Nuclear lamina as a dynamic molecular hub in cancer progression: Mechano-regulation, nucleophagy, autophagic secretion and post-translational modifications (Review)

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Abstract. The nuclear lamins, key structural components of the nuclear lamina, have emerged as dynamic regulators of cancer cell survival, mechanotransduction and metastatic progression. Rather than functioning solely as static nuclear scaffolds, A-type (lamin A/C) and B-type (lamin B1/B2) lamins undergo dynamic alterations that influence cellular behavior under mechanical and metabolic stress. The present review synthesizes the multifaceted roles of lamins in tumor biology, focusing on pro-migratory nuclear deformability, selective nucleophagy, autophagic secretion and post-translational modifications (PTMs). Reduced lamin A/C expression enhances nuclear deformability to facilitate cell transit through dense extracellular spaces, whereas higher expression preserves structural integrity against physical stress. Selective nucleophagy acts as a vital nuclear quality-control mechanism, eliminating damaged nuclear constituents to maintain genome stability. Matrix metalloproteinase-mediated cleavage of lamin A promotes cancer cell migration by softening the nucleus, with cleaved fragments co-secreted via amphisomes and autophagic extracellular vesicles. Furthermore, diverse PTMs, including phosphorylation, small ubiquitin-like modifier (SUMO)ylation, acetylation, farnesylation, palmitoylation and O-linked β-N-acetylglucosamine (O-GlcNAc)ylation, serve as functional switches that modulate nuclear mechanics, chromatin tethering, DNA damage responses and cell cycle progression. Targeting these lamin-modifying enzymatic pathways presents promising therapeutic opportunities to restore nuclear stability, impair metastatic invasion and overcome therapy resistance. Ultimately, nuclear lamina remodeling represents a central molecular hub and a potential therapeutic target in cancer progression.

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Abbreviations: CAF, cancer-associated fibroblast; CDK, cyclin-dependent kinase; ECM, extracellular matrix; EV, extracellular vesicle; FTase, farnesyltransferase; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HGPS, Hutchinson-Gilford progeria syndrome; HNSC, head and neck squamous cell carcinoma; KAT, lysine acetyltransferase; LAD, lamina-associated domain; LC3, microtubule-associated protein 1A/1B-light chain 3; LMNA, gene encoding lamin A/C; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NOD2, nucleotide-binding oligomerization domain-containing protein 2; O-GlcNAc, O-linked β-N-acetylglucosamine; OGT, O-GlcNAc transferase; PP, protein phosphatase; PTM, post-translational modification; Rb, retinoblastoma protein; SUMO, small ubiquitin-like modifier; TNBC, triple-negative breast cancer; UBC9, ubiquitin-conjugating enzyme 9; ZMPSTE24, zinc metallopeptidase Ste24

Key words: lamin, cancer, autophagy, nucleophagy, MMP, EV, phosphorylation, acetylation, palmitoylation

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1. Introduction

The nucleus is a highly specialized organelle in mammalian cells that stores genetic material and regulates key cellular activities, including gene expression, DNA replication and

DNA damage repair. The nuclear lamina, an intricately woven filamentous mesh located just beneath the inner nuclear membrane, is vital for maintaining nuclear architecture, chromatin organization and genome stability (Fig. S1). Its core components are type V intermediate filament proteins, including A-type lamins (lamin A/C) and B-type lamins (lamin B1/B2) (1-4). A- and B-type lamins display distinct spatial organization at the nuclear periphery, and together with nuclear envelope-associated proteins such as emerin, participate in maintaining nuclear structural stability, chromatin positioning and nuclear function (5-7). Lamin A and lamin C, encoded by the lamin A/C (*LMNA*) gene, are key structural components that maintain nuclear integrity and regulate vital cellular processes, including DNA replication, gene expression and mechanotransduction (8). Lamins, positioned at the interface between the cytoplasm and the nuclear genome, act as both mechanical scaffolds and dynamic signal transducers, responding to cellular and environmental stimuli (9).

In the present review, conflicting findings in lamin biology and cancer progression are critically appraised and compared. The study of nuclear lamins has evolved from viewing them as passive structural scaffolds to recognizing them as dynamic molecular switches that integrate mechanical, metabolic, epigenetic and signal transduction networks. However, the growing body of literature reveals several major discrepancies and paradoxes regarding the functional roles of lamins in oncogenesis, metastasis and cellular survival. The primary conflicting findings addressed in this review include: i) The mechanical paradox of lamin A/C expression, focusing on nuclear deformability vs. structural protection; ii) the context-dependent roles of lamin-associated nucleophagy; iii) the divergent functional outcomes of lamin post-translational modifications (PTMs); iv) proteolytic lamin cleavage, focusing on apoptotic dismantling vs. viable migratory adaptation. The review also describes the methodological limitations and knowledge gaps in lamin cancer biology.

2. Context-dependent roles of lamin A/C in nuclear deformability and mechanical stability

The effects of lamin A/C on cancer progression appear to be highly context-dependent, reflecting a trade-off between nuclear deformability and structural stability (10,11).

Pro-migratory nuclear softening (low lamin A/C). Low expression and degradation of lamin A/C increases nuclear deformability, allowing cancer cells to squeeze through narrow interstitial spaces, dense extracellular matrix (ECM), capillary pores (12,13) and blood vessel walls (Fig. 1). Consequently, global loss or downregulation of lamin A/C is associated with enhanced confined cell migration, increased metastatic capacity and a poor clinical prognosis in cancers such as triple-negative breast cancer (TNBC), ovarian, colon, and head and neck carcinomas (12,13).

Mechanostability and survival (high lamin A/C). Conversely, higher lamin A/C expression confers essential structural rigidity, enabling the nucleus to withstand severe mechanical compression within stiff tumor microenvironments without undergoing nuclear envelope rupture or irreversible DNA damage (9,12,14). Furthermore, basal lamin A/C expression is required to maintain cell polarity and cytoskeletal organization. Elevated *LMNA* mRNA expression has been associated with increased proliferation and migration in hepatocellular carcinoma (HCC) models (15). Moreover, excessive nuclear softness can limit cancer cell survival under high mechanical strain (12,14).

To reconcile these observations, lamin A/C appears to play a context-dependent, bidirectional role. Tumors may dynamically regulate lamin A/C expression or PTMs, temporarily softening the nucleus to permit invasive passage while maintaining sufficient structural resilience to prevent mechanical collapse and cell death (9).

3. Nucleophagy and lamina degradation

Context-dependent roles of lamin-associated nucleophagy. Selective autophagic degradation of the nuclear lamina (nucleophagy) exhibits context-dependent functional outcomes that vary with stress conditions and the lamin subtype involved (Fig. 2) (5,16). Under oncogenic stress, such as RAS activation, or following DNA damage, microtubule-associated protein 1A/1B-light chain 3 (LC3)/Atg8 directly interacts with lamin B1 within lamina-associated domains (LADs) and targets it for nucleophagic degradation (17) (Fig. 2A). This process is associated with cellular senescence and the restriction of abnormal proliferation, supporting a tumor-suppressive role for Lamin B1 nucleophagy (16).

Under DNA damage conditions, ubiquitin-conjugating enzyme 9 (UBC9)-mediated small ubiquitin-like modifier (SUMO)ylation of lamin A/C has been linked to LC3-associated nucleophagic clearance (18). Other stressors, including arginine deprivation, may also disrupt nuclear lamina integrity and promote autophagic clearance of nuclear material (19).

Matrix metalloproteinase (MMP)-3-mediated lamin A cleavage was associated with nuclear budding, autophagic transport, and extracellular vesicle (EV) release in the Colon26 and LuM1 metastatic colon cancer model (Fig. 2B) (20). This MMP-3/lamin A pathway differs from lamin B1 nucleophagy, and the biological effects of EV-associated cleaved lamin A on recipient cells remain unresolved.

Mechanisms of nucleophagy and lamin regulation. As a nuclear quality-control mechanism, nucleophagy selectively removes damaged nuclear envelope components, abnormal nuclear lamina, leaked nuclear DNA, and even partial nuclear structures, thereby preventing the accumulation of defective nuclear material and maintaining genome stability (5,21,22). Mechanistically, degradation of the nuclear lamina is one of the better-defined processes in nucleophagy. Dou *et al* (16,17) found that the autophagy protein LC3/Atg8 can directly interact with lamin B1 and associate with LADs. Under tumor-related stress conditions, such as RAS activation or DNA damage, this interaction mediates the selective degradation of lamin B1. This process differs from starvation-induced canonical autophagy and instead promotes cellular senescence and restricts abnormal cell proliferation through nuclear lamina remodeling. Changes in lamin B1 levels also affect cell proliferation, senescence, chromatin structure and gene expression, suggesting that nuclear lamina degradation is not merely the clearance of structural proteins but may also

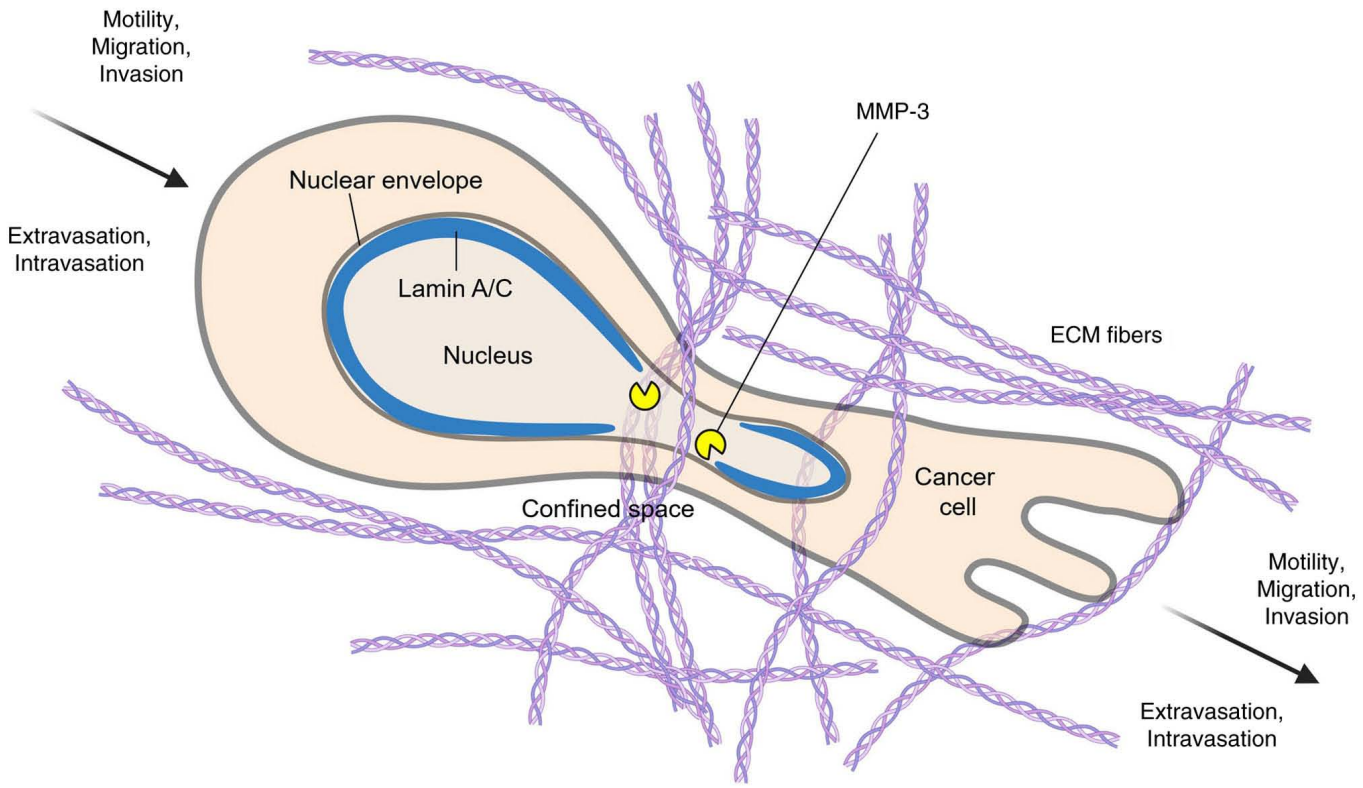

Figure 1. MMP-3-mediated cleavage of lamin A promotes cancer cell migration by softening and transforming nuclei and nucleophagic extracellular vesicle secretion. Increased nuclear deformability facilitates cancer cell migration, invasion, extravasation, and intravasation through confined spaces. ECM, extracellular matrix; MMP3, matrix metalloproteinase-3. Created with BioRender.com.

influence transcriptional regulation and chromatin homeostasis (23,24). In addition, abnormalities in A-type lamins and the nuclear envelope protein emerin can alter nuclear envelope structure and induce autophagic degradation of nuclear components (25).

PTMs of lamins also regulate nucleophagy. SUMOylation broadly regulates nuclear processes such as chromatin organization, nuclear transport, transcriptional regulation, DNA repair and genome stability (26,27). Under DNA-damage conditions, UBC9 accumulates in the nucleus and promotes SUMOylation of lamin A/C, thereby facilitating its interaction with LC3 and nucleophagy-associated clearance of lamin A/C and leaked nuclear DNA (18). Previous work also established that lamin A/C can be a target of SUMOylation and that UBC9 can interact with lamin A/C to promote this modification (18,28,29). By contrast, UBC9-mediated SUMOylation of lamin A can inhibit ubiquitination at lysine 144 (Lys144), increase lamin A stability, and is associated with increased proliferation, migration and tumor growth in HCC (Fig. 3) (30). These findings highlight the context-dependent effects of lamin SUMOylation, which can facilitate LC3-associated nucleophagic clearance under DNA damage conditions or reduce ubiquitin-dependent proteasomal degradation in the HCC model. These divergent outcomes may depend on the modified residue, cellular context, and interactions with ubiquitination and LC3 binding. In addition, arginine deprivation can reduce lamin A/C levels and induce DNA damage and nuclear DNA leakage, suggesting that metabolic stress may also trigger autophagic clearance of nuclear material by disrupting nuclear lamina stability (19).

Roles of lamin-associated nucleophagy in cancer progression and metastasis. Autophagy and nucleophagy can have context-dependent effects on cancer progression. Autophagy can suppress malignant transformation by removing damaged organelles and abnormal proteins, limiting the accumulation of danger signals and maintaining tissue homeostasis (31,32). Nucleophagy-mediated nuclear lamina degradation is also considered an important component of tumor-suppressive senescence responses (33-35). Lamin A/C regulation can have distinct mechanical consequences depending on the cellular context. Reduced lamin A/C levels can increase nuclear deformability and facilitate confined migration, whereas sufficient lamin A/C expression helps maintain nuclear integrity under mechanical stress (36). In non-cancerous fibroblast models, lamin A/C deficiency has been shown to impair cell polarization and disrupt cytoskeletal organization and mechanics (37). In HCC, *LMNA* has been reported to function as an oncogene (15). Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) promotes hepatocarcinogenesis through two distinct mechanisms: A receptor-interacting protein 2 (RIP2)-dependent proinflammatory pathway and a RIP2-independent nucleophagy pathway. The latter involves nuclear NOD2-lamin A/C interaction, lamin A/C degradation, impaired DNA damage repair and genomic instability. Histamine-mediated Ca^{2+}/calcium/calmodulin-dependent protein kinase II signaling can regulate lamin A/C expression and reduce lung cancer cell migration (38).

MMP-3-mediated lamin A cleavage, autophagic transport and EV secretion. Studies of MMP-3 have linked lamin A

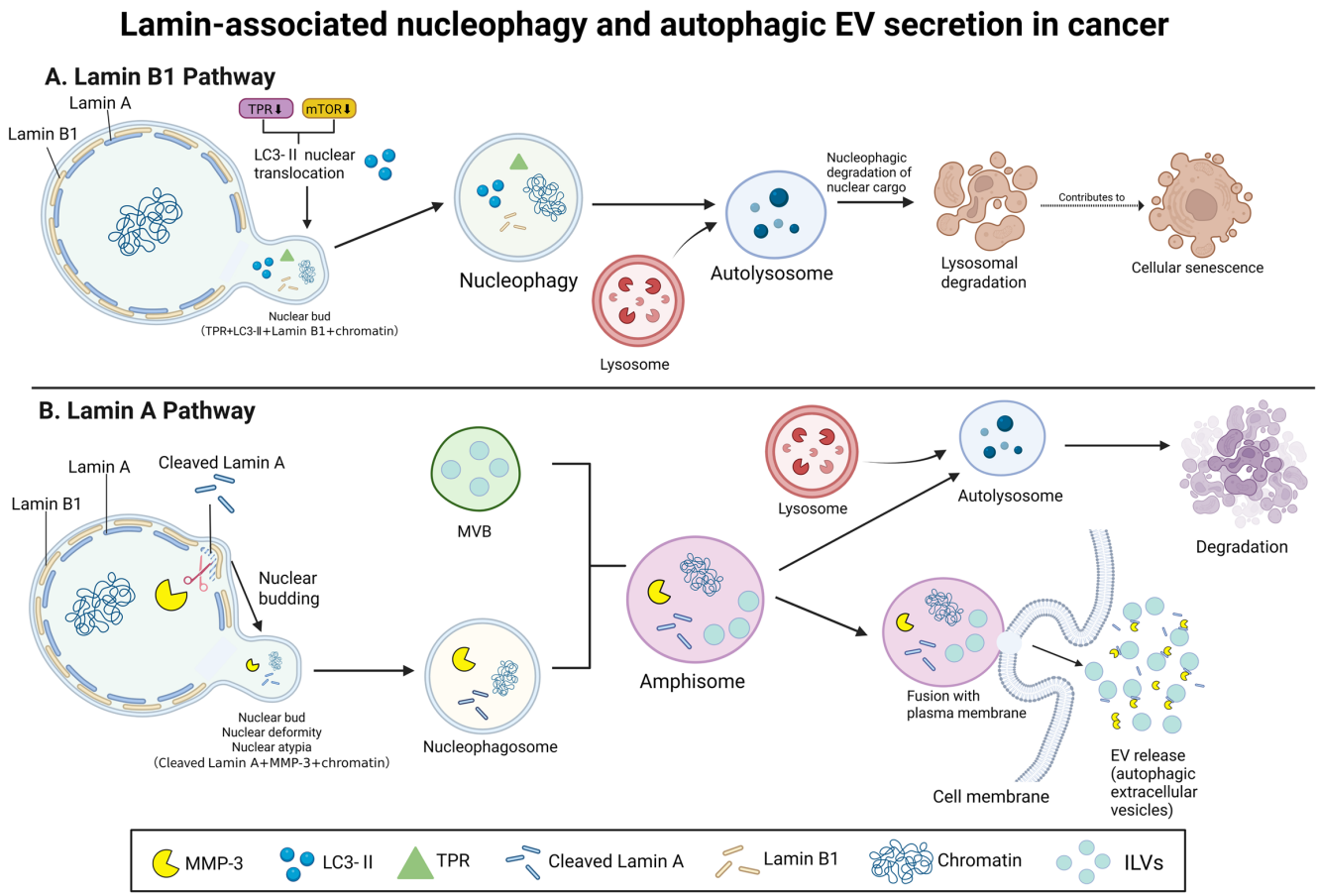

Figure 2. Lamin-associated nucleophagy and autophagic EV secretion in cancer. (A) TPR depletion or mTOR inhibition promotes LC3-II nuclear translocation, lamin B1-associated nuclear budding and nucleophagic degradation linked to cellular senescence. (B) MMP-3-mediated lamin A cleavage is associated with nuclear deformation, atypia and budding. Cleaved lamin A and MMP-3 enter nucleophagic structures that may form amphisomes with MVBs, followed by lysosomal degradation or EV release. EV, extracellular vesicle; ILV, intraluminal vesicle; LC3-II, lipidated microtubule-associated protein 1 light chain 3; MMP-3, matrix metalloproteinase-3; mTOR, mechanistic target of rapamycin; MVB, multivesicular body; TPR, translocated promoter region. Created with BioRender.com.

cleavage to nuclear deformability, nucleophagy, autophagic transport and autophagic EV release. In metastatic colon cancer cells and three-dimensional tumoroid models, MMP-3-mediated lamin A cleavage was associated with increased nuclear deformability and enhanced migration in confined spaces (Fig. 1). Cleaved lamin A and MMP-3 were detected within autophagosomes and amphisomes and were released into the extracellular space via EVs (Fig. 2B) (20). These observations support a model-specific association rather than establish a universal mechanism across cancer types.

An amphisome is an intermediate vesicular structure formed by the fusion of an autophagosome with a late endosome or a multivesicular body; it can subsequently fuse with a lysosome for degradation or with the plasma membrane for extracellular release. In tumor cells, amphisome formation and EV release can be promoted by IκB kinase, providing mechanistic context for autophagy-related secretion (39). EVs are heterogeneous and should not be assumed to share a single biogenesis pathway (40). Therefore, MMP-3-mediated extracellular release of cleaved lamin A may involve autophagy-related EV secretion, but the precise vesicular origin and cargo-selection mechanisms remain unclear (20,41-43). In metastatic colon cancer models, MMP-3 depletion has also been associated with reduced migration, invasion, EV secretion and metastasis, although the steps linking these outcomes remain incompletely defined (20,41-43).

Nuclear localization of MMP-3 and cleaved lamin A in metastatic head and neck squamous carcinoma (HNSC) in clinical samples and the LuM1 colon cancer cell line provide supporting evidence of potential clinical relevance, but they do not establish that autophagic secretion of lamin A is a general mechanism driving metastasis. Both experimental and endogenous MMP-3 overexpression can fragment lamin A (20), and lamin alterations have been linked to genome-stability phenotypes in several cancer contexts, such as small cell lung cancer (44-46). Related studies of A-type lamins (44), *LMNA* loss in small cell lung cancer (45), and lamin B1 regulation of 53BP1 recruitment (46) provide supplementary context rather than proof of a universal MMP-3/lamin A pathway. It remains unclear whether lamin A cleavage is required for nuclear deformation and enhanced confined migration, whether EV-associated cleaved lamin A exerts biological effects on recipient cells or the metastatic microenvironment, and whether this pathway operates in other tumor types and tissue contexts.

Most mechanistic evidence derives from a limited number of experimental models, particularly metastatic colon cancer

models, whereas observations in HNSC provide supportive clinical context rather than causal evidence. Further studies are required to determine the generalizability of these findings across tumor types.

Nuclear MMP-3-mediated cleavage of lamin may promote cancer progression by inducing genomic instability and transcriptional activation. Knockdown or knockout of the *MMP3* gene markedly reduces colon cancer cell migration, invasion, tumorigenesis (spheroid formation), EV secretion and metastasis (20,41-43), indicating that MMP-3 promotes cancer progression and metastasis. In addition, EV-MMP-3 can translocate from the extracellular space to the cell nuclei, where it transactivates the cellular communication network factor 2 gene, also known as the connective tissue growth factor gene (42,47). EVs from *MMP3*-knockout cells abolished this transcriptional activity in colon cancer cells (Colon26 and LuM1) (42).

Nuclear MMP-driven cleavage of lamins may also cause genomic instability. Extracellularly administered MMP-3 was reported to translocate into the nucleus within 30 min in the HCS-2/8 chondrosarcoma cell line and the MMP3-KO LuM1 colon cancer cell line (42,47). Separately, MMP-3-induced genomic instability has been linked to Rac1b and reactive oxygen species (48). A-type lamins preserve genome stability (44), whereas lamin A/C loss promotes R-loop-mediated genomic instability and poor survival in small cell lung cancer (45), and lamin B1 sequesters 53BP1 to control its recruitment to sites of DNA damage (46). Together, these findings suggest that nuclear MMP-driven cleavage of lamins may induce DNA damage and genomic instability.

The majority of these findings are derived from cell culture studies of colon cancer and HNSC cells. Therefore, further studies are needed to determine whether these mechanisms apply to other cancer types.

Nucleophagy-based therapeutic and translational implications. From a therapeutic and translational perspective, lamin-associated nucleophagy may provide context-specific targets for cancer intervention. The most direct evidence comes from the lamin B1 nucleophagy study by Dou *et al* (17), from research on shikonin-induced ATG5-dependent non-canonical nucleophagy with lamin B1 degradation in TNBC cells (49) and from findings on translocated promoter region nuclear basket protein (TPR) depletion or mechanistic target of rapamycin inhibition, both of which are associated with LC3-II nuclear translocation and nuclear budding containing TPR, LC3-II, lamin B1 and chromatin (Fig. 2A) (50). Other studies report lamin alterations accompanied by changes in autophagy, apoptosis or cell-cycle regulation rather than demonstrating lamin-dependent causality. These include Huaier-associated lamin B1 downregulation (51), etoposide-associated lamin B1 loss and senescence (52), bortezomib-associated lamin A cleavage (53), lamin A/C cleavage observed following treatment with As_4O_6 combined with polyphenols extracted from Korean *Artemisia annua* L. (54) and isoprenylcysteine carboxyl methyltransferase inhibitor-associated prelamin A accumulation (55). These observations support further investigation of lamin-associated pathways, but whether lamin alterations directly mediate the antitumor effects remains uncertain. Cancer-type specificity, therapeutic windows and safety profiles also require further validation.

4. Lamin A/C PTMs

General overview of lamin A/C PTMs. Alterations in lamin A/C expression, structure and regulation are implicated in various pathological conditions, including muscular dystrophies, cardiomyopathies, premature-aging syndromes, lipodystrophies and cancer (56-58). PTMs regulate lamin A/C assembly, stability, subnuclear localization, and interactions with chromatin and other nuclear proteins, thereby influencing cell-cycle progression, genome maintenance and stress responses (59-61). Major lamin A/C PTMs include phosphorylation, farnesylation, acetylation, SUMOylation, ubiquitination and O-linked β-N-acetylglucosamine (O-GlcNAc)ylation.

Phosphorylation is the most extensively studied lamin A/C modification (Fig. 3A). During mitosis, cyclin-dependent kinase 1 (CDK1)-mediated phosphorylation promotes nuclear lamina disassembly, facilitating chromosome segregation and subsequent nuclear envelope reformation (Fig. 3B) (62-64). Beyond mitosis, phosphorylation regulates lamin A/C solubility, nuclear mechanics, protein interactions and chromatin organization (63,65-68).

Farnesylation of the C-terminal CAAX motif in prelamin A is followed by proteolytic processing to generate mature lamin A. Disruption of this process, particularly impaired zinc metallopeptidase Ste24 (ZMPSTE24) cleavage, leads to the accumulation of farnesylated prelamin A and alterations in nuclear structure and mechanics (69,70).

Acetylation and deacetylation regulate the lamin A/C structure and interactions with chromatin-associated proteins. Acetyltransferases, including components of the non-specific lethal (NSL) complex (71-73) contribute to these processes, potentially affecting chromatin organization and nuclear architecture.

SUMOylation regulates lamin A/C localization, stability, and protein interactions, including those involving transcriptional regulators and DNA repair factors. Its dysregulation may influence cell proliferation, survival and responses to cellular stress (18,74-76).

Ubiquitination regulates lamin A/C turnover and stability, affecting nuclear stiffness, deformability and responses to mechanical stress (13,77,78). These effects are context-dependent, with both increased and decreased lamin A/C abundance associated with distinct pathological phenotypes (13,78).

O-GlcNAcylation links lamin A/C regulation to nutrient availability and metabolic signaling, potentially influencing nuclear organization and stress responses (79,80). Palmitoylation has also been identified as a potential lamin A/C modification (81), suggesting additional lipid-dependent regulatory mechanisms.

Collectively, these modifications contribute to the regulation of nuclear mechanics, chromatin organization and signaling pathways involved in cancer progression. Altered lamin A/C PTMs may influence proliferation, epithelial-mesenchymal transition, metastasis and stress responses (82,83). Enzymes regulating these modifications, including kinases,

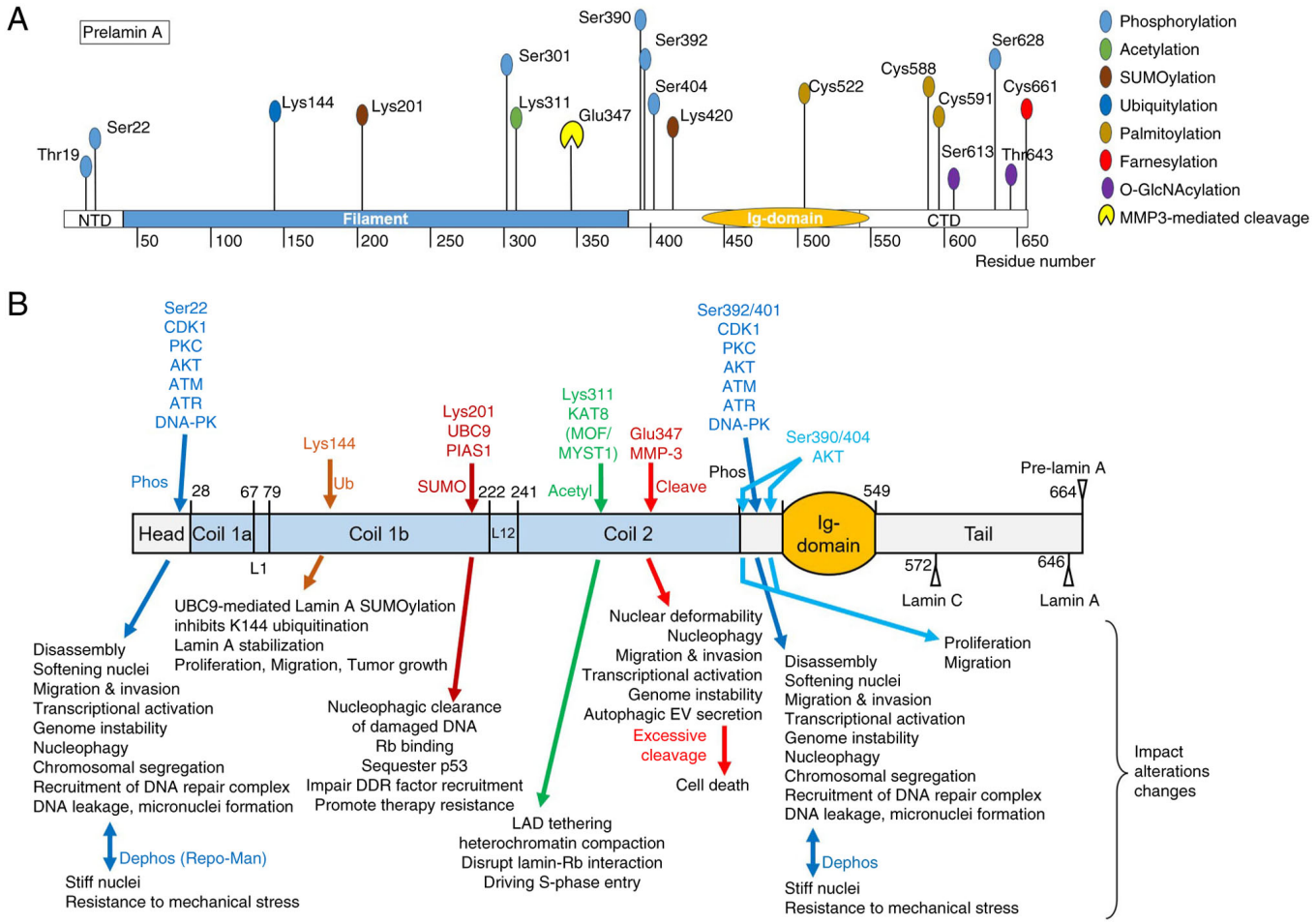

Figure 3. PTMs and cleavage of lamin A/C alter multiple cellular events. (A) Sites of PTMs and cleavage of lamin A. PTM sites are as listed in PhosphoSitePlus.org. (B) Enzymes reported to modify lamin A and their associated cellular effects. CDK1 phosphorylates Ser22, Ser392 and Ser401. AKT phosphorylates Ser390 and Ser404. KAT8 (also known as MOF or MYST1), within the NSL complex, acetylates Lys311. UBC9 and PIAS1 have been implicated in lamin A SUMOylation, including modification at Lys201. Acetyl, acetylation; AKT, protein kinase B; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; CDK1, cyclin-dependent kinase 1; dephos, dephosphorylation; DNA-PK, DNA-dependent protein kinase; KAT8, lysine acetyltransferase 8; NSL, non-specific lethal; phos, phosphorylation; O-GlcNAc, O-linked β-N-acetylglucosamine; PKC, protein kinase C; PTM, post-translational modification; PIAS1, protein inhibitor of activated STAT1; SUMO, small ubiquitin-like modifier; UBC9, ubiquitin-conjugating enzyme 9.

acetyltransferases, SUMO ligases, O-GlcNAc transferases and proteases, may represent potential therapeutic targets, while lamin A/C PTMs and cleavage products warrant investigation as candidate biomarkers. Several lamin A/C PTMs are curated in a PTM database (84).

Lamin A/C PTMs in cancer. Cancer cells commonly exhibit dysregulated gene expression, alterations in signaling pathways, genomic instability and abnormal nuclear morphology (85,86). Abnormal lamin A/C expression has been observed in cancer cells, with studies reporting both reduced and increased expression (10). Cytoplasmic mislocalization of lamin A/C and abnormal intranuclear lamin A/C organization have also been observed (85,87-90). Lamin A/C are emerging as important regulators of nuclear architecture, genome stability and signaling pathways involved in cancer progression (60,61). Their dysregulation may contribute to nuclear instability and tumor progression, depending on the cellular context and regulatory enzymes involved (Fig. 3B). Divergent functional outcomes of lamin PTMs in cancer are summarized (Table I; Fig. 4) (18,46,59,71,72,81,91-98).

Farnesylation of lamin A/C. Farnesylation is a lipid post-translational modification in which a 15-carbon farnesyl isoprenoid is attached to proteins containing a C-terminal CaaX motif, a reaction catalyzed by farnesyltransferase (FTase). Farnesylation regulates the membrane localization and signaling of several proteins, including Ras and Rho GTPases, and has been investigated as a therapeutic target in pancreatic, colorectal, acute myeloid leukemia, breast and lung cancer (99-101).

Lamin A is one of the best-characterized nuclear substrates of farnesylation (Table II) (99,100,102-106). Prelamin A contains a C-terminal CSIM motif, where Cys661 is farnesylated by FTase, anchoring the precursor protein to the inner nuclear membrane (104). This farnesylated intermediate undergoes sequential processing, including final proteolytic cleavage by ZMPSTE24, which removes the farnesylated C-terminal segment to generate mature lamin A. Impaired processing can cause accumulation of farnesylated prelamin A, resulting in altered nuclear morphology, mechanics, chromatin organization and genome instability (106). Hutchinson-Gilford progeria syndrome (HGPS), in which the persistently

Table I. Divergent functional outcomes of lamin PTMs in cancer.

PTM type	Dual/discrepant observations	Primary functional mechanisms
SUMOylation	DDR clearance vs. oncogenic E2F activation and p53 repression	UBC9-dependent SUMOylation at Lys201/Lys420 promotes nucleophagic clearance of damaged DNA (18,91). However, hyper-SUMOylation weakens lamin-Rb binding, releasing Rb prematurely and driving excessive E2F activation and proliferation (92,93). SUMOylated lamin A can also sequester p53 and impair DDR factor recruitment, promoting therapy resistance (46,94).
Acetylation/ deacetylation	Epigenetic stability vs. G_1/S delay and heterochromatin alterations	KAT8 (MOF)-mediated acetylation at Lys311 maintains LAD tethering and heterochromatin compaction (71,72). Conversely, lamin B1 acetylation delays G_1/S progression (95,98). Direct mechanistic proof for how acetylation regulates lamin assembly in cancer remains incomplete.
Palmitoylation	Differentiation permissiveness vs. dedifferentiated cancer state	ABHD7-mediated depalmitoylation softens the nucleus to allow myoblast differentiation (81). In cancer, maintaining palmitoylated lamin A may enforce a rigid, growth-permissive nuclear state that blocks differentiation and resists mechanical stress.
Phosphorylation	Mitotic disassembly vs. invasive softening and CAF transformation	AKT-mediated phosphorylation at Ser404 targets prelamin A for degradation (96), while loss of androgen receptor/PP1 interaction increases Ser301 phosphorylation and promotes CAF activation (97).

ABHD, α/β-hydrolase domain family; AKT, protein kinase B; CAF, cancer-associated fibroblast; DDR, DNA damage response; KAT8, lysine acetyltransferase 8; LAD, lamina-associated domain; PP1, protein phosphatase 1; PTM, post-translational modification; Rb, retinoblastoma protein; SUMO, small ubiquitin-like modifier; UBC9, ubiquitin-conjugating enzyme 9.

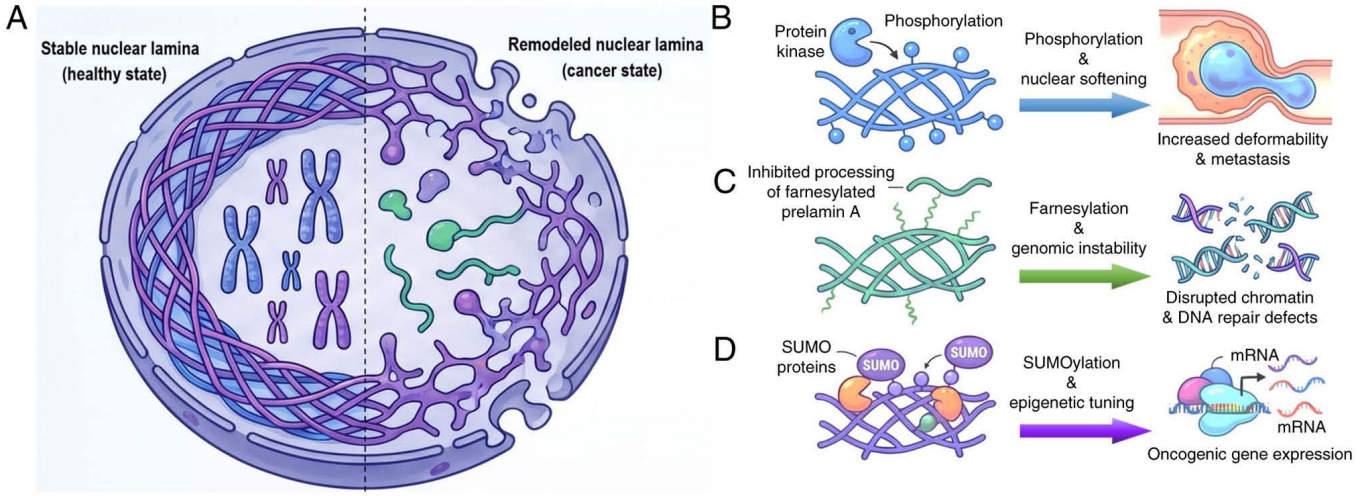

Figure 4. Lamin A/C PTMs act as molecular switches in cancer progression. (A) Lamin A/C is a structural protein that maintains the shape and stability of the cell nucleus. In cancer, PTMs may alter lamin A/C organization, nuclear mechanics and gene expression in ways that influence tumor growth and invasion. (B) Phosphorylation by kinases such as CDK1 and AKT regulates lamin A/C organization and may increase nuclear deformability, potentially facilitating cancer cell migration and invasion. (C) Impaired prelamin A processing leads to accumulation of farnesylated prelamin A, which may disrupt chromatin organization and DNA repair. (D) SUMOylation at reported sites, including Lys201/Lys420, may alter lamin A/C interactions with transcription regulators such as retinoblastoma protein, potentially influencing cancer-associated gene expression. AKT, protein kinase B; CDK1, cyclin-dependent kinase 1; PTM, post-translational modification; SUMO, small ubiquitin-like modifier.

farnesylated lamin A mutant progerin accumulates provides additional evidence linking defective lamin A processing to nuclear abnormalities (107). However, direct evidence linking lamin A farnesylation to cancer progression remains limited. Studies using farnesyltransferase inhibitors or systemic ZMPSTE24 disruptions show an effect on multiple proteins

Table II. Various sites of prenylation, their roles and relevance.

Target	Prenylation site	Enzyme	Role	Cancer relevance	Cancer types/models
Ras	Cys in CVIM/ CAAX	FTase	Membrane localization, signaling	Oncogenic MAPK/ PI3K activation	COS-1 cells (99,102)
Rho GTPases	Cys in CAAX	GGTase-I (FTase for RhoB)	Cytoskeletal remodeling	Migration, invasion	COS-1 cells (100,103)
Prelamin A (transient, normal maturation)	Cys661 (CSIM)	FTase	Nuclear membrane targeting, maturation	Nuclear instability, DDR defects	Human HGPS cells and cervical cancer (HeLa) (104,105)
Prelamin A	Cys661 (persistent)	FTase	Abnormal nuclear anchoring	Nuclear instability, DDR defects, genomic instability, metastasis (proposed)	*Zmpste24*$^{-/-}$ MEFs and HGPS fibroblasts (106)

CAAX, cysteine-aliphatic-aliphatic-any amino acid motif; DDR, DNA damage response; FTase, farnesyltransferase; GGTase-I, geranyl-geranyltransferase type I; HGPS, Hutchinson-Gilford progeria syndrome; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; PI3K, phosphoinositide 3-kinase.

and pathways, making it difficult to isolate lamin A-specific effects (108-110). Further investigation using targeted lamin A mutants and physiologically relevant cancer models is needed to determine whether altered farnesylation directly influences tumor progression and metastasis.

Phosphorylation of lamin A/C. Lamin A/C is one of the most heavily phosphorylated structural proteins in the nucleus, and its phosphorylation state determines lamina assembly, chromatin interactions, nuclear mechanics and cell-cycle transitions. The best-characterized phosphorylation events occur at Ser22 and Ser392, which CDK1 targets during mitotic entry (Table III) (63,96,111-113). These modifications induce lamina disassembly, allowing chromosome condensation and segregation (114). In interphase, low-level phosphorylation at these sites regulates lamin solubility and turnover, influencing nuclear stiffness and chromatin tethering (115). In cancer, dysregulated kinase signaling may alter lamin A/C phosphorylation, potentially affecting nuclear integrity and genomic stability (Fig. 3) (96).

Beyond these canonical sites, lamin A/C contains additional phosphorylation sites with distinct regulatory functions (96). Ser390, Ser403 and Thr19 are phosphorylated by stress-activated kinases, including protein kinase C and mitogen-activated protein kinases (MAPKs) (Table III), modulating lamin-chromatin interactions at LADs (Fig. 4A and B) (116). DNA damage-activated kinases, such as ataxia-telangiectasia mutated, casein kinase 2 and glycogen synthase kinase-3β, phosphorylate lamin A/C at residues that include Ser22 and Ser628, potentially influencing DNA damage responses (117-119). By reducing lamin-chromatin affinity, phosphorylation weakens LAD organization and gene expression (119). Altered lamin A/C phosphorylation may also affect retinoblastoma protein (Rb)/E2 transcription factor (E2F) signaling and cell-cycle regulation (120).

Phosphatases reverse this process by removing phosphate groups from lamin A/C, B1 and B2 to promote their repolymerization (Fig. 3B). Protein phosphatases such as protein phosphatase (PP)1 and PP2A have been implicated in the postmitotic dephosphorylation of lamin B and lamin A/C, respectively (121), and Repo-Man (CDC2A), a regulatory subunit of PP1g, contributes to lamin A dephosphorylation at the Ser22 position in its SUMOylated form (122,123). Ghosh *et al* (97) showed that the androgen receptor mediates the interaction between lamin A and PP1 in human dermal fibroblasts. Loss of the androgen receptor disrupts this interaction and increases lamin A phosphorylation at Ser301, a characteristic of cancer-associated fibroblasts (CAFs). The study also showed that Ser301-phosphorylated lamin A binds regulatory regions of CAF effector genes, and that a phosphomimetic Ser301 mutant alone can transform normal fibroblasts into cancer-promoting CAFs.

Acetylation of lamin A/C. Acetylation is a reversible PTM in which acetyl groups are added to lysine residues by lysine acetyltransferases (KATs) and removed by deacetylases [histone deacetylases (HDACs) and sirtuins]. Dysregulation of KATs and deacetylases is a hallmark of a number of tumors and contributes to oncogenic transcriptional programs, epigenetic plasticity and therapy resistance (124,125).

The best-characterized acetylation site is Lys311, which is modified by histone acetyltransferase (KAT8; also known as MOF or MYST1) (Table IV; Fig. 3) (71,126-128). Acetylation at Lys311 regulates the interaction of lamin A/C with chromatin and contributes to the maintenance of LADs, thereby shaping transcriptional repression and epigenetic stability (71). Additional acetylation events mediated by p300/CREB-binding protein and the NSL complex have been reported, although their specific sites are less well defined; these modifications appear to modulate the interactions of lamin A/C with transcriptional regulators and histone-modifying enzymes, influencing boundary formation between active and repressed chromatin compartments (116).

Table III. Various sites of lamin A/C phosphorylation with their role and relevance.

Site	Target	Kinase	Functional role	Cancer types/models
Ser22	Lamin A/C	CDK1, PKC, ATM	Lamina disassembly, nuclear softening, DDR signaling	Chicken liver cell line (DU249) (111), retinal pigment epithelial-1 (RPE-1) (111), cervical cancer (HeLa) and 293T cells (63)
Ser392	Lamin A/C	CDK1	Mitotic entry, chromatin release	DU249 cells (63), cervical cancer (HeLa) and 293T cells (63)
Ser404	Lamin A/C	AKT	Lamina reorganization, migration and nuclear mechanics	C2C12 mouse myoblasts and 293T cells (96)
Ser628	Lamin A	CK2 and GSK3β	DNA damage response, cellular senescence	LMNA mutant mouse and MEFs (112)
Thr19, Ser390, Ser403	Lamin A/C	PKC, MAPK	Chromatin tethering, epigenetic regulation	Frog egg extracts (113)

AKT, protein kinase B; ATM, ataxia-telangiectasia mutated; CDK1, cyclin-dependent kinase 1; CK2, casein kinase 2; DDR, DNA damage response; GSK3β, glycogen synthase kinase 3β; MEF, mouse embryonic fibroblasts; PKCα, protein kinase Cα.

Table IV. Various sites of acetylation, their role and relevance in lamin A functionality.

Site	Target	Enzyme	Functional role	Cancer types/models
Lys311	Lamin A	KAT8 (aka MOF/MYST1), within the NSL complex architecture	Regulates chromatin tethering, LAD stability, nuclear	MEFs and cervical cancer (HeLa) (71)
Lys 97, 108, 114, 270, 311, 378, 417, 450	Lamin A	p300/CBP, NSL complex (speculative)	Modulate transcription factor binding, chromatin boundary formation	Cervical cancer (HeLa) (126) and leukemia (MV4-11) (127)
Not defined	Lamin A	SIRT1	Promote heterochromatin compaction, epigenetic stability, nuclear integrity	*Zmpste24*$^{-/-}$ mice (128)

CBP, CREB-binding protein; KAT8, lysine acetyltransferase 8; LAD, lamina-associated domain; MEF, mouse embryonic fibroblast; NSL, non-specific lethal; SIRT, sirtuin.

Deacetylation of lamin A/C is primarily mediated by sirtuin 1, which promotes chromatin compaction and transcriptional repression (128). Through these mechanisms, acetylation and deacetylation of lamin A/C act as a regulatory switch that balances open and closed chromatin states (71,129).

Acetylation of lamin A/C may also influence the cell cycle by disrupting lamin-Rb binding, leading to premature Rb release, excessive E2F activation and S-phase entry, an event tumor cells frequently exploit to sustain proliferation (120).

In mechanotransduction, acetylation may alter the mechanical properties of lamin A/C and its coupling to the linker of the nucleoskeleton and cytoskeleton complex, affecting nuclear stiffness and the transmission of cytoskeletal forces to the genome, and potentially enabling cancer cells to adapt to stiff tumor microenvironments (9).

Although lamin A/C acetylation regulates nuclear architecture and chromatin interactions, its direct contribution to cancer progression remains poorly understood. Studies using site-specific acetylation mutants and cancer-relevant models are needed to establish whether these modifications influence tumor-associated phenotypes or have potential as biomarkers or therapeutic targets.

SUMOylation of lamin A/C. SUMOylation is a reversible PTM in which SUMO proteins are covalently attached to lysine residues on target proteins through an enzymatic cascade involving the E1-activating enzyme SUMO-activating enzyme (SAE)1/SAE2, the E2-conjugating enzyme UBC9 and various E3 ligases. In cancer, SUMOylation is widely dysregulated and contributes to malignant transformation by altering protein stability, subcellular localization, transcriptional activity and stress responses (130). SUMOylation also regulates tumor suppressors such as p53, Rb and PTEN (phosphatase and tensin homolog); aberrant SUMOylation can repress their activity, weakening checkpoint control and apoptosis (131).

Lamin A/C is SUMOylated at multiple lysine residues, regulating its structural, transcriptional and signaling functions. The best-characterized SUMOylation site is Lys201, which is modified by the SUMO E2 enzyme UBC9, with conjugation efficiency enhanced by SUMO E3 ligases such as protein inhibitor of activated STAT1 (signal transducers and activators of transcription 1) (18,132,133) (Table V). SUMOylation at Lys201 occurs within the central rod domain and influences lamin A/C polymerization and lamina stability, whereas SUMOylation at Lys420, located in the Ig-fold domain, modulates interactions with transcription factors and chromatin-associated proteins (133). These modifications may influence lamin A/C interactions with regulators such as p53, c-Fos and Rb, affecting transcriptional regulation and stress responses (116).

In cancer, hyper-SUMOylation may weaken lamin-Rb binding, potentially leading to premature Rb release and excessive activation of E2F transcription factors, which drives uncontrolled S-phase entry and proliferation (120). Dysregulated SUMOylation has also been linked to impaired repair efficiency associated with altered recruitment of DNA repair proteins and increased genomic instability (134). SUMOylation and other modifications may influence lamina stiffness and nucleo-cytoskeletal coupling, thereby regulating mechanosensitive signaling pathways such as Yes-associated protein and MAPK pathways (135,136).

Direct evidence linking lamin A/C SUMOylation to cancer remains limited. Studies using non-SUMOylatable mutants (such as Lys201Arg or Lys420Arg) in cancer-relevant models are needed to address this gap.

Palmitoylation of lamin A/C. Palmitoylation is a reversible lipid modification in which a 16-carbon palmitate group is covalently attached to cysteine residues via a thioester bond. This reaction is catalyzed by Asp-His-His-Cys motif-containing palmitoyl acyltransferases and reversed by acyl-protein thioesterases (137). In cancer, palmitoylation regulates oncogenic signaling, membrane trafficking, protein stability and subcellular localization (138).

In myoblasts, ABHD7 (α/β-hydrolase domain 7)-mediated depalmitoylation of lamin A is required for myoblast differentiation, suggesting that lamin A palmitoylation status contributes to the regulation of cellular differentiation (81). Whether this mechanism operates in cancer remains unknown. Persistent lamin A palmitoylation or reduced ABHD7 activity could help maintain a less differentiated state in tumor cells. Studies using non-palmitoylatable lamin A mutants in cancer-relevant models are needed to test this hypothesis.

O-GlcNAcylation of lamin A/C. O-GlcNAc modification is a dynamic post-translational process in which a single GlcNAc moiety is added to serine or threonine residues on nuclear and cytoplasmic proteins (139). O-GlcNAcylation is regulated solely by two enzymes, O-GlcNAc transferase (OGT) and O-GlcNAcase, which add and remove O-GlcNAc groups, respectively (140). The process often competes with phosphorylation in regulating protein stability and interactions, thereby influencing diverse cellular signaling pathways involved in other processes such as transcription, translation, metabolism and autophagy (141-144). Aberrant O-GlcNAcylation has been observed in several diseases, such as neurological (Alzheimer's disease, Parkinson's disease and Huntington's disease) and metabolic (diabetes and cardiovascular disease) types, particularly TNBC and colorectal cancers (142,145-148).

OGT interacts with lamin A and promotes its tail-cleavage processing, a step required for converting pre-lamin A into its mature form (Table VI) (79,149,150). Mutating OGT-binding motifs or O-GlcNAc sites (S613 and T643) on lamin A reduces tail-cleavage efficiency, suggesting that OGT binding and/or O-GlcNAcylation contributes to lamin A maturation and may link glucose-sensitive signaling to nuclear lamina biogenesis (79).

Lamin A/C also carries O-GlcNAc and other glycans during the G_2/M and S phases in lung carcinoma cells, suggesting a potential association between glycosylation and cell-cycle-dependent lamina regulation (151).

Whether lamin A/C O-GlcNAcylation contributes to cancer progression remains unknown. Studies using non-O-GlcNAcylatable lamin A/C mutants in cancer-relevant models are needed to address this question.

Lamin A/C PTMs and therapies. PTMs of lamin A/C represent a promising but underexplored avenue for cancer intervention. As aberrant PTMs and proteolytic cleavage of lamin A/C have been associated with tumor proliferation, metastasis, genomic instability and therapy resistance, the enzymes that regulate these modifications are potential therapeutic targets (Fig. S2).

Phosphorylation of lamin A/C by kinases, such as CDKs and protein kinase B, regulates nuclear lamina organization and dynamics. Several CDK inhibitors are approved for cancer therapy. CDKs are highly expressed in proliferating cells; therefore, CDK inhibitors preferentially target proliferating cells, and farnesylation inhibitors such as tipifarnib, which inhibit prelamin A farnesylation, have been evaluated in clinical trials (152,153). Lonafarnib (Zokinvy) is the most successful small molecule targeting the CaaX-box post-translational maturation pathway of prelamin A against HGPS and laminopathies, and is approved by the US Food and Drug Administration (154). Another small molecule, ARRY-371797, a MAPK inhibitor, has shown promising results in patients with *LMNA*-related DCM on a pilot scale (155,156). However, a subsequent large-scale randomized controlled trial was prematurely terminated due to clinical inefficacy (National Clinical Trial no. NCT03439514) (156). Aside from these exceptions, clinical-stage small molecules that target lamin A/C PTMs for cancer treatment remain completely undeveloped.

HDAC and sirtuin inhibitors may influence lamin A/C acetylation and chromatin interactions (157,158), and targeting SUMOylation and ubiquitination pathways may affect lamin A/C stability and cellular stress responses (159). A SUMOylation enzyme inhibitor, subasumstat (TAK-981) has displayed a manageable safety profile and stimulated innate and adaptive immune responses in early-stage trials involving patients with refractory hematological malignancies and advanced or metastatic solid tumors. It requires future trials to establish its place in cancer treatment (160), and O-GlcNAcylation inhibitors are being explored as potential anticancer agents (161).

Table V. Various sites of SUMOylation with their relevance in lamin A functionality.

Site	Target	Enzyme	Functional role	Cancer types/models
Lys201	Lamin A	UBC9, PIAS1	Regulates lamina assembly, polymerization and Rb binding	Cervical cancer (HeLa), 293T cells (133)
Lys420	Lamin A	UBC9, PIAS1	Modulates transcription factor interactions (p53, c-Fos), chromatin organization	Cervical cancer (HeLa), 293T cells (133)

PIAS1, protein inhibitor of activated STAT1; Rb, retinoblastoma protein; SUMO, small ubiquitin-like modifier; UBC9, ubiquitin-conjugating enzyme 9.

Table VI. Various sites of O-GlcNAcylation with their relevance in lamin A functionality.

Site	Target	Functional role	Cancer types/models
Ser109	YAP	Enhances YAP stability by blocking phosphorylation-dependent degradation	293T cells, mammary epithelial cells (MCF10A) (149)
Thr58, Ser62	Myc	Stabilizes protein; modulates turnover vs. phosphorylation	Rat embryo fibroblasts 52 (150)
T643, S613	Lamin A	Promotes lamin A tail cleavage	Mouse embryonic stem cells (79)

O-GlcNAc, O-linked β-N-acetylglucosamine; YAP, Yes-associated protein.

Given the multifaceted roles of lamin A/C PTMs, combination therapies targeting multiple modification pathways may offer therapeutic benefits. However, these agents act on numerous substrates besides lamin A/C, and whether their antitumor effects depend on altered lamin A/C modification remains to be established.

5. Proteolytic lamin cleavage: Apoptotic dismantling vs. viable migratory adaptation

The literature reflects a conceptual paradigm shift in protease-driven lamin cleavage regarding classical doctrine (apoptotic execution) vs. modern evidence (non-apoptotic metastatic remodeling).

Classical doctrine (apoptotic execution). Cleavage of lamin A/C by caspases, notably the interleukin-1β-converting enzyme-related protease caspase-6 (162,163) or granzymes A and B (164), has historically been viewed as a hallmark of programmed cell death and cytolysis, leading to nuclear dismantling. Excessive nuclear MMP activity has similarly been linked to apoptosis induction via caspase activation (165).

Modern evidence (non-apoptotic metastatic remodeling). Recent findings show that nuclear MMP-3 cleaves lamin A at Glu347 in living, non-apoptotic cancer cells (20). MMP-3-based cleavage of lamin A at Glu347 was proven by mass spectrometry and prediction. Living cells co-transport MMP-3, cleaved lamin A, LC3B and cluster of differentiation 63 via amphisomes and autophagic EVs (20). This controlled proteolysis may generate transient pro-migratory nuclear deformation that facilitates migration through 3D ECM barriers without causing cell death.

More broadly, proteases such as MMPs, serine proteases (including the urokinase plasminogen activator system) and cathepsins are frequently upregulated in cancer, where they remodel the extracellular matrix, process signaling molecules and shape the tumor microenvironment (166-168).

Multiple proteases have been identified as regulators of lamin A/C integrity through targeted cleavage (Table VII) (20, 47,48,162,164,165,169). Among them, MMP-3 has emerged as a key modulator of nuclear architecture in metastatic cancer, as described previously (20). While moderate cleavage may facilitate the nuclear plasticity essential for migration, excessive degradation of lamin A/C can compromise nuclear stability and potentially trigger cell death by removing essential protection against mechanical and genotoxic stress.

Earlier work in cardiomyocytes demonstrated that nuclear MMP-2 cleaves lamin A to generate a putative ~50-kDa fragment, without affecting lamin B (169). By contrast, MMP-3-mediated cleavage generates an ~30-kDa C-terminal lamin A fragment, with a putative cleavage site predicted by peptide-based analysis (20). These findings suggest that MMP-2 and MMP-3 may process lamin A differently, although their precise cleavage specificities require further validation. MMP-mediated proteolysis may alter nuclear structural integrity and cancer cell behavior by influencing nuclear deformability and migration. Consistent with this, our previous study associated MMP-3-mediated cleavage of lamin A with nuclear deformation and enhanced migration through confined spaces in metastatic colon cancer cells (LuM1/Colon26) (20). Supporting this concept, reduced lamin A levels have been associated with enhanced confined migration and increased metastatic capacity in TNBC models (13).

Table VII. Protease-mediated cleavage of lamins.

Protease	Target	Role	Cancer types/models
MMP-3	Lamin A	i) Induces pro-migratory nuclear deformity (atypia), nucleophagy, and the autophagic secretion of EVs; ii) transcriptional control; iii) induces genome instability; iv) induces apoptosis if excessive	i) Colon cancer (LuM1, CT26), HNSC, oral squamous cell carcinoma (HSC-3) (20); ii) TNBC (MDA-MB-231), chondrosarcoma (HCS-2/8) (47); iii) breast cancer (TCL1) (48); iv) CHO cell line (165)
MMP-2	Lamin A	Not determined	Cardiomyocytes and the ischemic-reperfused heart (169)
Caspase-6 (Mch2, ICE-related protease)	Lamin A	Apoptosis	Cervical cancer (HeLa) (162)
Granzyme A and B	Lamin B	Apoptosis and cytolysis	Leukemia cells (K562) (164)

CHO, Chinese hamster ovary; EV, extracellular vesicle; HNSC, head and neck squamous cell carcinoma; ICE, interleukin-1β-converting enzyme; Mch2, mammalian Ced-3 homolog 2; MMP, matrix metalloproteinase; TNBC, triple-negative breast cancer.

However, our previous study data indicate that MMP-3 overexpression induces lamin A cleavage in both living (non-apoptotic) and dying (apoptotic or autophagic) cells (20), underscoring the need to distinguish autophagic EVs from apoptotic EVs and to clarify how protease expression patterns influence lamin A cleavage across different cellular states (20).

Importantly, our previous study (20) found that nuclear MMP-3-positive, cleaved-lamin-positive and double-positive tumor cells were abundant in human HNSC specimens, suggesting potential clinical relevance. Although the association between MMP-3, cleaved lamin A and autophagic EV trafficking suggests a possible role in metastatic progression, the causal contributions of these processes require further investigation.

Collectively, these findings suggest that lamin proteolysis is not restricted to apoptotic nuclear dismantling but may also contribute to nuclear adaptation in viable migrating cancer cells, with biological consequences that depend on the protease involved and the cellular context.

6. Methodological limitations and knowledge gaps

Model system dependencies. Much of the mechanistic data regarding nuclear MMP cleavage, nucleophagy and EV co-secretion derives from *in vitro* models, predominantly metastatic colon cancer cells, with supporting observations in HNSC specimens (20). Validation in additional tumor types, primary tumor tissues and *in vivo* models remains necessary.

Incomplete mechanistic mapping. While high-throughput screens have mapped numerous PTM sites on lamin A/C (59,61,115), direct mechanistic evidence showing how specific PTM combinations dynamically alter lamin filament assembly, chromatin tethering and DNA damage repair in human tumors remains limited.

7. Conclusion

The nuclear lamina has transitioned from a passive structural meshwork to a dynamic molecular hub that regulates cancer cell survival, mechanotransduction and metastatic plasticity. The present review summarizes how tumor cells orchestrate lamin A/C- and B-type lamin dynamics through physical mechanics, autophagic degradation, EV secretion and PTMs.

Central to this paradigm is the mechanical paradox of lamin A/C. Tumor cells balance nuclear deformability and structural protection: Low lamin A/C expression promotes nuclear softness that facilitates migration through narrow ECM pores and vascular walls, whereas basal-to-high levels preserve nuclear integrity against mechanical rupture. Concurrently, selective nucleophagy may contribute to nuclear quality control by removing damaged nuclear components. Moreover, nuclear MMP-3-mediated lamin A cleavage indicates that lamina proteolysis is not restricted to apoptotic dismantling but can also occur in viable cancer cells, where it is associated with nuclear deformation and enhanced migration, and co-secretion of cleaved fragments via autophagic EVs.

Furthermore, lamin A/C PTMs, including phosphorylation, SUMOylation, acetylation, farnesylation, palmitoylation and O-GlcNAcylation, collectively influence lamina assembly, chromatin tethering, cell-cycle signaling and DNA repair, although the contributions of individual modifications to cancer progression remain incompletely understood. Inhibitors targeting enzymes involved in these modifications, including CDKs, FTases and SUMOylation-related enzymes, are in clinical use or development, although whether their antitumor effects involve lamin A/C modification remains to be established.

Moving forward, validating these mechanisms in site-specific knock-in *in vivo* models and expanding investigations across diverse tumor types remain essential. Ultimately, decoding the multidimensional regulation of lamin biology may provide a unifying framework for understanding nuclear vulnerability and developing novel nuclear-targeted cancer therapeutics.

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Authors' contributions

Study conceptualization was performed by TE and VT. Original draft preparation was performed by VT (PTMs), YW (nucleophagy) and TE (cleavage). EAT, TE, YW and VT reviewed and edited the manuscript. Visualization (figure preparation) was performed by TE (Figs. 1, 3, 4, S1 and S2), YW (Fig. 2) and VT (Fig. 3). Project administration and funding acquisition was the responsibility of TE. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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, AI 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 AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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