activities should be distinguished mechanistically. Proteolytic activity requires substrate unfolding, translocation and cleavage mediated by the AAA+ ATPase and protease domains, whereas chaperone-like activity may involve ATP-dependent substrate handling without subsequent degradation (21,22). In addition, LONP1 cooperates with mitochondrial protein import machinery and mtHSP70 during the maturation and assembly of newly imported mitochondrial proteins (23,24). Therefore, some reported folding-related functions may reflect coordinated activity between LONP1 and mitochondrial chaperone systems rather than an independent chaperone activity of LONP1 alone.

Biological functions of LONP1. LONP1 is a notable regulator of mitochondrial proteostasis that maintains mitochondrial protein homeostasis through selective protein degradation and coordinated protein folding processes. As an ATP-dependent mitochondrial protease, LONP1 removes oxidatively damaged, misfolded and dysfunctional proteins, while also regulating the turnover of specific mitochondrial proteins involved in metabolism and mitochondrial maintenance (25,26). These functions depend on the coordinated action of substrate recognition, ATP-dependent unfolding and translocation and proteolytic cleavage mediated by the AAA+ ATPase and protease domains. However, the biological consequences of LONP1 activity depend on substrate identity and cellular context. For example, HMGCS2 and CYP11A1 have been experimentally demonstrated as LONP1 substrates, with their degradation contributing to the regulation of renal mitochondrial metabolism and ovarian steroidogenesis, respectively (27,28). Importantly, proteins identified as LONP1-associated factors or interaction partners should not automatically be considered proteolytic substrates.

In addition to its proteolytic degradation function, LONP1 has also been suggested to contribute to mitochondrial protein maturation through chaperone-like functions. LONP1 can participate in the folding and assembly of newly imported mitochondrial proteins and cooperate with mitochondrial protein import machinery and mtHSP70 to maintain protein solubility and facilitate respiratory complex assembly (21-24). For example, cooperation between LONP1 and mtHSP70 has been implicated in the maturation and assembly of respiratory chain complex subunits such as NDUFA9 (23,24). Importantly, these folding-related functions should be distinguished from LONP1-mediated proteolysis and should not necessarily be interpreted as equivalent to the activity of classical molecular chaperones. Rather, current evidence suggests that LONP1 may contribute to protein maturation through ATP-dependent substrate handling while also cooperating with mitochondrial chaperone systems. Thus, LONP1-mediated protein quality

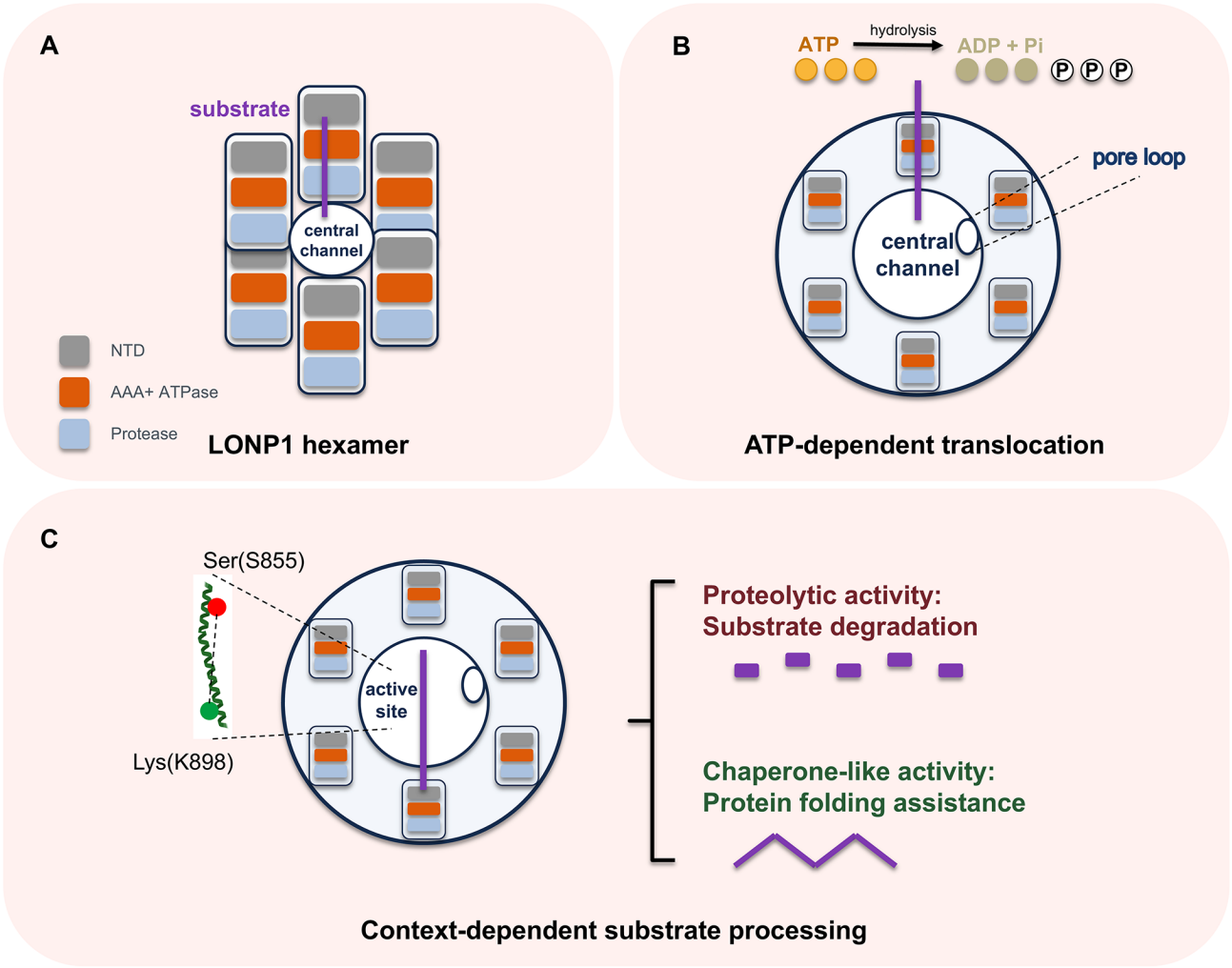


Figure 1. Structural organization and functional mechanisms of mitochondrial LONP1. (A) Schematic representation of the LONP1 hexamer, showing the NTD, AAA+ ATPase domain, protease domain and central channel. (B) ATP-dependent substrate translocation, illustrating ATP hydrolysis-driven substrate movement through the central channel. (C) Context-dependent substrate processing, highlighting the proteolytic activity of LONP1 in substrate degradation and its chaperone-like activity in protein-folding assistance. Ser855 and Lys898 are indicated in the schematic of the proteolytic domain. LONP1, Lon peptidase 1; NTD N-terminal domain.

control may involve both intrinsic substrate-processing activity and coordinated interactions with other mitochondrial proteostasis factors.

LONP1 also participates in mitochondrial genome maintenance by regulating proteins involved in mtDNA replication and repair. LONP1 interacts with the mitochondrial DNA polymerase γ complex component PolG2 and contributes to the regulation of mitochondrial replication machinery stability (29). By contrast, under environmental stress conditions, cadmium exposure induces LONP1 upregulation, resulting in increased degradation of the mtDNA repair enzyme uracil-DNA glycosylase 1 and subsequent impairment of mitochondrial DNA integrity (30). These findings suggest that the effects of LONP1 on mitochondrial genome maintenance vary according to cellular context and stress conditions.

Through selective regulation of mitochondrial proteins and cooperation with mitochondrial proteostasis systems, LONP1 integrates protein quality control with metabolic adaptation and cellular stress responses. In physiological conditions, LONP1 activity contributes to mitochondrial function by maintaining protein quality, metabolic enzyme homeostasis and respiratory complex integrity. However, under pathological conditions, altered LONP1 expression or activity may reshape mitochondrial metabolism and stress signaling. For example, LONP1 deficiency in cardiomyocytes disrupts mitochondria-associated membranes, leading to ER stress, mitochondrial fragmentation and activation of mitochondrial stress responses (31). Conversely, elevated LONP1 expression in tumor cells promotes ROS-dependent activation of p38 and NF-κB signaling, increasing the expression of EMT-associated and inflammatory genes and contributing to tumor microenvironment remodeling (32). Moreover, upstream signaling pathways such as transient receptor potential cation channel subfamily C member 6-extracellular signal-regulated kinase 1/2 can regulate LONP1 expression and influence mitochondrial dynamics in neuronal models (33) (Fig. 1).

3. LONP1 and disease

LONP1 dysfunction is implicated in metabolic, neurodegenerative, cardiovascular and malignant diseases. However, its pathological effects are highly context dependent. Changes

in LONP1 expression do not necessarily reflect changes in proteolytic activity and increased expression may represent either a pathogenic response or a compensatory adaptation. Therefore, LONP1-related evidence should be interpreted by distinguishing expression, enzymatic activity, causal effects across human tissues and experimental models.

LONP1 in metabolic disease. LONP1 contributes to metabolic homeostasis by maintaining mitochondrial proteostasis and regulating the turnover of mitochondrial proteins. In Type 2 diabetes, decreased LONP1 expression in pancreatic β-cells is associated with impaired protein quality control, respiratory chain dysfunction and oxidative stress. Experimental studies further indicate that LONP1 protects β-cells from glucolipotoxic stress (34-36). Similarly, LONP1 expression is decreased in patients with metabolic dysfunction-associated steatohepatitis and experimental models and negatively correlates with hepatic steatosis, inflammation and fibrosis severity; restoration of LONP1 in experimental models improves mitochondrial function and metabolic homeostasis (37-40). During acute liver failure, downregulation of LONP1 expression impairs hepatocyte gluconeogenesis, whereas restoration of LONP1 improves mitochondrial metabolism and ultrastructure (41).

These findings support a protective role for LONP1 in metabolic diseases. However, reduced expression in patient tissues primarily indicates an association and further mechanistic studies are required to determine whether impaired LONP1 function is a causal driver of disease progression.

LONP1 in neurodegenerative and musculoskeletal diseases. LONP1 contributes to mitochondrial proteostasis in neurodegenerative diseases. In Alzheimer's disease, pathogenic amyloid-beta 42 (Aβ42) suppresses LONP1 expression and protease activity, leading to mitochondrial proteostasis imbalance, protein aggregation, mitochondrial fragmentation and impaired energy metabolism, whereas restoration of LONP1 improves cognitive performance in experimental models (42). In Parkinson's disease, LONP1 interacts with the GBA1-encoded lysosomal enzyme β-glucocerebrosidase and this interaction has been associated with mitochondrial respiratory chain homeostasis and Parkinson's disease pathology (43).

LONP1 also contributes to mitochondrial homeostasis in musculoskeletal tissues. In experimental skeletal muscle disease, LONP1 deletion causes accumulation of the misfolded mutant ornithine transcarbamylase, activating the mitophagy-lysosomal degradation pathway and contributing to muscle atrophy (44). In osteoarthritis models, interventions targeting mitochondrial stress can restore mitochondrial proteostasis by regulating key factors such as LONP1, suggesting that LONP1-associated mitochondrial dysfunction may contribute to osteoarthritis progression (22).

LONP1 in cardiovascular diseases. The heart has high energy demands and relies heavily on mitochondrial function to maintain contractile activity and cellular homeostasis. LONP1 contributes to cardiac mitochondrial proteostasis across developmental, ischemic and aging-related contexts. During cardiac development, LONP1 is required for the metabolic transition from glycolysis to oxidative phosphorylation. LONP1 deficiency activates the p-eIF2α-activating transcription factor 4 pathway, suppresses mitochondrial transcription factor A and mtDNA-encoded respiratory chain proteins and promotes glycolytic metabolism, resulting in increased ROS accumulation and impaired cardiomyocyte proliferation (45). In the adult heart, LONP1 is also involved in ischemic preconditioning and its upregulation protects against ischemia/reperfusion injury by limiting Complex I-dependent ROS production (46,47).

LONP1 dysfunction is also associated with chronic cardiac pathology and aging. Although LONP1 expression may increase in the aging heart, mitochondrial dysfunction and oxidative stress can persist, suggesting that increased abundance does not necessarily indicate preserved proteolytic activity (48). Similarly, in pressure overload-induced heart failure, LONP1 protease activity is reduced despite relatively stable expression, potentially owing to oxidative post-translational modifications such as carbonylation and tyrosine nitration. Restoration of LONP1 activity by the mitochondria-targeted antioxidant mitoTEMPO improves cardiac function (49). Together, these findings suggest that the functional state of LONP1, rather than its expression level alone, is a key determinant of cardiac mitochondrial proteostasis.

LONP1 in cancer. LONP1 expression is frequently altered in cancer and has been associated with tumor progression and clinical outcomes (50,51). During tumor initiation and progression, LONP1 participates in metabolic reprogramming and may contribute to tumor cell survival under unfavorable conditions (20). As an ATP-dependent mitochondrial protease and chaperone, LONP1 maintains mitochondrial protein quality control and metabolic homeostasis. Bota and Davies (52) demonstrated that mitochondrial Lon preferentially degrades oxidatively damaged aconitase, particularly under conditions of moderate oxidative modification, highlighting its role in limiting the accumulation of damaged mitochondrial proteins and maintaining mitochondrial homeostasis. This proteostatic function may be particularly relevant to tumor cells exposed to persistent oxidative and metabolic stress. LONP1 has also been implicated in the turnover of mitochondrial metabolic proteins and the regulation of cellular energy metabolism (53). In addition, LONP1 can enhance antioxidant capacity and inhibit apoptosis, potentially supporting tumor cell survival under metabolic and therapeutic stress (32).

The metabolic effects of LONP1 appear to vary across tumor types and disease stages. In colorectal cancer, LONP1 silencing alters the mitochondrial proteome, impairs respiratory chain function and oxidative phosphorylation, reduces ATP production and oxygen consumption and increases ROS accumulation, ultimately leading to mitochondrial dysfunction and apoptosis (54). These findings indicate LONP1 can support tumor cell survival by maintaining mitochondrial proteostasis and bioenergetic function. Consistent with this role, colorectal cancer cells with high LONP1 expression have been associated with metabolic plasticity involving both glycolysis and oxidative phosphorylation, whereas metastatic cells may suppress mitochondrial respiration to adapt to local energy and oxidative stress conditions (55,56). By contrast, in gastric carcinogenesis, *Helicobacter pylori* infection has been reported to upregulate LONP1 through a hypoxia-inducible

factor 1 alpha (HIF-1α)-dependent mechanism, promoting glycolysis and reducing mitochondrial aerobic respiration (57-59). LONP1 may also exert stage-dependent effects, with cytoprotective functions during early tumorigenesis and promotion of invasion and progression through the PI3K/AKT-EMT axis in advanced disease (60). In central nervous system tumors, LONP1 function similarly appears to depend on tumor grade. In low-grade gliomas, LONP1 has been associated with reduced mtDNA damage and slower disease progression, whereas in high-grade gliomas it has been implicated in resistance to radiotherapy and chemotherapy through HIF-1α-mediated enhancement of mtDNA repair (61).

In hepatocellular carcinoma, LONP1 is upregulated in tumor tissues and higher expression has been associated with poorer disease-free and overall survival. Mechanistically, LONP1 has been reported to promote HCC cell proliferation and migration through degradation of mitochondrial aconitase 2, with consequent effects on ferroptosis, cuproptosis and mitochondrial function (51). HCC also exhibits extensive epigenetic dysregulation involving DNA methylation, histone modifications and non-coding RNAs, which may contribute to the heterogeneous molecular and metabolic states of tumor cells (62). However, the available evidence does not establish a direct regulatory relationship between these epigenetic alterations and LONP1.

Taken together, current evidence suggests that the role of LONP1 in tumor metabolism is context-dependent rather than uniform across cancers. Further studies are needed to clarify the mechanisms underlying these context-specific effects and to determine whether LONP1 represents a therapeutically actionable vulnerability in specific tumor types.

LONP1-related genetic disorders. Genetic studies have established LONP1 as a disease-associated gene underlying a spectrum of mitochondrial and developmental disorders. The best-characterized phenotype is cerebral, ocular, dental, auricular and skeletal anomalies (CODAS) syndrome, a rare autosomal-recessive disorder caused by biallelic LONP1 variants. Patients commonly exhibit developmental delay, cataracts, dental and auricular abnormalities, short stature and skeletal abnormalities, although the clinical manifestations are variable (63,64). Biallelic LONP1 variants have also been identified in patients with mitochondrial diseases without the typical CODAS phenotype, including mitochondrial encephalopathy, lactic acidosis, muscle weakness and neurodegeneration (64,65).

The phenotypic and genetic spectrum of LONP1-related disorders has continued to expand. LONP1 variants have been associated with neurological manifestations including epilepsy and severe mitochondrial encephalopathy, while both autosomal-recessive and autosomal-dominant inheritance patterns have been reported (65,66). Notably, variants associated with different clinical phenotypes show distinct distributions across functional regions of LONP1, suggesting a potential genotype-phenotype relationship (66). Collectively, these findings indicate that LONP1 dysfunction is associated with diverse mitochondrial, developmental and neurological phenotypes, highlighting clinical heterogeneity among LONP1-related genetic disorders.

LONP1 in other systemic diseases. LONP1 exhibits cell-type and tissue-dependent functions across the respiratory, renal and reproductive systems. In the respiratory system, LONP1 maintains epithelial homeostasis and regenerative capacity, whereas its dysregulation can contribute to pulmonary pathology. Loss of LONP1 in airway epithelial cells causes mitochondrial dysfunction, abnormal progenitor cell differentiation and epithelial remodeling, while its deletion in alveolar type II cells promotes cellular senescence and a senescence-associated secretory phenotype, exacerbating pulmonary fibrosis (67,68). By contrast, LONP1 is upregulated in pulmonary artery smooth muscle cells during pulmonary hypertension, where it promotes glycolytic reprogramming and vascular remodeling through degradation of mitochondrial pyruvate carrier 1 (69). These findings highlight the distinct effects of LONP1 depending on cell type and pathological context.

In the renal and reproductive systems, LONP1 contributes to mitochondrial proteostasis and tissue homeostasis. Loss of LONP1 in podocytes causes mitochondrial dysfunction and podocyte injury, thereby aggravating renal disease (70). In oocytes, LONP1 is required for maintaining oocyte quality and ovarian reserve and its deletion disrupts follicular development and accelerates oocyte loss (71,72). Age-associated alterations in LONP1 expression and function may further impair mitochondrial proteostasis and contribute to cellular aging (44,73).

Together, these findings indicate that LONP1 may have diverse and context-dependent functions across organ systems. Its loss of function is typically associated with mitochondrial dysfunction, fibrosis, or cellular degeneration, whereas increased LONP1 activity can promote pathological proliferation and metabolic remodeling in specific cell types. Therefore, the functional state of LONP1, rather than its expression level alone, should be considered when evaluating its pathological significance and therapeutic potential (Table I).

4. Regulatory mechanisms of LONP1

As a key component of mitochondrial proteostasis, LONP1 is regulated at multiple levels, including transcriptional, post-transcriptional and post-translational mechanisms, with their relative contributions varying across cellular and pathological contexts. At the transcriptional level, HIF-1α and nuclear factor erythroid 2-related factor 2 have been reported to promote LONP1 transcription under hypoxic and oxidative stress conditions, respectively, suggesting that LONP1 expression is incorporated into cellular stress responses (57,74). In pancreatic β-cells, activating transcription factor 5 (ATF5) also regulates LONP1 expression and decreased ATF5 expression has been associated with decreased LONP1 levels in diabetic mouse models (34-36). At the post-transcriptional level, pathogenic Aβ42 was reported to reduce LONP1 mRNA stability through methyltransferase like 3-mediated m6A modification in an Alzheimer's disease model, resulting in decreased LONP1 expression (42). Together, these findings indicate that LONP1 abundance is dynamically controlled by coordinated transcriptional and RNA-level mechanisms in a context-dependent manner.

Post-translational mechanisms regulate LONP1 stability and enzymatic activity. Notably, oxidative stress may exert divergent effects on LONP1 by affecting both protein abundance and functional properties. While stress-responsive

Table I. LONP1-associated diseases and mechanisms.

First author/s, year	Disease	Functional molecule	Functional mechanism	Evidence level	Experimental model	LONP1 expression	(Refs.)
Li *et al*, 2025	Type 2 Diabetes	mtHSP70	LONP1 cooperates with mtHSP70 to facilitate mitochondrial protein folding; LONP1 deficiency promotes mitochondrial protein misfolding, β-cell dysfunction and hyperglycemia.	Human + *in vivo* + cell	Human pancreatic islets; mouse β-cell models; human β cells/islets	Downregulated	(34)
Xu *et al*, 2026	MASH	DHODH	LONP1 selectively degrades DHODH, reducing orotic acid production and attenuating MASH-associated liver fibrosis.	Human + *in vivo* + cellular	Patients with MASH; hepatocyte-specific Lonp1 KO mice; hepatocytes	Downregulated	(37)
Bai *et al*, 2023	Chronic kidney disease	HMGCS2	LONP1-mediated degradation of HMGCS2 maintains mitochondrial function and limits renal injury and fibrosis.	Human + *in vivo* + cellular	Patients with CKD; two mouse CKD models; renal tubular epithelial cells	Downregulated	(27)
Baden *et al*, 2023	Parkinson's disease	GBA1/GCase	GCase interacts with LONP1 in mitochondria; disease-associated GBA1 mutations enhance its interaction with mitochondrial quality-control machinery and impair complex I integrity and energy metabolism.	Cellular + organoid	Stable cell lines; GBA1-mutant iPSC-derived neurons; midbrain organoids	Not specified	(43)
Wang *et al*, 2023	Alzheimer's disease	Aβ42	Aβ42 interacts with LONP1 and impairs its assembly and protease activity, contributing to mitochondrial proteostasis defects and dysfunction.	Human + *in vivo* + cellular	Human AD brain; neuronal cells; CRND8 APP transgenic mice	Downregulated	(42)
Luo *et al*, 2016	Gastric carcinogenesis	HIF-1α	H. pylori induces HIF-1α-dependent LONP1 expression, promoting glycolytic reprogramming and gastric epithelial cell proliferation.	*In vivo* + cellular	H. pylori-infected mouse gastric epithelial models;	Upregulated	(57)
Li *et al*, 2025	Pulmonary arterial hypertension	MPC1	LONP1 directly degrades MPC1, promoting glycolytic reprogramming, proliferation, migration and pulmonary vascular remodeling.	*In vivo* + cellular	Pulmonary artery smooth muscle cells; monocrotaline-induced rat PH model	Upregulated	(69)

Table I. Continued.

First author/s, year	Disease	Functional molecule	Functional mechanism	Evidence level	Experimental model	LONP1 expression	(Refs.)
Gibellini *et al*, 2018	Colorectal cancer	β-catenin	LONP1 upregulation is associated with β-catenin signaling and promotes metabolic reprogramming and EMT in colorectal cancer cells.	Human + cellular	Human CRC tissues; SW480 and SW620 cells	Upregulated	(55)
Zhao *et al*, 2022	Embryonic heart development defect	ATF4, TFAM, GLUT1	LONP1 deficiency activates the p-eIF2α-ATF4 pathway, suppresses TFAM, increases GLUT1 expression and disrupts the metabolic transition to oxidative phosphorylation during heart development.	*In vivo* + cellular	Cellular Mouse embryonic cardiac tissue; cardiomyocytes	Downregulated	(45)
Liu *et al*, 2024	Polycystic ovary syndrome	CYP11A1	LONP1 promotes CYP11A1 degradation through a direct interaction, thereby suppressing ovarian androgen synthesis.	Human + *in vivo* + cellular	Patients with PCOS; rodent PCOS models; ovarian cells/tissues	Not specified	(28)

LONP1, Lon peptidase 1; mtHSP70, mitochondrial heat shock protein 70; MASH, metabolic dysfunction-associated steatohepatitis; DHODH, dihydroorotate dehydrogenase; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; CKD, chronic kidney disease; GBA1, glucosylceramidase β1; GCase, glucocerebrosidase; iPSC, induced pluripotent stem cells; Aβ42, amyloid-β42; AD, Alzheimer's disease; APP, amyloid precursor protein; HIF-1α, hypoxia-inducible factor 1 alpha; H. pylori, Helicobacter pylori; MPC1, mitochondrial pyruvate carrier 1; PH, pulmonary arterial hypertension; CRC, colorectal cancer; ATF4, activating transcription factor 4; TFAM, mitochondrial transcription factor A; GLUT1, glucose transporter 1; CYP11A1, cytochrome P450 family 11 subfamily A member 1; PCOS, polycystic ovary syndrome.

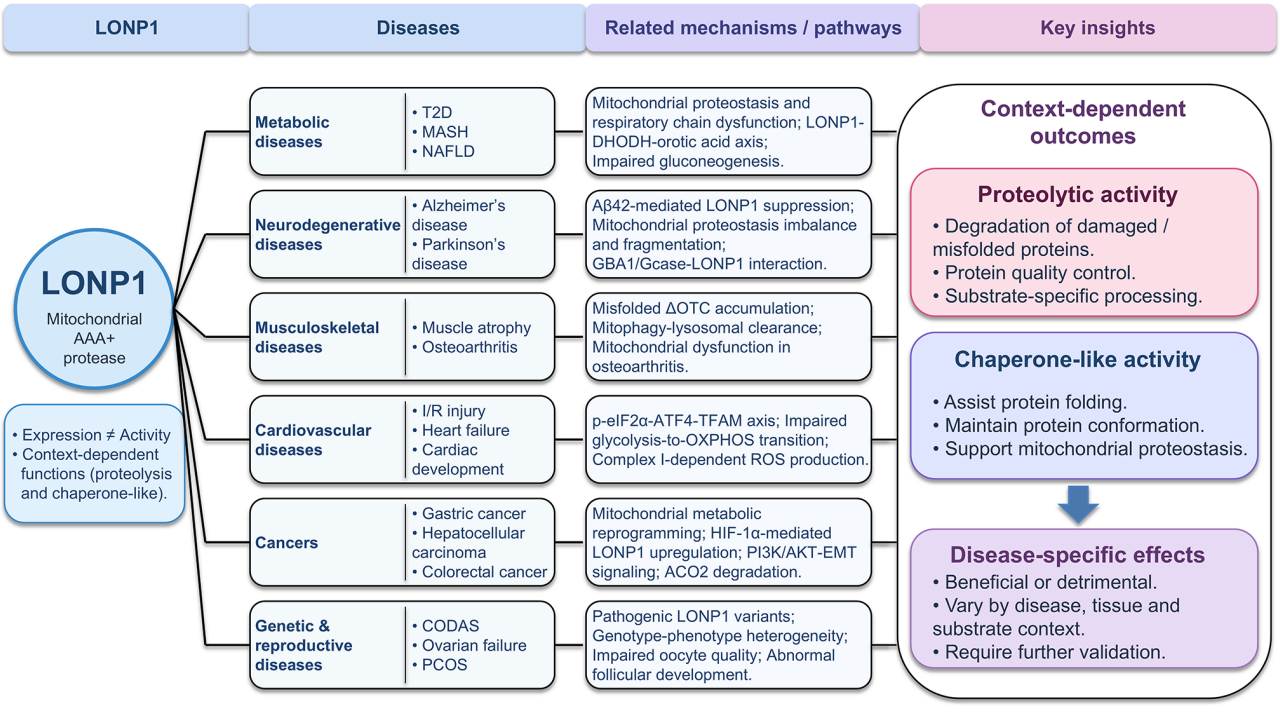


Figure 2. Overview of LONP1-associated mechanisms across metabolic, neurodegenerative, musculoskeletal, cardiovascular, malignant, genetic and reproductive disorders. LONP1 can influence mitochondrial proteostasis, respiratory chain function, metabolic reprogramming, oxidative stress and cell survival through substrate-specific and context-dependent mechanisms. Its proteolytic and chaperone-like activities may contribute to distinct or overlapping outcomes depending on the disease, tissue and substrate context. LONP1 expression does not necessarily reflect its functional activity and its disease-specific effects require further investigation. LONP1, Lon peptidase 1; ΔOTC, mutant ornithine transcarbamylase.

transcriptional pathways can increase LONP1 expression, oxidative modification of LONP1 has been reported to alter its conformation and substrate affinity (75,76). Beyond oxidative modification, phosphorylation represents another mechanism controlling LONP1 activity under specific pathological conditions. In the hypoxic tumor microenvironment, Akt-mediated phosphorylation of LONP1 has been reported to enhance its proteolytic activity and contribute to tumor metabolic reprogramming (77). In addition, sirtuin-3 negatively regulates LONP1 stability by deacetylating LONP1, thereby promoting K63-linked ubiquitination, ESCRT0-dependent sorting and subsequent lysosomal degradation (78).

Importantly, these regulatory mechanisms should not be considered as independent events but rather as interconnected layers that collectively determine LONP1 function. Cellular stresses such as hypoxia and oxidative stress can simultaneously activate transcriptional programs that increase LONP1 expression and induce post-translational modifications that alter its stability or enzymatic properties. Therefore, increased LONP1 abundance does not necessarily indicate enhanced proteolytic activity, as the functional output of LONP1 is further shaped by phosphorylation, oxidative modification and degradation pathways. Conversely, post-translational regulation can modulate the persistence and activity of newly synthesized LONP1, creating a dynamic balance between LONP1 production, functional activation and turnover.

5. LONP1 as a potential therapeutic target

Preclinical studies suggest that LONP1 inhibition may suppress tumor cell proliferation, invasion and resistance to apoptosis-inducing treatments, supporting LONP1 as a potential therapeutic target in selected cancers. However, LONP1 is essential for mitochondrial proteostasis and metabolism and systemic inhibition may therefore disrupt normal mitochondrial function. Main challenges include inhibitor selectivity, mitochondrial delivery, tissue toxicity and definition of an appropriate therapeutic window.

Small-molecule approaches have been explored to target LONP1. CDDO and its derivatives reversibly inhibit LONP1 by blocking ATP hydrolysis through an allosteric mechanism, whereas CDDO-anhydride competitively inhibits LONP1 ATPase activity. Structural and mutational analyses identified a hydrophobic pocket adjacent to the ATP-binding site as a potential binding site for CDDO derivatives (79). Structure-based drug design subsequently yielded selective boronic acid-based LONP1 inhibitors with nanomolar potency and limited activity against the 20S proteasome, together with structures of inhibitor-bound human LONP1 (80). These studies provide biochemical and cellular proof of concept for pharmacological LONP1 inhibition, but the available compounds remain preclinical tools or candidates, with limited evidence for *in vivo* efficacy and safety.

Mitochondrial delivery represents an additional barrier because LONP1 resides within the mitochondrial matrix. Cellular potency alone may therefore not predict effective target engagement *in vivo* and the intracellular distribution, mitochondrial accumulation and tissue exposure of LONP1 inhibitors require systematic evaluation. Potential toxicity is also an important consideration, as sustained LONP1 inhibition could compromise mitochondrial proteostasis in normal tissues.

Antibody-based targeting represents a more exploratory approach. A recent computational study proposed Antibody_82M1 against the ATP-binding region of LONP1 in the context of prostate cancer (81). Although favorable predicted binding and stability were reported, these findings remain at the design stage. In particular, delivery of a large antibody into the mitochondrial matrix represents a major unresolved challenge and its cellular activity, mitochondrial target engagement, pharmacokinetics, toxicity and *in vivo* efficacy have not been established. Thus, Antibody_82M1 currently represents a conceptual strategy rather than evidence of therapeutic efficacy.

Future development of LONP1-targeted therapies should prioritize selective inhibitors with efficient mitochondrial and tissue-specific delivery, defined pharmacokinetics and acceptable toxicity. Comparative evaluation of binding mechanisms, selectivity, mitochondrial target engagement, cellular activity and *in vivo* efficacy will be essential for establishing therapeutic potential. Combination strategies may also be explored in tumors with demonstrated dependence on LONP1-mediated mitochondrial proteostasis (80,82). At present, however, the absence of clinically validated LONP1 inhibitors underscores the need for further pharmacological and *in vivo* studies before LONP1-targeted therapies can enter clinical development (83) (Fig. 2).

6. Conclusion

LONP1 is a key regulator of mitochondrial proteostasis whose multifunctional activities integrate protein quality control with mitochondrial homeostasis. Its protease and chaperone-like functions appear to contribute differently depending on cellular and physiological context, while its broader roles in inter-organelle communication and metabolism further highlight the complexity of LONP1 regulation.

LONP1 dysregulation is associated with diverse diseases, but its pathological effects are not uniformly directional. Loss of LONP1 function can impair mitochondrial proteostasis and promote cellular dysfunction, whereas increased LONP1 activity may support pathological adaptation in specific disease contexts. This context dependence, together with the limited understanding of substrate specificity and the relative contributions of proteolytic versus chaperone-like functions, remains a major challenge for therapeutic targeting.

Future studies should define the determinants of substrate recognition and functional switching across tissues and disease states, while establishing how LONP1 can be selectively modulated without compromising mitochondrial proteostasis in normal tissues. Addressing these questions, together with rigorous evaluation of mitochondrial delivery and toxicity, will be essential for determining the therapeutic boundaries of LONP1 and its potential for safe clinical translation.

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Authors' contributions

DC wrote the manuscript. QL and YZ acquired and interpreted the data. DX conceived and designed the review. ZZ reviewed the manuscript for intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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