# Lipid Metabolism and Proteostasis Interdependencies and Implications for Nuclear Envelope Dysfunction and Neurodegenerative Disease

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**Abstract**

The maintenance of cellular homeostasis features the interplay between the mechanisms of proteostasis and lipid metabolism with the integrity of the nuclear envelope (NE). When disruptions to this balance occur, cells become more susceptible to the pathogenesis of diseases that involve ER stress or neurodegeneration, such as nonalcoholic fatty liver disease (NAFLD) and Alzheimer's disease (AD). Focusing on the impact of endoplasmic reticulum (ER) stress and unfolded protein response (UPR) signaling, this review analyzes the molecular mechanisms that support the interconnected pathways of lipid metabolism and proteostasis: AMP-activated protein kinase (AMPK) and Stearoyl-CoA Desaturase 1 (SCD1) are two examples of molecular targets to preserve NE integrity and mitigate proteotoxic stress. Examination of these mechanisms can lead to the development of treatments—potentially involving small molecules and gene therapies—to restore lipid and proteostasis balance. By comprehending the interdependency between proteostasis and lipid metabolism, we can develop a new understanding of the complex cellular pathways involved with the ER and NE to develop therapeutics to address diseases associated with the dysfunction of these organelles.

## Introduction

Proteostasis and lipid metabolism have both been recognized as integral parts of normal cellular function. Proteostasis—the mechanism that governs the production and regulation of proteins—is commonly linked with neurodegenerative diseases. Similarly, lipid metabolism, which oversees the synthesis and utilization of lipids, plays a role in modulating proteins (Nong et al.). Building on this notion, emerging research suggests that perturbations in lipid metabolism often cascade into dysfunctions in the proteostasis system to highlight a correlation between the two mechanisms.

This review discusses how dysregulation of these roles of proteostasis and lipid metabolism within the nuclear envelope contributes to disease states. Key drivers of cellular dysfunction in neurodegeneration, endoplasmic reticulum (ER) stress, and the unfolded protein response (UPR) are resultantly affected pathways from such dysregulation. We aim to provide an overview of the function of key enzymes and degradation systems to examine the interplay between molecular mechanisms found in cellular homeostasis. The analysis of these pathways allocates the development of therapeutics—such as small molecules and gene therapies—for conditions concerning the dysfunction of the NE and cellular aging.

## Proteostasis Networks and Lipid Metabolism

The proteostasis network ensures cellular homeostasis, which focuses on the correct synthesis and degradation of proteins. Encompassing an array of molecular chaperones and quality control mechanisms, this network is critical for sustaining cellular function. Simultaneously, lipid metabolism—specifically within the endoplasmic reticulum (ER) and nuclear envelope (NE)—supports the functional and structural integrity of intracellular signaling and cellular membranes. The interdependence between lipid metabolism and proteostasis becomes a factor when analyzing its role in the pathogenesis of diseases.

The mitigation of forming protein aggregates and proper folding of nascent polypeptides, as well as the direction of misfolded proteins to degradation pathways, are all processes involved in the PN. Heat shock proteins (HSPs)—such as HSP70 and HSP90—are integral in facilitating this folding process in the duration of both unstressed and stressed conditions (Ma et al.): HSP70 binds to nascent polypeptides to prevent premature folding and aggregation, while HSP90 buffers the effects of cellular stress and stabilizes proteins in signal transduction. Consequently, both proteins assist in proteome stability. The use of HSP70 has therapeutic potential since upregulation of HSP70 has been shown to enhance proteostasis and reduce the progression of protein aggregation disorders in preclinical models (Sarfowah).

The ubiquitin-proteasome system (UPS) and autophagy mechanisms oversee the degradation of misfolded or damaged proteins and ensure quality control. The UPS system confers substrate specificity to be responsible for a majority of cellular protein degradation (Ma et al.);(Heo et al.). The enzymes involved include E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. On the other hand, autophagy encapsulates proteins and damaged organelles with autophagy that subsequently fuse with lysosomes for degradation (L. Lei et al.). The selection between utilizing UPS and autophagy is reliant on the size of the misfolded or damaged proteins: smaller, soluble proteins favor UPS while larger aggregates are targeted by autophagy. The interaction between these two pathways promotes the adaptability of the PN, which is beneficial in periods of proteostatic stress (L. Lei et al.).

Particularly through membrane dynamics and communication between cells, lipid metabolism within the NE and ER supports cellular homeostasis. Facilitating the exchange between itself and the ER, the NE is comprised of the inner nuclear membrane (INM) and outer nuclear membrane (ONM) (Korbecki et al.). Conversely, the ER produces glycerophospholipids and triacylglycerols (TAGs) as the main site for lipid biosynthesis, making it a significant factor for membrane biogenesis. (Romanauska and Köhler). Studies demonstrate that elevated levels of diacylglycerol are characteristic of the distinct lipid composition and a precursor for TAG synthesis and phospholipid (Romanauska and Köhler): this unique environment for lipids ensures the structural integrity and viscosity of the INM and influences the folding and stability of membrane-embedded proteins (Sahu and Lorigan). As a result, disruptions can contribute to disease processes and impair NE integrity.

Levels of lipid saturation are regulated with little margin of error in order to prevent lipotoxicity even in increased unsaturated fatty acid (UFA) levels. To mitigate the effects of excess UFAs and preserve the integrity of the INM, cells reprogram lipid storage mechanisms in situations with metabolic stress, predominantly across the ER and the NE (Romanauska and Köhler). Furthermore, lipid droplets (LDs)—formed from the ER and ONM—protect the nucleus from ramifications of lipid overload to sequester neutral lipids. For instance, the LDs are upregulated when the ER is stressed via the ATGL-mediated lipolysis pathway when formed. This buffers the effects of lipid-induced proteotoxicity (Romanauska and Köhler).

Central contributors to the pathogenesis of diseases involve disturbances in lipid metabolism and proteostasis. Dysregulation is a strong influence on nonalcoholic fatty liver disease (NAFLD), while nonalcoholic steatohepatitis (NASH) and hepatic steatosis can result from excessive accumulation of lipids within hepatocytes (Östlund et al.); (Adom et al.). Contrarily, the accumulation of misfolded proteins from disruptions in proteostasis overwhelms the PN and results in the pathophysiology of neurodegenerative diseases such as Alzheimer’s disease (L. Lei et al.).

Beyond disease, the interdependence between lipid metabolism and proteostasis is demonstrated by lipid-induced proteotoxicity: the formation of protein aggregates can stem from the accumulation of UFAs that negatively disrupt proteostasis. The metabolic stress subsequently subtracts lipids from cellular compartments, including the nucleus, to mitigate proteotoxic stress by altering lipid droplet formation and distribution (Tripathi et al.). However, this temporary alleviation of proteotoxic stress can impact nuclear function (Romanauska and Köhler).

**Lipid Metabolism and Protein Degradation at the Nuclear Envelope**

Lipid metabolism stabilizes the integrity and thus the functionality of the nuclear envelope; this helps regulate nucleocytoplasmic exchange and genome organization. The two membranes, the inner nuclear membrane (INM) and outer nuclear membrane (ONM), work in tandem with the nuclear pore complexes (NPCs) to facilitate protein interactions and influence membrane dynamics (Rush et al.). Studies have shown increased permeability and compromised cellular signaling that resulted from reductions in DAG species to destabilize the NE (S. Lee et al.).

Another component in maintaining the NE's identity is the lipid environment of the INM, which is influenced by CTDNEP1 and other proteins. To ensure the production of species containing polyunsaturated fatty acids (PUFAs), such as diacylglycerol (DAG) species, CTDNEP1 regulates phosphatidic acid phosphatase lipin 1. Since PUFA-containing DAGs sustain the fluidity of the INM, CTDNEP1's absence, which precipitates a reduction in PUFA-containing DAGs, imbalances the stability of INM-resident proteins like SUN2: these proteins are integral for nuclear architecture and nucleo-cytoskeletal coupling. Research with lipidomic profiling displays decreases in SUN2 localization at the INM after a loss of CTDNEP1 to decrease PUFA-DAG levels (S. Lee et al.).

Another integral factor of lipid metabolism at the NE is autophagy; with nucleoporins, such as Nup159, acting as cargo receptors for autophagic markers, autophagy mediates the degradation of nuclear pore complexes (NPCs) under nutrient-deprived conditions (Hanley). Therefore, lipid turnover supports both membrane synthesis and the removal of obsolete or damaged components, as reductions in nucleoporin levels result from autophagy-mediated degradation of NPCs during nitrogen starvation (C. Lee et al.).

In the nucleoplasmic domain of SUN2, the amphipathic helix (AH) prefers membrane packing defects; the consequent degradation through the proteasome results from the dissociation of SUN2's AH from the INM and change in lipid composition. In vitro studies highlighted an increase in proteasomal degradation after disruption of the AH-lipid interaction in SUN2 (S. Lee et al.). Thus, this suggests that lipid composition determines protein stability and NE integrity, as the NE proteins are sensitive to their lipid milieu (Pepelnjak et al.).

As storage depots for lipids that are neutral, nuclear lipid droplets (nLDs) have had their biogenesis impacted by the INM; for instance, the synthesis of triacylglycerol at the INM influences nuclear organization. Moreover, studies suggest increases in nuclear volume and subsequent chromatin structure reorganization have formed from nLDs that are preferentially formed at the INM under conditions of lipid oversupply (Krshnan et al.). This shows that lipid droplets demonstrate the role of lipid metabolism in both membrane integrity and nuclear systems, as lipid droplets aid in the regulation of nuclear components (Palikaras et al.).

Proteins such as TPR, which are involved in the modulation of the number of NPCs, are sensitive to lipid metabolism. Therefore, disruptions in lipid homeostasis can alter NPC integrity and affect disease progression and aging (Cologna et al.). Reduction in NPC density is correlated with age-related declines in lipid metabolism and is followed by impaired cellular function (C. Lee et al.).

The ubiquitin-proteasome system (UPS) degrades SUN2 through phosphorylation of SUN2 by Casein Kinase 2 (CK2); this triggers SUN2 recognition by the SCFβTrCP ubiquitin ligase complex and the consequent ubiquitination and degradation of the macromolecule. Furthermore, CTDNEP1 maintains the stability of CK2 by regulating the composition of lipids at the INM so that CK2 can promote SUN2 degradation (Foster et al.). The inhibition of CK2 activity reduces SUN2 degradation and underscores the kinase's role in regulating NE protein turnover (Krshnan et al.).

A process influenced by lipid metabolism, nucleoporins undergo selective degradation through autophagy during nutrient deprivation. Reduction in nuclear transport efficiency is associated with the loss of Nup159 (C. Lee et al.). The binding of autophagic markers like Atg8 and Nup159—after Nup159 is exposed to the cytoplasm—demonstrates interdependencies between lipid metabolism and protein degradation pathways at the NE through the promotion of autophagic turnover of NPCs (Boyle and Wilfling).

The disruption in these pathways leads to higher susceptibility to diseases such as cancer and muscular dystrophy and greater instability in the nuclear envelope. For instance, aberrant nuclear morphology and an increased frequency of lagging chromosomes during mitosis result from an accumulation of non-degradable SUN2 (Krshnan et al.). An increase in mitotic error was found after elevated levels of non-degradable SUN2. This solidifies a direct link between chromosomal instability and lipid metabolism disruptions (Ramundo et al.).

Impact of ER stress and UPR signaling on lipid metabolism, proteostasis, and diseases

ER stress is a condition where the endoplasmic reticulum (ER), the organelle that maintains cellular homeostasis through the synthesis and folding of proteins, becomes unbalanced. This results in the unfolded protein response (UPR) being initiated to restore optimal function. The

response adjusts overall protein synthesis by enhancing protein folding capabilities and degrading misfolded or damaged proteins (Krshnan et al.). However, severe cellular dysfunctions—which include compromises to the NE—result when ER stress becomes chronic and UPR is continuously triggered (Singh et al.). This can be demonstrated through the integrity of the NE, as chronic ER stress can increase NE permeability, significantly affecting nucleocytoplasmic transport and cellular structure (Bueno and Rojas). These disruptions include NE invaginations and ruptures that interrupt overall dysfunction; this could result in cellular senescence or apoptosis, further emphasizing the critical interdependence between ER stress and NE dysfunction with lipid metabolism and proteostasis.

There are three signaling branches utilized by UPR: IRE1, PERK, and ATF6. The splicing of XBP1 mRNA - which encodes a transcription factor that upregulates the expression of chaperones involved in ER-associated degradation (ERAD) - is activated by IRE1. PERk, conversely, phosphorylates eIF2α (Ohri et al.). This selectively enhances the translation of ATF4 to influence the genes expressed in stress responses while further reducing general protein synthesis. Lastly, upon activation, ATF6 is cleaved in the Golgi apparatus to release a transcription factor that upregulates genes that are targeted by UPR (D. Lee et al.). Further research under chronic stress links the modulation of lipid metabolism to proteostasis, as the suppression of lipid biosynthesis pathways has a correlation with the activation of PERK (Pachikov et al.).

When not correctly managed, the accumulation of misfolded proteins disrupts the integrity of the nuclear lamina's structure. Increased production of reactive oxygen species (ROS) can further disrupt the nuclear lamina through the oxidative modification and damaging of NE proteins during prolonged ER stress (Kristiani and Kim). Oxidative damage of NE proteins and subsequent structural compromise stem from an increase in ROS production via chronic ER stress (S. Lee et al.).

Chronic ER stress plays a strong role in the pathogenesis of idiopathic pulmonary fibrosis (IPF) as it leads to cellular injury and fibrosis, which impairs the capacity of alveolar epithelial cells to manage stress. For example, a reduction in the regenerative capacity of alveolar epithelial cells stems from chronic ER stress (Bueno and Rojas). ER hormesis, however, introduces the notion of mild ER stress being a possible mechanism to promote cellular resilience against conditions related to NE dysfunction. Since mild ER stress degrades misfolded proteins through the stimulation of the UPR and autophagy, the accumulation of damaged components within the NE is prevented (Yeap et al.). Conditions like chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) display the effects of this adaptive response and have shown improved cellular function and slower disease progression (Bollenbecker et al.). Therefore, studies suggest that promoting mild ER stress may be a viable future therapeutic avenue for managing such diseases that involve NE dysfunction. This concept of ER hormesis demonstrates

the balance between stress responses and cellular resilience mechanisms in the integrity of the nuclear envelope (F. Cheng et al.).

Diseases associated with neurodegeneration and aging further demonstrated the relationship between ER stress and lipid metabolism for NE integrity. One study, utilizing advanced neuron models derived from aged and Alzheimer's disease (AD) donors, demonstrates that cellular dysfunction can result from disruptions in lipid metabolism within the ER and impairment of proteostasis due to NE dysfunction. Furthermore, ER stress—often resulting from lipid imbalances—overwhelms the cellular machinery responsible for protein folding and degradation, worsening such proteostatic disruptions (Ajoolabady et al.). In proteomic studies, AD tNeurons display an increase in proteostasis deficits, while aged tNeurons, compared to young tNeurons, exhibit an increase in these deficits. Aged neurons also demonstrate an increase in lysosomal damage markers, while AD neurons show an increase as the compromised state of the NE—specifically within the endosome-lysosomal system—further disrupts intracellular signaling and organelle function (Chou et al.). This indicates a cycle of acceleration in cellular aging and promotion of the accumulation of amyloid-beta (Aβ) and tau—phenomena apparent in AD—due to undermining proteostasis and NE integrity through ER stress and lipid metabolism dysregulation.

**Therapeutic Implications**

Stearoyl-CoA Desaturase 1 (SCD1)—an enzyme integral to the synthesis of monounsaturated fatty acids from saturated precursors—is a potential target within lipid metabolism. In models of diet-induced steatosis, the down-regulation of SCD1—through inhibitors such as CAY10566—has been shown to reduce lipid accumulation as the enzyme is influential in hepatic lipid metabolism. For instance, studies showed a reduction in hepatic steatosis in preclinical models after the application of SCD1 inhibitors (Y. Zhou et al.). Moreover, AMP-activated protein kinase (AMPK) is a regulator of cellular energy homeostasis that promotes fatty acid oxidation while inhibiting lipogenesis and has been shown to have a relationship with SCD1 activity (Steinberg and Hardie). In turn, AMPK activation mitigates hepatic lipid deposition by enhancing lipophagy to degrade lipid droplets. In experimental models, SCD1 inhibition—that led to the activation of AMPK—caused hepatic triglyceride levels to decrease. This showcases the therapeutic potential for the utilization of SCD1 inhibitors (Poznyak et al.).

Another target that could be used to treat diseases associated with NE dysfunction is the NLRP3 inflammasome. A key component of the inflammatory response associated with atherosclerosis, the NLRP3 inflammasome exacerbates lipid accumulation and leads to plaque formation within arterial walls by triggering the release of pro-inflammatory cytokines after its activation by cholesterol crystals.

Another therapeutic solution to atherosclerosis is ApoA-I mimetics that promote cholesterol efflux (Zhen et al.). These mimetics mitigate inflammation and reduce plaque burden by increasing the expression of cholesterol transports to improve lipid profiles. For example, a reduction in arterial plaque formation stems from the use of ApoA-I mimetics (Y. Zhou et al.); this underscores the usage of ApoA-I mimetics as a cardiovascular therapeutic for diseases caused by disruptions in lipid metabolism and proteostasis (Sviridov et al.).

Given the rise of clinical implementation of gene therapies, gene transfer mediated by adeno-associated virus (AAV) has garnered interest in disorders involving proteostasis and lipids, including familial hypercholesterolemia (Sviridov et al.). As a possible long-term solution for managing dyslipidemia, this approach ensures balance in lipid metabolism and the NE. Additionally, modulating cholesterol crystal-induced inflammation through gene therapy that targets the NLRP3 inflammasome represents another possible strategy (Tanase et al.). Therefore, the interdependence between proteostasis and lipid metabolism can be designated as a novel treatment for metabolic and inflammatory diseases (Y. Zhou et al.).

**Challenges and Future Directions**

While enticing, the hurdle of navigating the complexity and interconnectivity of such metabolic networks must still be addressed. For example, decreased energy production is a possible side effect of utilizing SCD1 inhibition to reduce hepatic steatosis (Rao et al.). Unintentional effects can be created when targeting a single enzyme or pathway, as such action typically affects multiple aspects of cellular metabolism (Y. Zhou et al.).

Due to epigenetic and environmental factors, the variability of patient response also makes the formulation of universal treatments that can be administered on a larger scale much more difficult. One factor is the presence of sexual dimorphism that may require alternative approaches between biological sexes in diseases such as NAFLD (Martin-Grau and Monleon). Cancerous disorders also question the long-term efficacy of lipid-targeted therapies. In therapies like satins, some patients displayed chronic resistance, which emphasizes a need for a potential combination of strategies (Sviridov et al.).

The molecular mechanisms involved in the targets of treatments must be addressed to determine their effectiveness and uncover possible new therapies. For example, the role of therapeutic potential in treating NAFLD can be explored through continued analysis of the role of SCD1 in lipophagy (J. Wang et al.). Similarly, the roles interleukin-10 (IL-10) and lipid metabolism play in liver disease can be further addressed, while more effective treatments in cancer research can be uncovered through the integration of lipidomics and proteomics (L. Zhao et al.). By pursuing the interdependence between proteostasis and lipid metabolism, we can develop new avenues for therapies that address diseases that result from the disruption of these mechanisms.

## Conclusion

These findings highlight the relationship between the nuclear envelope integrity and the mechanisms of proteostasis and lipid metabolism. Particularly within the endoplasmic reticulum and nuclear envelope, disruptions in these pathways are conducive to neurodegeneration and lipid imbalances through the cellular environments they create. This is evident through the triggering of proteostatic and lipid metabolic dysfunctions that compromise NE integrity by ER stress and unfolded protein response (UPR) signaling. These disruptions further accelerate cellular aging and lead to lipid-induced proteotoxicity and, in neurons, the accumulation of neurotoxic proteins such as amyloid beta (Aβ) and tau.

Therapeutic targets can also be developed through a current understanding of proteostasis and lipid metabolism. Treatments that involve small molecules like inhibitors of Stearoyl-CoA Desaturase 1 (SCD1) can modulate AMP-activated protein kinase (AMPK), as they have preserved NE integrity by promoting autophagic clearance of damaged proteins and reducing lipid accumulation. The potential of targeted therapies is highlighted by the roles of molecular chaperones and the ubiquitin-proteasome system (UPS) to counteract proteotoxic stress observed in related diseases. Since these treatments can also influence the endosome-lysosomal systems, conditions that involve neurodegeneration can also be managed. While still in preclinical studies, these possibilities have the potential to uniquely address the root ramifications of the nuclear envelope or neurodegenerative diseases.

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