Advances in research on the relationship between the LMNA gene and human diseases (Review)

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Received June 18, 2024; Accepted August 29, 2024

DOI: 10.3892/mmr.2024.13358

Abstract. The LMNA gene, which is responsible for encoding lamin A/C proteins, is recognized as a primary constituent of the nuclear lamina. This protein serves crucial roles in various cellular physiological activities, including the maintenance of cellular structural stability, regulation of gene expression, mechanosensing and cellular motility. A significant association has been established between the LMNA gene and several major human diseases. Mutations, dysregulated expression of the LMNA gene, and improper processing of its encoded protein can result in a spectrum of pathological conditions. These diseases, collectively termed laminopathies, are directly attributed to LMNA gene dysfunction. The present review examines the recent advancements in research concerning the LMNA gene and its association with human diseases, while exploring its pathological roles. Particular emphasis is placed on the current status of LMNA gene research in the context of tumors. This includes an analysis of the abundance of LMNA alterations in cancer and its interplay with various signaling pathways. The aim of the present review was to provide novel perspectives for studying the development of LMNA-related diseases and additional theoretical insights for basic and clinical translational research in this field.

Contents

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Key words: LMNA gene, signaling pathway, tumor, molecular mechanism, laminopathies

1. Introduction

The cytoskeleton is composed of three primary components: Microtubules, actin filaments and intermediate filaments (1). The nuclear lamina, a thin and dense protein network, is situated beneath the nuclear membrane, forming a highly organized mesh (2,3) (Fig. 1). Lamins, which are intermediate filament proteins located in the nuclear lamina, are categorized into A-type and B-type proteins (4,5). The nuclear lamina performs multiple cellular functions, including providing mechanical stability, facilitating protein nuclear localization, enabling cell migration, regulating chromatin organization, and participating in DNA replication and repair (6-10). Research has indicated that the nuclear lamina is also implicated in laminopathies, such as Emery-Dreifuss muscular dystrophy (EDMD) and dilated cardiomyopathy (DCM), and premature aging syndromes, such as Hutchinson-Gilford progeria syndrome (HGPS) and Werner syndrome (11,12).

In human cells, A-type lamins, comprising lamin A and lamin C, are encoded by the LMNA gene. Lamin C is a splice variant of lamin A, and, due to their structural similarity, they are often collectively referred to as lamin A/C for research purposes (13-15). Impairment of lamin functions can lead to the development of a wide range of disorders (11,16). The function and expression of lamin A/C vary across tissue types and cancer sub-types, resulting in no specific pattern of lamin A/C expression in cancer (17-19). Lamin A and lamin C expression levels are typically measured together; however, lamin A and lamin C expression may not always be equally altered in certain diseases, further complicating the understanding of the effect of lamin A/C on disease progression (17-19). An increasing number of diseases have been reported to be associated with

mutations or altered expression levels of genes controlling nuclear lamina, such as intestinal polyps and cancer, which adds to the complexity of studying these proteins (17-19). The present review aimed to examine the molecular structure of the lamin family, explore the relationship between the LMNA gene and various diseases, and discuss the association of nuclear lamina with tumors and signaling pathways that may be perturbed by lamin. The objective of the study was to provide valuable insights for basic and clinical translational research into laminopathies and related cancer.

2. Classification of lamina and its components

The nuclear fibrillar layer, located at the underside of the nuclear membrane, is composed of lamina and its associated proteins. These proteins connect nuclear proteins to heterochromatin and have been identified as intermediate filament proteins with a V-shaped structure. Based on differences in gene structure and nucleotide sequences, lamin is classified into six isoforms: Types I and II, which include acidic and basic keratins; type III, which includes vimentin, desmin, peripherin and glial fibrillary acidic protein; type IV intermediate filament group, which includes neurofilament proteins and a fourth neurofilament subunit, α-internexin protein; type V, which consists of lamins located in the nucleus; and group VI, which consists of lens-specific intermediate filaments, CP49/crystallin and filensin. All lamins have good elasticity and are usually related to cell morphology (20). Intermediate filament proteins, positioned between actin microfilaments and microtubules, have an average diameter of 10-12 nm (21). While the majority of lamins are found in the nuclear lamina, a small proportion are present in the nucleoplasm (4,22-24). The functionality of lamin proteins varies across different tissues due to its interactions with membrane proteins and heterochromatin, facilitated by diverse binding chaperones (23-25). Structurally, lamins comprise three primary components: A central α-helical structural domain; a bulbous amino-terminal in the head region; and a carboxy-terminal in the tail domain (4). The central α-helical structural domain is further subdivided into four α-helical fragments, designated as d1A, 1B, 2A and 2B. These fragments are interconnected by short sub-structural domains termed L1, L12 and L2. The amino-terminal head structural domain exhibits variable size, while the carboxy-terminal tail structural domain encompasses nuclear localization signals, Ig structural domains and the CAAX box (4) (Fig. 2).

The LMNA gene encodes lamin A/C proteins, which are classified as lamin A-type proteins based on their structural configuration (26-28). In mammals, seven main types of lamin have been identified. The lamin A proteins, including the major isoforms lamins A and C and the minor isoforms lamins AΔ10 and C2, are all encoded by the LMNA gene (29). Conversely, the lamin B proteins comprise three isoforms: Lamin B1, encoded by the LMNB1 gene, and lamins B2 and B3, which are encoded by the LMNB2 gene (29). Lamins A, C, B1 and B2 are the predominant lamin proteins in human cells, serving a crucial role in maintaining nuclear integrity. While the amino-terminal head and central rod-like structural domains of lamin A closely resemble those of lamin B, lamin A is distinguished by a unique 90 amino acid fragment at the carboxyl-terminal tail, forming an extended structural domain (4) (Fig. 2). It has been suggested that lamin B predates lamin A in evolutionary terms. Notably, the intron position of human LMNB1 is conserved in LMNA and LMNB2; however, LMNB2 contains an additional intron between the regions coding for helix 1A and helix 1B that is absent in other intermediate filament proteins, including LMNA, thus suggesting that LMNB2 and LMNA may have evolved from LMNB1 (29,30). Lamin A-type proteins are expressed in most differentiated somatic cells, but their production is minimal in embryonic stem cells and the sub-epidermis, which suggests a potential association between lamin A and the differentiation process of organelles (31). By contrast, lamin B-type proteins are expressed regardless of the degree of cellular differentiation and are essential for normal organ development. Furthermore, lamin B is expressed in almost all cells (31,32). The LMNA gene is translated and spliced to form the lamin A precursor, pre-lamin A, which undergoes farnesylation of the CAAX box to produce mature lamin A (4,22,23,33). Conversely, lamin C precursors directly form mature lamin C due to the absence of the CAAX box (33). The LMNB1 and LMNB2 genes are located on human chromosomes 5q23.2-q31.3 and 19p13.3, respectively. Lamin B-type proteins contain the CAAX box but do not undergo farnesylation, forming mature lamin B-type proteins directly after translation (34). In addition to farnesylation, lamin proteins undergo phosphorylation and ubiquitination. Various protein kinases can phosphorylate lamins, with CDC2, protein kinase (PK)C and PKA being the three known kinases that post-translationally modify lamins (4). CDC2 induces lamin cleavage, PKC phosphorylation regulates lamin uptake into the nucleus, and PKA phosphorylation inhibits lamin polymerization (35-37). Lamin A/C proteins possess ubiquitination-like modification sites within their rod and tail structural domains; mutation of the site within the rod structural domain results in reduced levels of SUMOylation of intracellular lamins and altered sub-nuclear localization (38).

In somatic cells, lamin A-type and B-type proteins form spatially independent reticular structures with overlapping regions, fulfilling distinct cellular roles (39-45). Transcriptionally silent genomic regions, including mitoplasts, telomeres and inactivated X chromosomes, are predominantly localized within the nuclear lamina. Lamin B proteins has been identified as a global chromatin regulator (46,47). At least two chromatin-binding regions have been identified in lamins: One situated between the rod structural domain terminus and the IG structural domains in the tail region, and another within the rod structural domains (48,49). Whole genome sequencing techniques have revealed genomic regions preferentially associating with Lamin proteins, termed lamina-associated domains (LADs) (50). These results suggest that lamin may have an important role in maintaining cell homeostasis. In-depth investigation of lamin proteins is essential for analyzing nuclear homeostasis at the molecular level and exploring its association with disease pathogenesis.

3. Relationship between LMNA and human diseases

The LMNA gene encodes the multifunctional intermediate filament proteins lamin A/C. Mutations in LMNA, dysregulation of expression levels and improper protein processing can

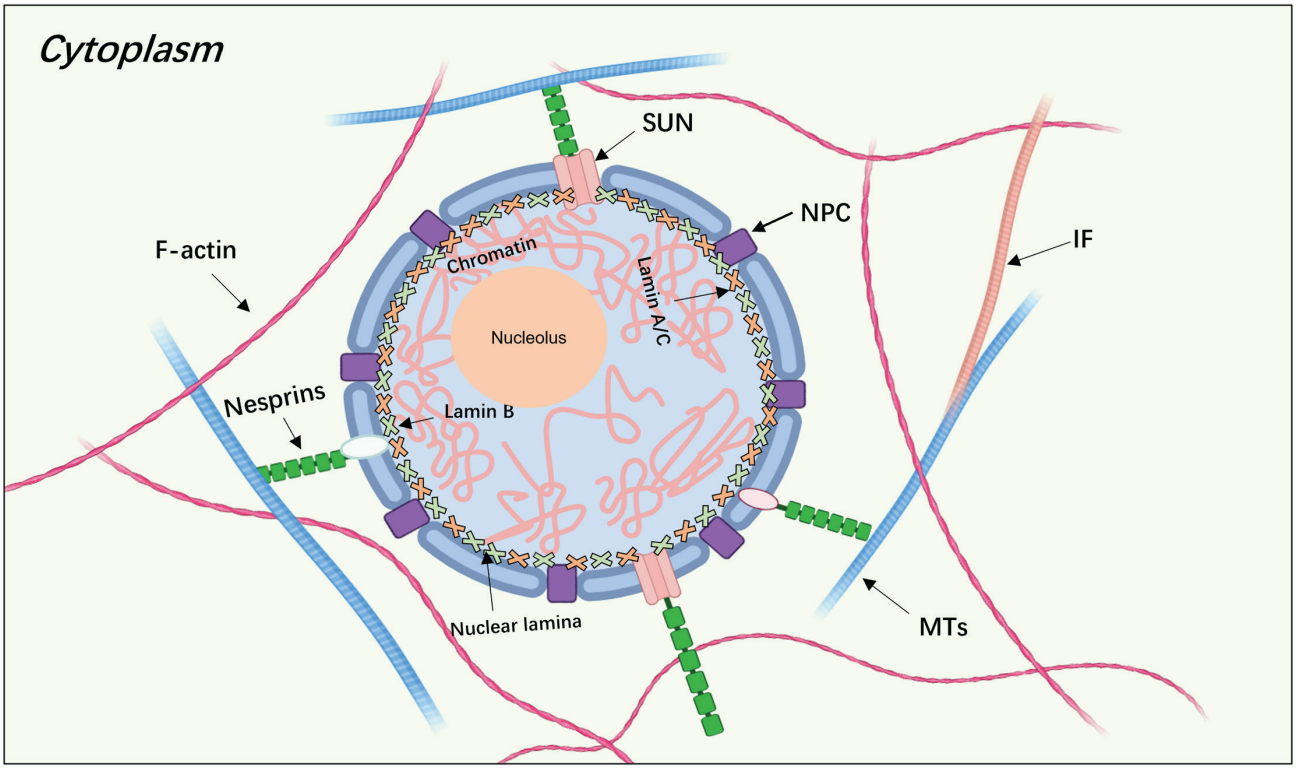

Figure 1. Cell nucleus and its surrounding cytoskeletal components. The outer skeleton of the nucleus is composed of MTs, IF, F-actin and nesprins, which envelope the nucleus and protect its stable morphology. The surface of the nucleus is composed of SUN, NPC and other structures, and the lower layer is composed of lamins, including A-type lamins and B-type lamins, forming a dense network structure in the inner layer of the nuclear membrane. These structural and cytoskeletal proteins serve a protective role in maintaining the functional homeostasis of the nucleus. MTs, microtubules; F-actin, actin filaments; IF, intermediate filaments; SUN, Sad1-UNC84; NPC, nuclear pore complex.

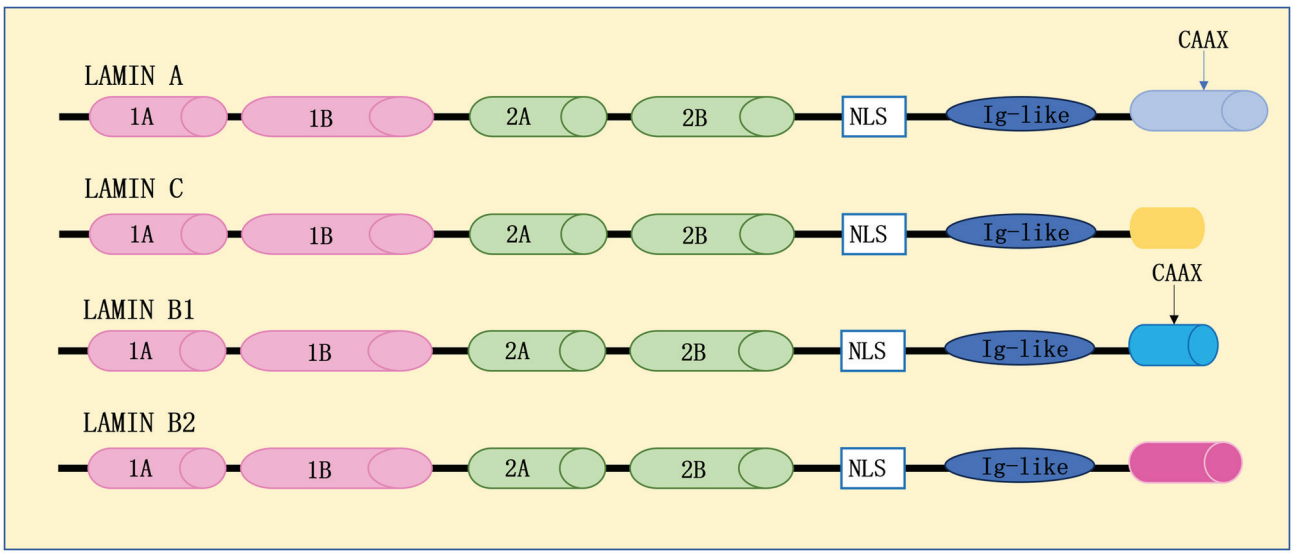

Figure 2. Distribution of important domains of lamins. The lamins consist of three components: The head domain, the central coiled helical rod domain and the tail domain. The central coiled helical rod domain comprises subdomains 1A, 1B and 2 (2A and 2B), while the tail domain includes NLS domains, Ig-like domains and carboxy-terminal CAAX cassettes (excluding lamin C and lamin B2). NLS, nuclear localization signal.

result in various diseases collectively referred to as laminopathies (13). Lamin proteins are absent in a number of human diseases, and mutations affect the course of some human diseases (Table I). Laminopathies are classified as primary or secondary based on their etiology. Primary laminopathies are caused by LMNA gene mutations and include striated muscle disorders, lipodystrophy syndromes and peripheral neuropathy (11,16,34,51). Secondary laminopathies primarily result from Zmpste24 defects, where lamin A precursors fail to undergo Zmpste24-dependent cleavage to form mature lamin A (11,16,51). Additionally, secondary laminopathies can arise from mutations in non-lamin genes that interact

Table I. Diseases associated with the LMNA gene.

Name of disease	Type of disease	Change in lamins	(Refs.)
Striated muscle disorders	Primary	LMNA mutant	(1,5,11)
Lipodystrophy syndromes	Primary	LMNA mutant	(5,8,16,17,56)
Peripheral neuropathy	Primary	LMNA mutant	(5,8,9,17,23,34)
Progeroid syndromes	Primary	LMNA mutant	(5,9,10,16,23,31,51,60)
Premature aging	Secondary	Lamin A deficiency	(1,11,16,51)
Restrictive dermopathy	Secondary	LMNA mutant	(11,17)
Dilated cardiomyopathy	Secondary	LMNA mutant	(8,11,17,23,28,52,53)
Hypertension	Secondary	LMNA mutant	(54,55)
Valve disease	Secondary	LMNA mutant	(11)
Coronary artery disease	Secondary	Lamin C deficiency	(54)
Emery-Dreifuss muscular dystrophy	Secondary	LMNA deficiency	(5,9-12,16,17,23,28)

with lamin, leading to disorders such as progeria and restrictive dermopathy (11,16,51). LMNA gene mutations have been found to significantly impact cardiac function, with dilated cardiomyopathy (DCM) being a major contributor to heart failure. It has been reported that ~6% of DCM cases worldwide can be attributed to LMNA gene mutations. Notably, missense mutations in the α-helix-rod structural domain of LMNA result in lamin C defects, ultimately leading to the onset of DCM (11,52,53). DCM is characterized by reduced left ventricular or biventricular pumping function, potentially causing hypertension, valvular disease or coronary artery disease. DCM caused by LMNA mutations has been associated with a more severe clinical phenotype and poorer prognosis compared with DCM of other etiologies (54). Treatment for cardiac dysfunction caused by LMNA mutations remains marginally effective, with interventions aimed at reversing molecular changes (55). Notably, EDMD was the first disease identified as being associated with LMNA (12). EDMD clinical manifestations often include muscle weakness and cardiac conduction abnormalities (28). Wang *et al* (11) demonstrated that mutations in specific structural domains of the LMNA gene, leading to LMNA functional inactivation, can cause EDMD. Elucidating the mechanistic role of LMNA in laminopathies is crucial for developing novel diagnostic and therapeutic strategies for nuclear laminopathies in clinical settings.

Lamin A/C expression has been observed to be significantly upregulated in the adipose tissue of individuals diagnosed with obesity and type 2 diabetes (41). Kim *et al* (56) revealed that obesity can induce an increase in lamin C expression within adipose tissue macrophages (ATMs). Furthermore, lamin C was found to contribute to obesity-induced insulin resistance through activation of the NF-κB signaling pathway, which may mediate ATM inflammation (56). Current therapeutic approaches for type 2 diabetes primarily focus on lifestyle modifications, including dietary changes and exercise regimens, coupled with the administration of metformin and hypoglycemic agents (including insulin); however, there remains a notable absence of targeted treatments for this condition (57). Additionally, research has uncovered that alterations in lamin C can lead to the development of lipodystrophy syndromes. Notably, certain familial forms of lipodystrophy have been predominantly attributed to a heterozygous substitution occurring at amino acid position 482 within the terminal structural domain of lamin C (58).

The expression level of LMNA gene is closely related to the aging process. HGPS is a typical disease of aging, and ~90% of HGPS cases worldwide are reported to be caused by mutations in the LMNA gene (16). Specifically, base substitutions within LMNA exon 11 (c.1824C>T) can activate a cryptic splice site, resulting in the production of an irreversible form of farnesylated mutation known as progerin protein (59,60). Although progerins cannot be incorporated into the nuclear fiber layer, their expression interferes with normal cellular mitotic processes. This interference induces genomic instability and premature senescence (61-63). The expression of lamin A/C proteins is intimately linked to nuclear stiffness, which gradually decreases with age. In cardiomyocytes, a decrease in lamin A/C expression has been observed with advancing age, corresponding to changes in nuclear stiffness (64). The reduction in lamin A/C can also lead to the downregulation of growth-associated transcription factors and cytoskeletal regulators in cardiomyocytes, resulting in cardiac dysfunction. Kirkland *et al* (64) demonstrated that maintaining lamin C expression prevented an age-dependent decline in cardiac function. Furthermore, lamin C may exert a significant influence on the aging process by impairing PGC1α and inhibiting the NAMPT-NAD^+ signaling pathway (65). Simon *et al* (66) discovered that genomic stability can be maintained by enhancing the interaction of LMNA with mADPr, which contributes to human longevity. During cell differentiation, increased expression of lamin A/C has been shown to mediate cellular senescence by regulating the expression of p16/INK4A through the lamin A/C-p53 network; this regulation is crucial for selectively inducing cellular senescence (67). These findings collectively suggested that LMNA may serve a decisive role in progeria and is associated with the development of several myotonic dystrophy syndromes. Mutations in the LMNA gene may ultimately lead to the development of LMNA-associated disorders by affecting cellular physiology. Consequently, LMNA may serve as a key target in the treatment of these disorders.

4. Changes in the abundance of LMNA expression in malignant tumor cells

Cancer development is characterized by dysregulated gene expression, altered signaling pathways, increased overall genomic instability and abnormal nuclear morphology (17,68). The LMNA gene encodes lamin A/C proteins, which interact with proteins such as emerin, retinoblastoma protein (pRb), c-Fos, SREBP1 and MOK2, influencing cellular physiological functions. Lamin A/C proteins serve a crucial role in various signaling pathways, including p53, MAPK, ERK 1/2, Wnt, TGF-β, Notch and NF-κB (17). The abnormal activation of these pathways is frequently associated with tumor development. Consequently, the expression level of the LMNA gene may be closely linked to the process of tumor progression.

In certain tumor cells, the expression levels of the LMNA gene are aberrantly altered, and this alteration may be used as a molecular marker for the clinical diagnosis of specific tumors (35). In developed countries, where lung cancer exhibits a high mortality rate, Siegel *et al* (69) and Broers *et al* (70,71) observed that lamin A/C expression was reduced in undifferentiated lung epithelial cells. The expression of LMNA varies across different lung cancer cell lines. Kaufmann *et al* (72) and Broers *et al* (70,71) discovered that LMNA expression was elevated in non-small cell lung cancer cell lines but was absent or lowly expressed in small cell lung cancer cell lines. Furthermore, Guinde and Frankel (73) demonstrated that upregulation of microRNA (miRNA/miR)-9 in lung cancer cells inhibited the expression of lamin A without affecting lamin C expression; the ratio of lamin A to lamin C was observed to be 1:8 in lung cancer cells, deviating from the typical 1:1 ratio in other cell lines. This alteration in ratio may lead to increased nuclear deformation, ultimately enhancing the migratory ability of lung cancer cells (73,74). These findings may provide novel targets for small molecule drug design to inhibit lung cancer metastasis.

In breast cancer, it has been reported that Akt targets the degradation of lamin A/C by altering its downstream gene expression (75). LMNA is involved in the developmental process of breast cancer and is typically aberrantly expressed in breast cancer cells. Capo-chichi *et al* (75) demonstrated that knockdown of LMNA by short hairpin RNA resulted in the appearance of cancer-like morphology and an increase in aneuploid cells in primary mammary epithelial cells, which are typical features of cancer (76-80). This finding suggested that LMNA may have potential as an early clinical marker for breast cancer diagnosis.

Ovarian cancer, the most lethal gynecological tumor worldwide, presents complex treatment challenges and a generally poor prognosis due to the frequent spread of cancer cells to organs beyond the ovary at the time of diagnosis (81,82). In ovarian cancer cells, downregulation of LMNA expression has been shown to promote carcinogenesis, possibly due to caspase-6-mediated downregulation of LMNA gene expression (83).

In leukemia and lymphoma, hypermethylation of the CpG island promoter region can silence LMNA gene expression, resulting in lamin A/C protein deficiency (84). Additionally, low expression of LMNA has been detected in neuroblastoma and keratoacanthoma (85,86).

While downregulation of LMNA expression is observed in some types of cancer, upregulation occurs in others. Studies have detected increased LMNA expression in prostate cancer and human pre-metastatic colorectal adenocarcinoma, where it is correlated with the enhanced metastatic ability of tumor cells (87,88). In colorectal and prostate cancer cells, LMNA may enable enhanced invasion of surrounding tissues and growth by increasing cell motility (18,88). The relationship between LMNA expression and cancer cell migration is complex. Decreased LMNA expression in highly invasive and proliferative breast cancer cells has been shown to lead to increased nuclear deformability, enhancing cell migration in the interstitial space (89). Similarly, downregulation of LMNA expression resulted in a significant increase in the migratory capacity of ovarian cancer cells (90). However, this effect may not apply universally. In lung cancer, distal metastasis of cancer cells typically occurs through pulmonary capillaries, which are less permeable compared with other metastatic pathways (91,92). Roncato *et al* (93) demonstrated that knockdown of LMNA in the melanoma metastatic cell line B16F10 reduced lung metastasis and impaired cell survival in the lung. LMNA also promoted circulating tumor cell migration by protecting the nucleus from mechanical stress (94,95). During distal metastasis, tumor cells must withstand mechanical stresses encountered in the bloodstream. Lamin A/C proteins provide mechanical stability to the nucleus. In addition, knockdown of LMNA in breast cancer cell lines resulted in increased apoptosis due to fluid shear stress, thus inhibiting the migratory ability of tumor cells (94). Conversely, when LMNA is overexpressed in cancer cells, it can enhance their ability to withstand circulating fluid shear stress, promoting distal metastasis (15,94,96). Kaspi *et al* (97) revealed that LMNA deficiency in lung cancer cells may be associated with the loss of epithelial membrane antigen during epithelial-to-mesenchymal transition (EMT), and that LMNA deficiency in these cells could increase cancer cell motility and migration (97). In circulating tumor cell cells, reduced LMNA expression has been reported to result in nuclei that are more easily deformed, allowing migration through narrower spaces compared with in cells with high LMNA expression (94). Wang *et al* (90) revealed that LMNA overexpression in ovarian cancer cells resulted the nuclei were so rigid that molecules could not pass through nuclear pores. Conversely, when LMNA expression was low, the nucleus became highly susceptible to damage, leading to increased genomic instability and cell death after passing through pores. This suggests that both high and low levels of LMNA expression negatively regulate the migratory ability of cells (90).

Based on the aforementioned research, the clinical significance of lamin A/C expression abundance in tumors has been explored. In colon cancer, a correlation has been observed between low LMNA expression and increased recurrence in patients with stage II and III colon cancer; therefore, low LMNA expression may serve as a biomarker for risk prediction of colorectal carcinogenesis (98). In non-muscle-invasive bladder cancer (NMIBC), LMNA dysregulation was not associated with its prognosis, but it could be used as a diagnostic biomarker to distinguish patients with NMIBC from healthy subjects (99). In breast cancer, a lower expression of LMNA appears to be associated with worse clinical outcomes (100).

Table II. LMNA expression in malignant tumors.

Type of tumor	LMNA expression level	(Refs.)
Lung cancer	Low expression	(17,70,72-74,93,97)
Breast cancer	Low expression	(17,75,89,100)
Ovarian cancer	Low expression	(81,83,90,113)
Colorectal cancer	Low expression	(8,17,103,123)
Leukemia	Low expression	(84)
Lymphoma	Low expression	(84)
Neuroblastoma	Low expression	(85)
Keratoacanthoma	Low expression	(86)
Prostate cancer	High expression	(88,105)
Pre-metastatic colorectal carcinoma	High expression	(87)

LMNA serves a crucial role in maintaining cell morphology, and severe nuclear aberrations in cancer cells can accelerate cancer progression and lead to poor prognosis (101,102). In breast cells, nuclear aberrations similar to those in breast cancer cells were observed in mammary epithelial cells with low LMNA expression (75), and Bell *et al* (89) found that altered nuclear regulation in invasive breast cancer cells was affected by abnormal LMNA expression levels. Alhudiri *et al* (101) further corroborated that low LMNA expression in breast cancer was associated with a worse prognosis compared with high LMNA expression. The expression of LMNA differs among various tumor cells (Table II). In tumor cells with low LMNA expression, the nucleus is more likely to deform, which in turn makes it easier to cross the interstitial space and enhance the ability of tumor cells to invade adjacent tissues. However, these cells are less prone to distal metastasis due to their susceptibility to mechanical damage and death during the metastatic process. Conversely, tumor cells with high LMNA expression may be more likely to undergo distal metastasis (Fig. 3). Consequently, the high or low expression of LMNA may be associated with the metastatic ability of tumor cells. In-depth studies of the mechanism of action of LMNA in tumors are required, which may provide improved drug targets for metastatic tumors.

5. Signaling pathways perturbed by LMNA in tumor cells

LMNA performs essential functions in cells, and previous studies have established an association between LMNA and tumor development. Notably, tumor-related signaling pathways may be affected by abnormally expressed LMNA (Fig. 4). Elucidating the perturbation of signaling pathways by LMNA in tumors may aid in the establishment of a solid foundation for its in-depth study in oncology.

LMNA is closely associated with cancer development and progression. In colorectal cancer cells, the motility of cells expressing GFP-lamin A has been reported to be increased, and this effect may be attributed to the activation of the EMT pathway by LMNA gene expression, which promotes tumor cell metastasis (103,104). Prostate cancer, one of the most common types of cancer in men, is associated with an increasing incidence with age, and has a poor prognosis and a high metastatic potential. The identification of novel biomarkers, such as LMNA, may provide improved treatment options for prostate cancer (105-107). Kong *et al* (88) observed heterogeneous LMNA expression in prostate cancer, with higher expression in paracancerous tissues infiltrated with pre-existing tumor cells compared with the tumor center. This finding suggested that LMNA may be associated with the metastasis and motility of prostate cancer cells, and could serve as a biomarker for differentiating between tumor grades (88). This previous study indicated that LMNA was highly expressed in tissue-invasive prostate cancer, and may promote prostate cancer cell proliferation, migration and invasion through the phosphatidylinositol-3-kinase/AKT/PTEN axis (88). The interaction between lamin A/C and emerin may also enhance cancer cell metastasis, possibly due to increased nuclear stability resulting from high LMNA expression in breast cancer cells (108). Therefore, LMNA may not only serve as a diagnostic marker but also as a potential target for inhibiting prostate cancer metastasis.

In breast cancer cells, reduced LMNA expression has been reported to lead to the formation of tetraploid and aneuploid mammary epithelial cells. Aneuploidy and polyploidy can subsequently induce growth arrest through the p53/p21 pathway (75,104). The clinical treatment of highly invasive triple-negative breast cancer (TNBC) faces significant challenges, and miRNAs present a potential target for the diagnosis, treatment and prognosis of TNBC (109). Chiarini *et al* (109) discovered that upregulation of miR-129 could reduce LMNA expression in breast cancer cells. Given the close relationship between LMNA and breast cancer development, the miR-LMNA axis may represent a novel therapeutic pathway for breast cancer. In invasive bone tumors, Chiarini *et al* (109) revealed that high expression of LMNA reduced the nuclear recruitment of Yes-associated protein/TAZ and decreased the invasive ability of tumor cells.

6. Effects of the interaction of LMNA with other proteins on tumor progression

The influence of the LMNA gene on cancer progression extends beyond its effects on tumor-associated pathways. In tumors, the interactions of LMNA with various cellular proteins can significantly impact disease progression. TPX2, a hallmark protein in ovarian cancer that is associated with poor prognosis (110), has been shown to regulate lamin A/C stability. Meng *et al* (111) and Sidera *et al* (112) demonstrated that TPX2 can modulate lamin A/C phosphorylation levels in ovarian cancer cells, thereby affecting their stability and inhibiting cellular processes. Hsp90, a highly conserved chaperone protein, is crucial for tumor cell invasion and DNA damage repair, making it a potential therapeutic target. Wang *et al* (113) observed that LMNA knockdown altered Hsp90 distribution in ovarian cancer cells, increasing nuclear localization while decreasing cytoplasmic presence. In hepatocellular carcinoma (HCC), a major contributor to global cancer-related deaths (114-116), LMNA has been reported to interact with sperm-associated antigen 4, a member of the SUN family, and LINC complexes (117,118). This interaction

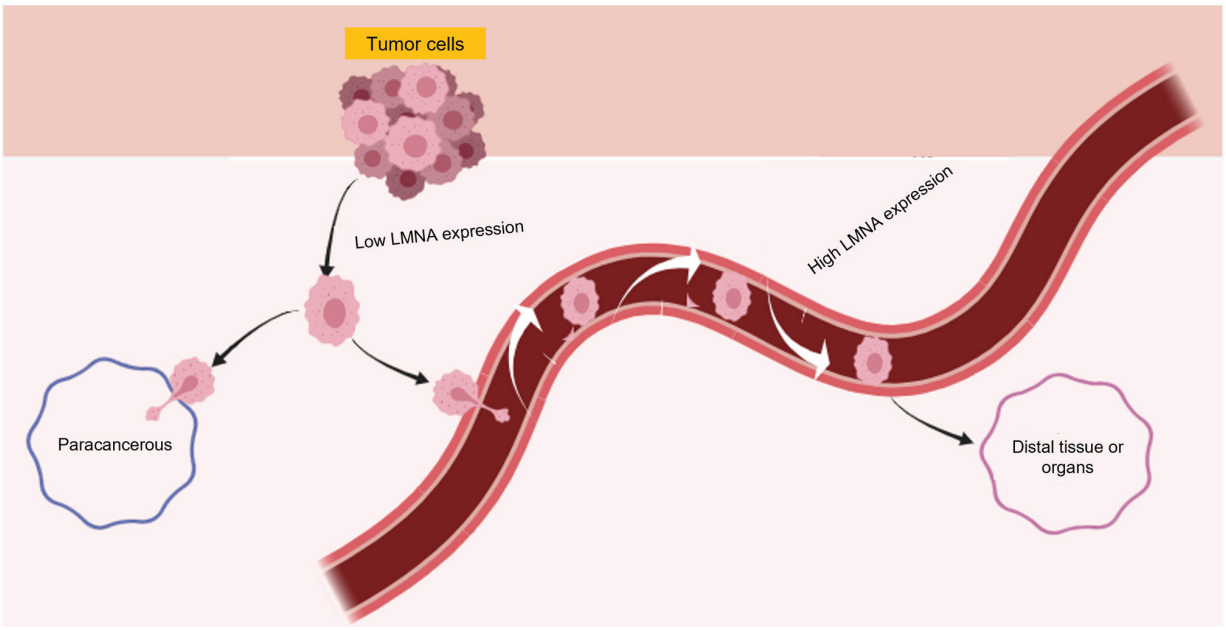

Figure 3. Effect of LMNA on tumor cell metastasis. LMNA has different effects on the metastasis and invasion of tumor cells. Low expression of LMNA can enhance transmembrane activity, enhance cell invasion, cause proximal invasion of tumor cells, or increase invasion of nearby tissues and organs. In the blood vessels, high expression of LMNA can enhance the ability of cells to resist pressure, which leads to the increased ability of distal metastasis.

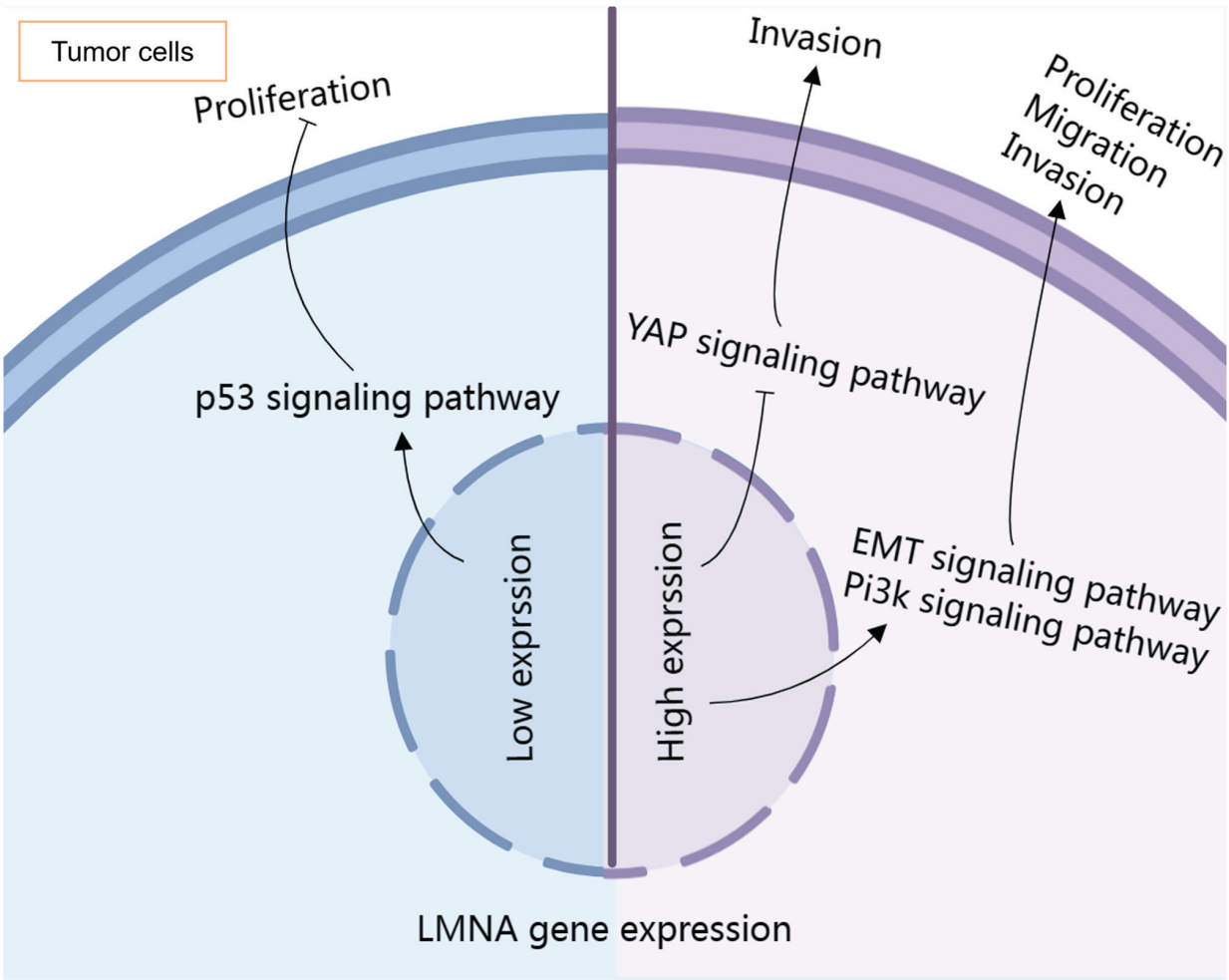

Figure 4. Effects of LMNA expression levels on common signaling pathways in tumor cells. LMNA perturbs different signaling pathways in tumors and affects various physiological functions of tumor cells. Low expression of LMNA in tumors can activate the p53 signaling pathway and inhibit the proliferation of tumor cells. High expression of LMNA in tumors, can activate the YAP, EMT and PI3K signaling pathways, thus promoting the invasion, migration and proliferation of tumor cells. YAP, Yes-associated protein; EMT, epithelial-mesenchymal transition; PI3K, phosphatidylinositol-3-kinase.

can increase the expression of SREBP1, a key regulator of adipogenesis (114,119,120), which can increase the expression of enzymes related to lipid metabolism, thereby promoting HCC development (121). Additionally, post-translational modification of lamin A at the K265/270 site has been shown to enhance HCC cell proliferation and prevent senescence under hypoxic conditions (122). In colon cancer, the interaction between LMNA and c-Fos, a regulator of cell transformation (123,124), has been studied. Under specific microenvironmental conditions, GDF15 was found to separate c-Fos from lamin A/C, activating c-Fos, and promoting cancer cell invasion and metastasis through EMT-related gene expression (123). The antitumor activity of polyphenols extracted from *Artemisia annua* L. (pKAL) in colorectal cancer cells has been linked to p53-mediated upregulation of the LMNA gene (104). Furthermore, LMNA has been shown to protect pRb tumor suppressor proteins, key regulators of cell proliferation and differentiation, from proteasomal degradation (125). These findings highlight the multifaceted role of LMNA in tumor progression through its interactions with various proteins. LMNA participates in post-translational modifications and protein interactions that maintain stability or enhance activity of oncogenic proteins, thereby influencing tumor physiology. Further investigation into these interactions may provide comprehensive insights for developing novel cancer treatment strategies.

7. Conclusion

The LMNA gene-encoded lamin A/C proteins, which are crucial intermediate filament proteins for maintaining cellular nuclear morphology, serve a pivotal role in various cellular processes, including DNA damage repair, gene expression regulation and cell differentiation. These proteins are intricately linked to human health. While significant progress has been made in elucidating the mechanisms of LMNA-induced diseases, substantial challenges remain in developing specific clinical treatments. Current experimental data have indicated that LMNA significantly influences the treatment and prognosis of LMNA-associated diseases and cancer in clinical settings, and studies have elucidated the mechanisms underlying the role of LMNA in these conditions and suggested its potential as a biomarker. However, there is a notable lack of effective progress in the specific clinical treatment of LMNA-induced diseases and tumors. For example, DCM caused by LMNA mutations typically has a poorer prognosis compared with DCM resulting from other etiologies; however, the underlying mechanisms remain to be fully elucidated. Notably, the expression patterns of LMNA in various types of cancer are inconsistent, thus adding complexity to LMNA-related tumor studies. LMNA expression has been reported to be downregulated in ovarian and breast cancer, whereas it is upregulated in prostate and colorectal cancer. This variability complicates the research on the role of LMNA in tumors. Moreover, since the LMNA-encoded nuclear lamin A protein is an integral component of the cell nucleus, targeting LMNA as a therapeutic approach may potentially affect normal cells. The present review delineated the tumor-associated pathways potentially influenced by LMNA and the interacting proteins present in tumor cells. This approach aims to identify associated pathways and interacting proteins that could be targeted with enhanced selectivity. Current research suggests that LMNA is associated with the progression of highly invasive and metastatic tumors; therefore, further in-depth investigation into the function and molecular mechanisms of lamin A/C is warranted. In conclusion, continued research into the role of LMNA holds positive theoretical significance and clinical translational value for the prevention, specific treatment and prognosis of LMNA-related diseases and tumors.

Acknowledgements

Not applicable.

Funding

This work was supported by grants from the Scientific Research Project of Education Department of Yunnan Province (grant nos. 2023Y0787 and 2024Y217).

Availability of data and materials

Not applicable.

Authors' contributions

JZ and YT designed the review. JZ and HZ wrote the first draft of this review, while CP, QH and KZ collected the information needed for the review, and also helped design and write review. YT revised the article. Data authentication is not applicable. All authors read and approved the final version of the 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.

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