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REVIEW

A-type lamins involvement in transport and implications in cancer?

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ABSTRACT

Nuclear lamins and transport are intrinsically linked, but their relationship is yet to be fully unraveled. A multitude of complex, coupled interactions between lamins and nucleoporins (Nups), which mediate active transport into and out of the nucleus, combined with well documented dysregulation of lamins in many cancers, suggests that lamins and nuclear transport may play a pivotal role in carcinogenesis and the preservation of cancer. Changes of function related to lamin/Nup activity can principally lead to DNA damage, further increasing the genetic diversity within a tumor, which could lead to the reduction the effectiveness of antineoplastic treatments. This review discusses and synthesizes different connections of lamins to nuclear transport and offers a number of outlook questions, the answers to which could reveal a new perspective on the connection of lamins to molecular transport of cancer therapeutics, in addition to their established role in nuclear mechanics.

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Introduction

Nuclear lamins, the constituents of the nuclear lamina which underlie the inner membrane of the nuclear envelope, have been the subject of significant research due to their roles as biophysical support for the mammalian nuclear envelope and biomarkers for various aggressive cancers [1–3]. The major lamin isoforms – lamin A, B, and C – collectively form the lamin network, and assist in regulating many nuclear mechanisms that are critical for cell survival. The lamin network inside the nucleus is analogous to the actin network within the cytosol in several ways – i.e. each help give rigidity to their local environment and attach to transmembrane proteins such as the LINC complex and intracellular integrin domains, respectively. These protein complexes allow for forces to transmit across their respective membranes and ensure these proteins participate in mechanosensing [1,4,5].

Misregulation of lamin A and C – A-type lamins – have been attributed to hypotrophic diseases, neurological diseases, dysplasia and many other types of ailments – all coined as laminopathies – as well as a variety of cancers [6–11]. While there are certainly intersections between mutations in *LMNA* (the gene that codes for A-type lamins) and a variety of pathological laminopathies, here we focus on the functional role of lamins as they relate to cancer. We refer the reader to excellent reviews of laminopathies [7,8]. Below we begin by providing an overview of B- and A-type lamins before focusing on A-type lamins' functional role in nuclear transport and their possible implications in cancer.

B- and A-type lamin overview

B-type lamins, coded by the *LMNB1* and *LMNB2* genes, are responsible for a variety of nuclear tasks such as organizing the other types of nuclear lamin networks [12], compensating in mechanical stiffness in cells with low A-type lamins [13], connecting the the nucleus to the cytoskeleton [14], and various other vital nuclear tasks for cell survival outlined in [15]. Mutations in *LMNB* genes appear to manifest in various neurological diseases that coincide with mutations or abnormal levels of *LMNA*, suggesting a strong correlation between *LMNA* and *LMNB* genes [16,17]. B-type lamin dysregulation have some correlation to specific cancers, including their ratio to A-type lamins, but B-type lamins are not likely to be used as a broadspan cancer biomarker due to difficulties

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discerning differences across varying tissues and cell groups [18,19]. Therefore, in an effort to hone this review, B-type lamins will be discussed in brevity, contrary to A-type lamins.

The gene *LMNA* encodes the A-type lamins: lamin A and lamin C. A-type lamins are intermediate filament proteins that form a filamentous network juxtaposed to the nuclear membrane. Because of this network and the aforementioned connection to the LINC complex, which spans the nuclear envelope, A-type lamins have been implicated in mechanotransduction. Cells deficient in either lamin A, C, or both were shown to have oddly shaped nuclei and abnormal nuclear mechanics [20,21]. Both A-type lamins (lamin A and C) are part of the nuclear lamin network, but neither can bind to the nuclear membrane directly like B-type lamins [22,23]. Rather, the filamentous network localizes to the nuclear membrane and attaches to SUN and Nesprin transmembrane proteins that are then attached to cytoskeletal filaments, which in total form the LINC complex. While A-type lamins are normally resistant to dissolution, they will break down and become soluble within the cell due to phosphorylation, similar to vimentin cytoskeletal intermediate filaments, during mitosis [23]. Additionally, A-type lamins play both direct and indirect roles in gene regulation and transcription [20,24–26], which may further complicate impact of mutant or dysregulated A-type lamins.

Normal levels of all lamin types allow for a flexible nuclear envelope [27]. These levels of lamin also protect from nuclear blebbing and high nuclear stresses that cause DNA damage or apoptosis [28]. Interestingly, metastatic cancer cells exhibit a much lower level of A-type lamins, and when these cells migrate through small pores in the ECM, the nuclear stresses and strains are so great, that the cancer cells undergo a change in nuclear shape that is conserved over time, and potentially even apoptosis if the mechanical stresses are too great [19]. Chen et al. performed experiments that transiently knockdown approximately 50% of Lamin A in cancer cells; as a result the compliance of the nucleus was up to four times greater than that of control cells [29]. In addition to certain cancers, stem cells and neutrophils similarly exhibit low lamin A and C that enables intravasation, the migration of cells through blood vessel walls, during wound healing [30]. This is purported to be the same reason that some metastatic cancers exhibit low lamin levels [19,29,30].

Lamin A/C

Lamin A is an intermediate filament protein that has a total of 664 amino acids, and an approximate molecular weight of 70 kDa. Compared to lamin C, lamin A has ~ 90 unique carboxyl-terminal amino acids with respect to lamin C after pre-lamin A undergoes the post-translation proteolysis [31,32]. While most of its protein structure is similar to lamin C, only lamin A contains CAAX located at the carboxyl terminus [33]. Lamin C has a total of 572 amino acids, yet only 6 are unique with respect to Lamin A, see Figure 1a for a depiction [22,31,34]. Lamin C has a molecular weight of 60 kDa [35]. Lamin C depends on lamin A to incorporate into the lamina filament network at the inner nuclear membrane [36]. Given the reliance on lamin A, lamin C is often discussed together with lamin A. Thus, the exact role of lamin C both physiologically and in disease is less clear than lamin A. However, it has been proposed by a group that analyzed bone, kidney, connective, ovarian and brain tissue types that the ratiometric change of Lamin A and C shifting more heavily toward the C isoforms could be an indication of worsening prognosis and a potential avenue of treatment [37].

While lamin A and C have a large structural similarity due to common amino acids sequences – specifically 566 shared amino acids – lamin A undergoes a processing step before its incorporation into the lamina network [32–34]. Proteolysis turns pre-lamin A into lamin A, removing the last 18 amino acids from pre-lamin A which corresponds to a drop in molecular weight of 14 kDa [22]. This proteolytic event causes the mature lamin A to lose its polyisoprenyl group, preventing it from being bound to the inner nuclear lipid membrane as is lamin B (Figure 1a) [22,23].

Lamin A is implicated in chromatin organization and packing [38,39], dynamically mechanoprotecting DNA when the cell is subjected to transient stresses [40], as well as DNA damage repair [30,40,41], which will be discussed further

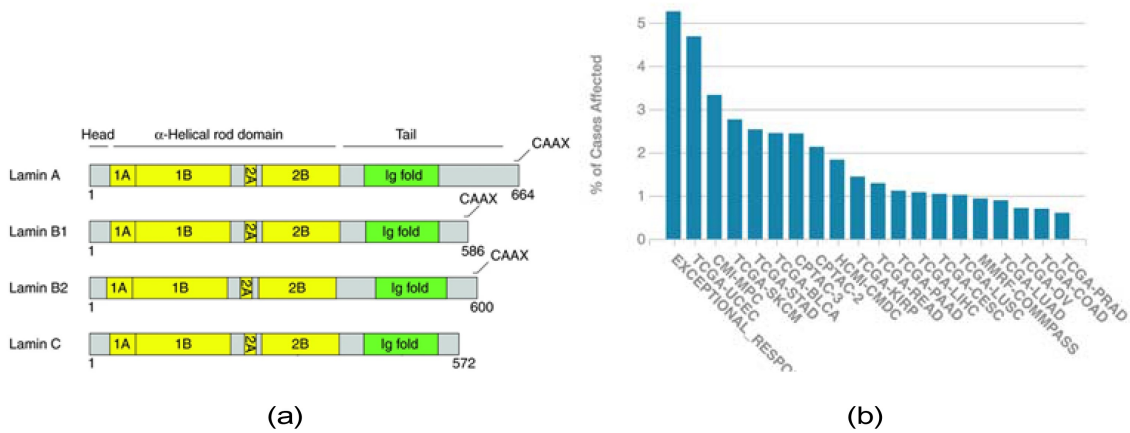

Figure 1. Protein structure of common lamin outlined in [33] (a) and mutations of the *LMNA* gene seen in various cancer studies of multiple cancer tissue origins depicted on NCI's GDC [81] (b).

in section 5. Mutations and misregulation of A-type lamins can create conditions under which nuclear membrane rupture is more frequent causing a variety of issues such as compounded DNA damage [29,30,41]. Moreover, mutations of A-type lamins have been associated with inhibited active nucleo-cytoplasmic transport, which is seen in Hutchinson–Gilford progeria syndrome, but there is also have reason to believe that A-type lamin mutations such as the hyperstiff mutation Δ50LA could cause nuclear transport changes [30,42]. Knockdown of A-type lamins also causes a suppression of HSP90 [19], and limits interaction with IFFO1 [43], both of which aid in DNA repairing. On a similar note, lamin defects can allow for nonselective permeability which in turn causes DNA repair molecules such as 53BP1 to end up exiting the nucleus in their time of need [30]. If DNA repair is impaired, mutations may occur more readily in these cells. This scenario is known to occur in cancers, and the positive feedback system (increased DNA mutation and decreased DNA repair) may contribute to the tell-tale phenomenon seen in more aggressive cancers–genetic diversity and drug resistant cells.

A-type lamins are also connected to motility of cancer cells, growth rate, metastasis, and overall aggressiveness of cancers [1,19,29,38,44]. Cancer cells appear to dynamically modulate lamin A and C concentrations, with peripheral and core local regions of the same tumor having different levels of the two A-type lamins [19,44]. Specific types of tumors are known to over- or under-express A-type lamins, suggesting that altering cell and nucleus stiffness could confer a survival advantage that may be advantageously selected by tissue type or other local environmental pressure. For example, Kong et al. investigated three lines of prostate cancer, and they all exhibited varying degrees of lamin A/C overexpression for highly aggressive metastatic cancers. In contrast, Harada et al. and Chen et al. found very different results in specific glioblastoma and lung carcinoma cell lines – low expression of lamin A/C allowed for three times faster tumor growth within the first week of growth, and allowed for an increase in migration by up to 4 times the rate of cell with normal lamin expression [19,29,44]. Because of the propensity of A-type lamin expression to change in cancers, they are used as biomarkers to assess cancer aggressiveness (Figure 1b) [3,18,45–48]. However, given the complexities of A-type lamin expression in cancer, as well as the influence of A-type lamins on different aspects of nuclear physiology beyond metastatic potential [49] and stem-cell/tumor-initiating cell-like behavior [37], we believe it is prudent to clarify the functional roles of A-type lamins with respect to their possible connection to cancer.

Lamins and nuclear mechanics

The lamin filament network, similar to the actin filament network for the cytoplasm, helps transmit forces to the interior of the nucleus with the help

of SUN and other LINC proteins [50,51]. The lamins also directly contribute to the Young's modulus of the cell. According to multiple researchers, lamin A protein quantity correlates more strongly with cell stiffness compared to lamin C, having a correlation coefficient near 1 while lamin C has a correlation of ~ 0.75 [29,38]. Incidentally, both A-type lamins contribute to the stiffness/structural stability of the nucleus considerably more than B-type lamins [20,29,52]. Again, similar to actin filaments, where actin stress fiber formation is a response to the underlying stiffness of the ECM [53], the lamin levels at the inner membrane of the nuclear membrane are believed to respond to transient stresses in a 'use it or lose it' need-based system to protect the cell from DNA damage, such as the mechanical stresses the cell incurs when the cell travels through tight extracellular matrix pores, and prevents the cell from then undergoing apoptosis [40,54].

Lamin-Nup coupled interactions

We purport lamins to be influential to transport due to their binding interactions with specific Nups in the nuclear envelope that allow for proper NPC formation. Therefore, one cannot talk about lamins, and their subsequent effects on transport without discussing Nups, and lamins' influence on correct NPC formation.

The nuclear pore complex (NPC) and its constituent Nups form the gateway for molecules into and out of the nucleus in mammalian cells. Importantly, access to the nucleus is both passive (via diffusion) for small molecules and active (via nuclear localization sequences and importer proteins) for larger molecules and even viruses. The NPC forms a channel across both membranes of the nuclear envelope, and the Nups are bound to stress-bearing proteins (lamins) of the nucleus. The connection of lamins and Nups allows stress transmission to the NPC, likely causing it to deform when the cell nucleus is subjected to stresses, e.g, from cell movement through small pores. These forces are transmitted via the LINC complex and lamin networks, and may significantly affect the basket conformation of certain Nups – which could impact both active and passive transport across the nuclear membrane [51,55,56]. In fact, changes in nuclear transport of YAP due to the NPC undergoing different levels of mechanical strain has already been documented [56]. Typically, for healthy non-defective NPCs, the stresses are within the elastic reversible regime of deformation [27,57]. However, cancer cell Nups may exhibit differences that have not been observed in healthy cells that can modify NPCs. For instance, depending on A-type lamin concentrations, the nuclear envelope may behave more like a rigid body (high lamin concentrations) or a highly compliant body (low lamin concentrations) [19,29], that would strongly affect the transmission of membrane strains to the Nups/NPC through the membrane bound Nup-lamin interactions [56].

A few researchers noticed cancer nuclear area/volume varies in addition to cells having irregular nuclear envelope contours (compared to non-cancerous cells) [1,18,58,59], which may further compound protein/transport dysregulation two-fold: (1) complex stress concentrations at sharp geometrical changes, i.e., at irregular nuclear folds, local Nups could be atypically stressed/strained significantly more than the Nups would be in a healthy cell with a more consistent angle of curvature on the nuclear envelope. (2a) Assuming that cancer cells have a higher area density of Nups on the nuclear membrane than healthy cells, an increase in nuclear surface area due to misregulated A-type lamin levels [59] seen in cancer would yield a disproportionately higher total number of Nups on the nuclear surface compared to a healthy cell–meaning a significant increase of the number of 'gates' for molecular transport in cancer [60]. (2b) The other scenario that could be true, which would still cause a similar transport dysregulation would be if Nup area density is conserved between cancer and healthy cells, meaning the Nups must exhibit a more hyperactive transport. With a larger total nuclear volume, the gates would thus have to work overtime to equilibrate proteins, small molecules, and genetic material per unit volume in order to have similar concentrations seen in a standard cell. Out of the two scenarios, high Nup density (2a) seems to be more likely to occur in cancers rather than rather

than fewer, but hyperactive Nups (2b) based on experiments carried out by Sakuma et al. In their experiments, they found that cancer cells and healthy cells have an equal reduction of NPCs when exposed to siRNAs that reduce NPC formation, but only cancer cells die, showing a reliance on high NPC densities for survival [60]. Additionally, Lewin et al. have explicitly found an increase in NPC counts in chemo-resistant cancer types, reinforcing the (2a) phenomenon [61].

On the same lines as nuclear size and irregular contours (local curvature) altering transport, cell/nucleus shape (global curvature, i.e., eccentricity of the nucleus), which are dependent on lamin [19,27,29], and the ECM surrounding the cell can also cause differences in transport due to the stresses the cells incur from the ECM (note that this would be stiffer in cancerous tissue) [51,55,56,62–65]. Garcia explains that nuclear circularity affects the passive diffusion rate, or the permeability of the nuclear membrane for small molecules. Through empirically informed computational models, they found that there is a greater nuclear permeability for ellipsoidal nuclei, which could occur due to stiffer ECM or lower levels of lamin A. This could tie into the fact of the lamin-Nup binding sites being strained in an atypical manner, causing the Nup gateway to be open and less discriminant toward the molecules wanting passage as seen by another researcher cited within this review. In fact, the model predicted that the permeability constant at the point which the nuclear membrane is the most flat for the ellipsoidal configuration was almost 50% greater of a permeability constant than that of the same portion of the nucleus in the circular configuration [62].

Mutations with respect to transport

Mutations in either lamins or Nups can convolute the nuclear membrane transport process. Researchers have recently shown that Nup mutations or dysregulations can alter nuclear transport processes [60,66–68]. For instance, researchers have documented mutations in phenylalanine-glycine (FG) domains of Nups that cause precipitated transport abnormalities when compared to native FG domains of yeast cells, yielding asymmetric increases of nuclear permeabilities of different molecular weight cargoes. Coincidentally, mutations and other irregularities of expression of these FG domains have been found in certain cancers [66,68]. Other directions of research have included how transport specifically coincides with cancer, such as carcinogenic mutations/modifications in cargo, transporters, and the NPC itself [60,69]. While there are reviews that have helped to compile potential mechanisms connected with changes in nucleo-cytoplasmic transport [70], fewer studies have focused on how lamin mutations could lead to dysregulated transport.

Changes in gene transcription due to copy number variations (CNVs) of *LMNA* could change the concentration/density of Nups within the nuclear membrane by affecting the area density of Nups that are supported by the lamin network, assuming that lamin binding sites are the limiting factor of the lamin-Nup interactions [7]. Such an effect would indirectly affect nucleo-cytoplasmic transport [71,72]. On the other hand, lamin mutations can cause issues in Nup-lamin binding if the conformation of the binding site is affected by the mutation. Mutations and misregulation of lamins have been shown to cause clustering of active transport complexes [30]. Defective lamin A can prevent proper binding to Nups such as Nup153 and Nup155, which is how some laminopathies manifest [51,71,72]. Depending on the type of change in lamin expression or mutations in *LMNA*, augmented or inhibited nucleo-cytoplasmic transport can result – either of which can lead to strongly modified cell phenotype [73,74].

A conceptual diagram of these mechanisms is presented in Figure 2. Note that while a culmination of multiple mutations occur in cancer, it is possible that none, one, multiple, or all of these processes may exist in a given neoplastic cell population. These concepts will be discussed in conjunction with cancer in section 6.

Lamin expression in cancer

Cancer is defined as cell division that is uninhibited by any sort of signaling or stimulus due to gene mutations. In fact, the research community has found that the typical cancerous cell has a conglomeration of many different genetic

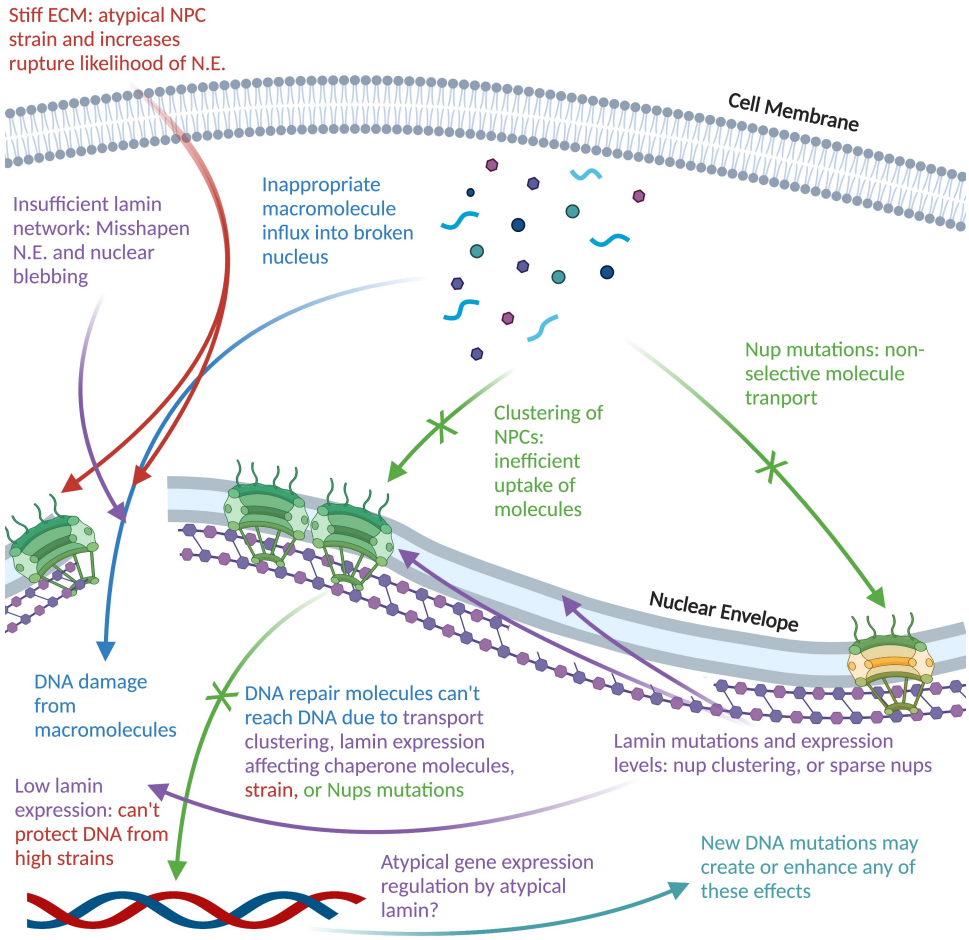

Figure 2. Any of the purple, red or green statements in the above figure may independently occur in cancer cells. However, the existence of any of these issues may lead to an increased likelihood of other shown phenomenon and atypical nuclear trafficking. Note that insufficient lamin network may be a byproduct of cancers that inherently underexpress lamin based on their soft tissues. Created with BioRender.com.

mutations, with the general minimum being around 60 core mutations that combine to allow for abnormal growth, proliferation, and resistance to apoptosis [75–77]. These core mutations are likely an aggregation of many lesser, originally benign mutations, and as the cancer continues to grow in mass, mutations to the amount of 10^{13} or greater may be found. Mutations can occur through various ways, but some preexisting mutations, such as in lamins or Nups can predispose cells to DNA damage and subsequent mutations. Aggregation of further mutations may accelerate the potential for cancer, or if the cell is already cancerous, increase cancer aggression and drug resistance. In fact, aggressive cancer cells can have hyperactive nuclear export, the ability to inactivate temporarily Nups, or altered membrane makeup (such as with an addition of potentially pathological glycoproteins) to ensure neoplastic mechanisms are unhindered by chemotherapeutics [50,70,78–80]. Additionally, many cancers are known to have dysregulated and/or mutant nuclear envelope proteins, including both A and B-type lamins, see Figure 1b for mutation percentages of the *LMNA* gene for various cancer types [1]. Additionally, data on CNVs of the *LMNA* gene seen in the same NCI database as Figure 1b shows that there is an extremely strong propensity for a gain of CNVs within the majority of analyzed cancer types, with the highest study (the TCGA-UC S study) showing about 35% of the cancer lines within the study having a gain of CNVs, whereas

0% of the cancers within the study had a loss of CNVs. On average, gain in CNVs throughout all studies was around 15%, while the number of cancers within a study that showed a loss of CNVs was averaged to be around 1% [81]. A research group further probed *LMNA* CNVs and their relation to atypical gene expression across cancers, and revealed that the two are strongly correlated, stating that *LMNA* CNVs impacted transcription of many genes [82]. These two facts combined give further credence to the idea that the *LMNA* gene has significant roles to play in cancer, despite seeing inherently heterogeneous A-type lamin levels across different cancer tissue types.

Interestingly, A-type lamins are suggested to regulate cell proliferation in addition to gene regulation, which is at the core of carcinogenesis [24,83]. This may explain why so many research groups have incidentally found mutant lamins in cancer, as well as their use as biomarkers.

Lamins and Nups work hand in hand in many nuclear processes. Given this tight connection, there are many intersections in pathways, and mutations of either may cause similar phenotypic responses [51]. For instance, like A-type lamins, Nups are also responsible for gene regulation [84]. Nucleoporins can cause an increase or decrease in protein levels and some are implicated in carcinogenic mechanisms [67,70,85]. For instance, a research group showed that knockdown of Nup62 caused resistance to a chemotherapeutic [67]. Therefore, to decouple A-type lamins and Nups, mutations/dysregulations of both types should be studied within the same cell type, such as through CRISPR. This way, additive processes (such as if mutations existed in both A-type lamins and Nups that independently caused 'gain of function') and subtractive processes (the collective opposite) could yield a wealth of information–increasing our understanding of common cancer mutations, altered transport, nuclear mechanics, and how that affects treatment options.

Cancerous tissue is known to have higher levels of extracellular matrix and is typically stiffer than healthy tissue of the same type [86,87]. While many tumor cells contribute in secreting this ECM, they are also aided by cells afflicted by the neoplasm's cellular signaling such as the cancer associated fibroblasts [86–88]. These cancer associated fibroblasts are known to excrete a significant amount of the ECM present in tumors. This stiffer than physiologic tissue has a direct influence on cell shape, which was previously discussed in section 5 with regard to how the cell/nucleus' shape effects both active and passive transport [55,56]. The phenomenon of cell shape related to substrate mechanics has been well documented [89,90], and may complicate lamin and transport activity seen in these cancerous cells. For instance, the strain due to substrate mechanics may have an affect on nuclear surface folds and transport capabilities due to channel geometrical changes, all while causing a positive feedback for lamin production, increasing the concentration of lamin–causing other potential changes in transport that have not been studied [91,92].

An example of this potential phenomenon is seen in Figure 3; Kong et al. found that the cells at the periphery of a tumor have lower lamin concentration than the core, which is plausibly due to the positive feedback with the surrounding tissue stiffness that was mentioned previously, but what if the ease of access to nutrients also impacts the lamin concentration? Without a proper concentration of lamin, transport may suffer, so in a situation where resources are sparse, does the cell compensate by increasing lamin (binding sites) to allow additional Nups to be bound on the nucleus' surface for faster transport of materials into the nucleus when they enter the cell? If so, then the inverse would be true for a cell closer to the resource tap (capillaries), because transport rates wouldn't be an issue for survival. Additionally, when inspecting the figure referenced above, two additional questions come to mind: do the lamin concentrations, which are clearly seen as different for benign and aggressive tumors correspond to Nup concentrations? If so, does that mean nuclear transport rates differ based on the grade of cancer, which could be a means to exploit? This would coincide with the results depicted in Figure 4(a,b), where proliferation rates are directly affected by modulation of lamin, which may indicate a difference in nuclear 'activity' [60].

Changes in Nup stiffness and its subsequent change in chemotherapeutic uptake can be seen both in vivo and in vitro. (1) Nups in cancer cells

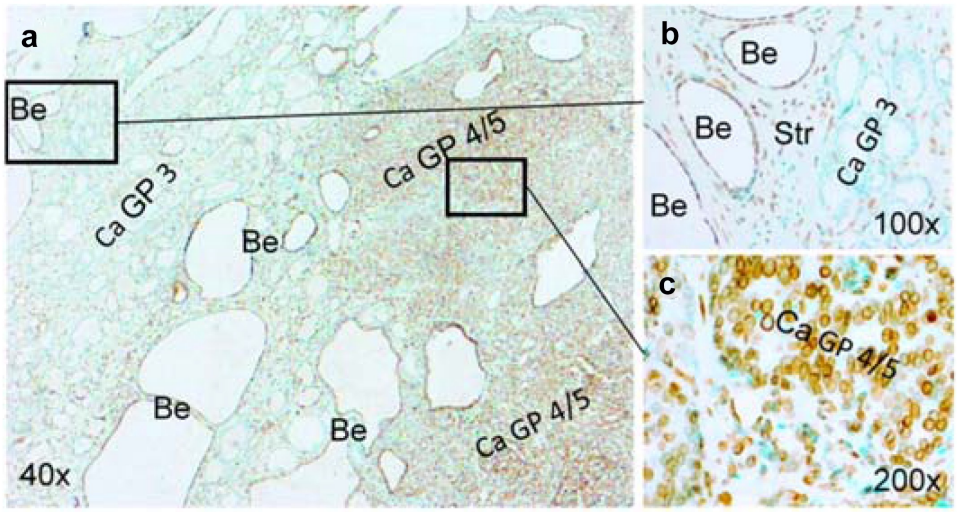

Figure 3. Lamin levels within a single tumor mass can differ [44], which likely depend on the surrounding ECM, but could it also correspond to ease of access to resources? Darker staining corresponds to a higher lamin concentration, and in (a) the core tumor has significantly higher lamin than the periphery. (b) and (c) are zoom-in regions of different subsets of the cancer population notated: Be (benign), and aggressive tumors, Ca GP 3 (low-grade Gleason Pattern tumors) and Ca GP 4/5 (high-grade Gleason Pattern tumors). See [44] for how they define each tumor grade.

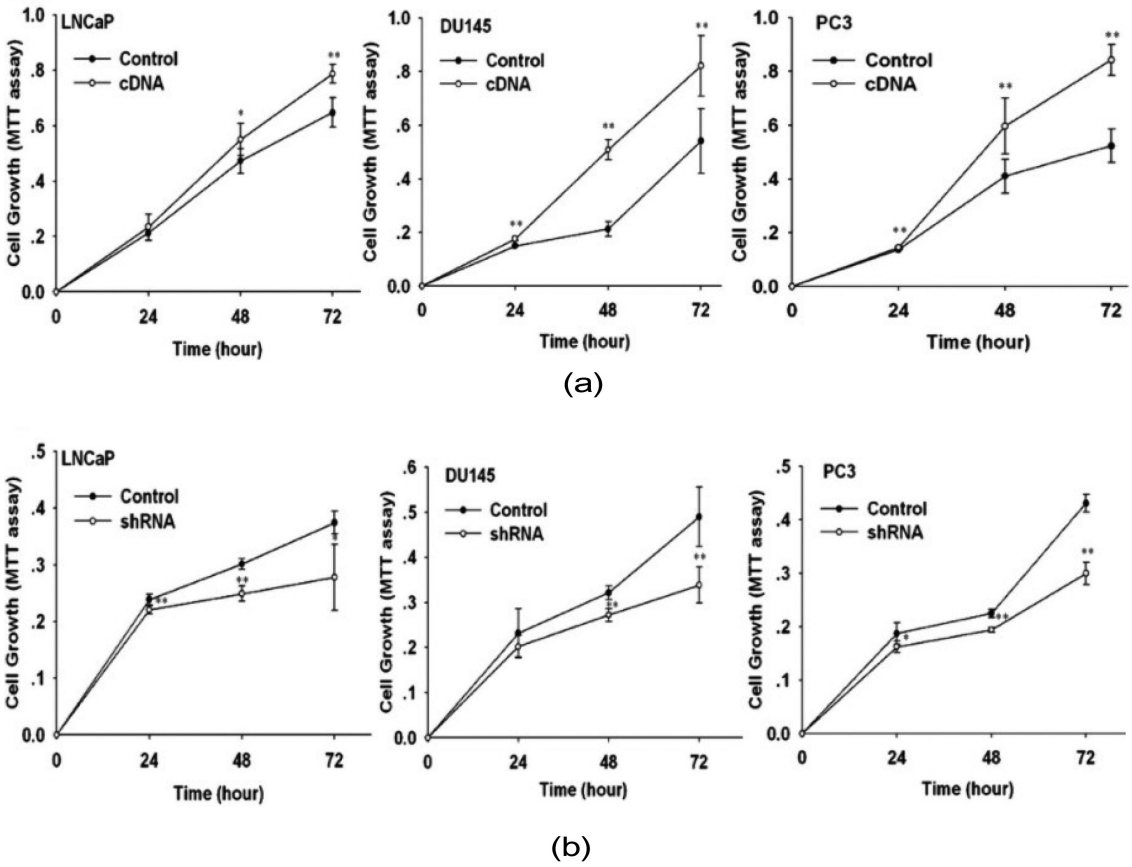

Figure 4. Positive (a) and negative (b) modulation from baseline (see control) for three different prostate cancer lines: LNCaP, DU145, and PC3 [44]. An upregulation of lamin shows a higher proliferation rate for each cell line, whereas a knockdown shows a decrease. This proliferation rate could coincide with an increase in transport through the nuclear envelope, allowing for a greater amount of nuclear 'activity', including protein, transcription, and other transport to facilitate fast growth.

lose their resilience after being mechanically strained (such as when squeezing through tight pore sizes in the ECM during migration or slipping between epithelial cells when entering the blood stream for metastasis) when the cell is near death [1]. This may change molecules effectively transported in and out of the nucleus especially when undergoing treatments such as chemotherapeutics, further challenging drug efficacy prediction targeting nuclear transport. This may explain why many cancers are more susceptible to a combination therapy over just one or the other. One chemotherapeutic reduces the selectivity of the cancer cell's NPCs by affecting the Nup resilience, and allows for the other chemotherapeutic to enter the nucleus in a less hindered fashion than the respective monotherapy would. If nuclear stiffness, the resulting strain of the Nups, and selectivity of molecule uptake are causally related, changes in nuclear strain related to lamin expression would be yet another explanation for lamin-based selectivity differences that may be seen between cancer cells.

Questions of interest and future work

We find the connection between lamins and nuclear transport to be curiously strong in cancer, and elucidating this relationship may inform a potentially effective treatment. While there are still a vast amount of unknowns in this area, we believe that finding how transport is specifically affected by lamin concentrations could be a highly interesting piece of information to optimize treatment efficacy in cancer. A series of questions of what happens with lamin-Nup coupling in cancer are presented in Figure 6.

Since it is known that several cancers exhibit abnormal levels of A-type lamins for advantageous reasons such as rapid mass growth and mobility, we believe that understanding why specific cancers have chosen to overexpress while others underexpress lamin proteins may elucidate different dominating mechanisms that exist between the different cancers. Figure 4a and 4b are first steps to this sort of question, which explain proliferation rates when lamin is modulated in three different prostate cancer cell lines. However, if these protein levels are overexpressed compared to the baseline cell in healthy prostate tissue, does this same advantageous mass growth and mobility trend hold true in cancerous cells that inherently underexpress lamin protein levels compared to the baseline cell in their respective healthy tissue?

When referring to Figure 5 and the respective article, mutations in FG domains of Nups in yeast change the permeability of different molecular weight cargoes asymmetrically, that is, some are preferentially permeable to one of the two molecular weights normalized to the wild-type yeast. While structural mutations and dysregulations are seen in cancers–such as with Nup62, Nup98, Nup214 and others [57,67,68], structural changes due to changes in mechanical strains applied to the Nups may have similar effects on permeability. Along these lines, one can pose a variety of questions. Are molecule uptake rates through the nuclear envelope of cancer cells that inherently underexpress A-type lamin (compared to their corresponding healthy tissue cell's lamin concentrations) different than those that inherently overexpress A-type lamin? Are the molecule uptake rates symmetrical for all different molecular weights, or do the specific cancers have a preference toward one molecular weight similar to what is seen in Figure 5?

If FG mutations within Nups in yeast cells can cause an increase of 3 and 4 times greater permeability of different molecular weights when compared to the wild type, changes in Nup structure (whether it be FG mutations or significant structural changes due to mechanical strains) in human cancer cells causing specific molecular weights to have a greater rate of permeability into the nucleus is a plausible hypothesis. The fact that molecule trafficking rates were not uniformly increased regardless of specific molecular weight in Figure 5, ithat is, every mutation would stay on the solid line showing an equal increase of permeability normalized to the wild type for both molecular weights – like a nonselective transport mutation would cause, makes a deep dive of this sort of study prudent for human cells. Testing a variety of lower molecular weights and a larger band of molecular weights would be important considering the fact that most chemotherapeutics are less than 10 kDa, but future nanocarriers may increase that current size. Affinity studies such as

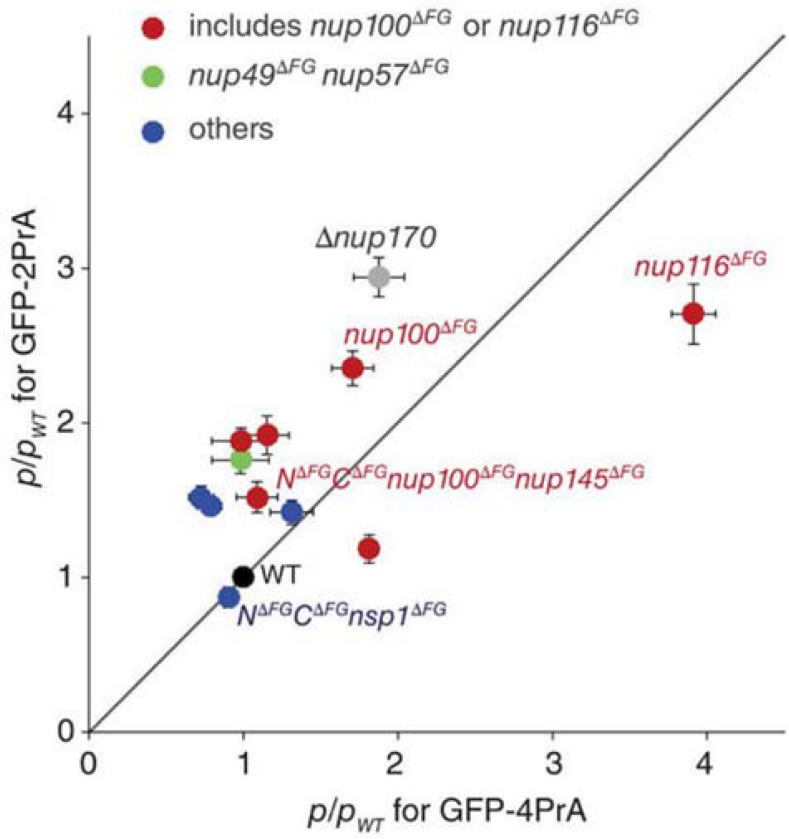

Figure 5. Two different molecular weight trafficking rates in yeast cells of containing different FG Nup mutations. An individual mutation type is normalized to the wild-type yeast to see transport differences [66]. Interestingly, it is possible for certain mutations to show a 'preference' to one molecular weight over another. Might this happen in human cells with Nup mutations or structural changes?

charge, hydrophobicity, and surface targeting modifications within a single molecular weight may need to be studied in conjunction with Nup structural changes (whether through mutations or mechanical strains), as it could help explain one of the many reasons for antineoplastic resistance within a specific cell lineage.

If overexpression of A-type lamins allows for an increase in molecular uptake through the nuclear membrane that is not exhibited in normal cells or in cancers that have microevolutionarily chosen the opposite lamin expression tendencies, then lamins can not only be used as a biomarker indicating that cancer exists, but also as a clue for which type of treatment to use. We suspect that lamin A/C overexpression could regulate molecular transport through the nucleus such that specific sizes of cargoes are preferred while underexpression may encourage trafficking for a different molecular size. This increase in nuclear transport of specific molecules (but not broad molecular weights) has already been observed in two prostate cancer cell lines: DU145-DR and 22Rv1-DR [93]. One could imagine that specific molecules should then be designed to exploit the enhanced uptake to deliver cytotoxic drugs, which would only be effective in cells that show particular lamin expression patterns. This would minimize normal cell consumption of this molecule and induce minimal nonspecific cell toxicity, all while disrupting or killing cancer cells with specific lamin phenotypic expression. Of course the molecule can also be designed with specific active targeting, to minimize the quantity of treatment required to further minimize the collateral damage.

Levels of lamin in the nucleus fluctuate depending on stiffness of the ECM [92]. We hypothesize that lamin expression tendencies (over- or underexpression of the intermediate filament protein), can be modified by changing the stiffness of the

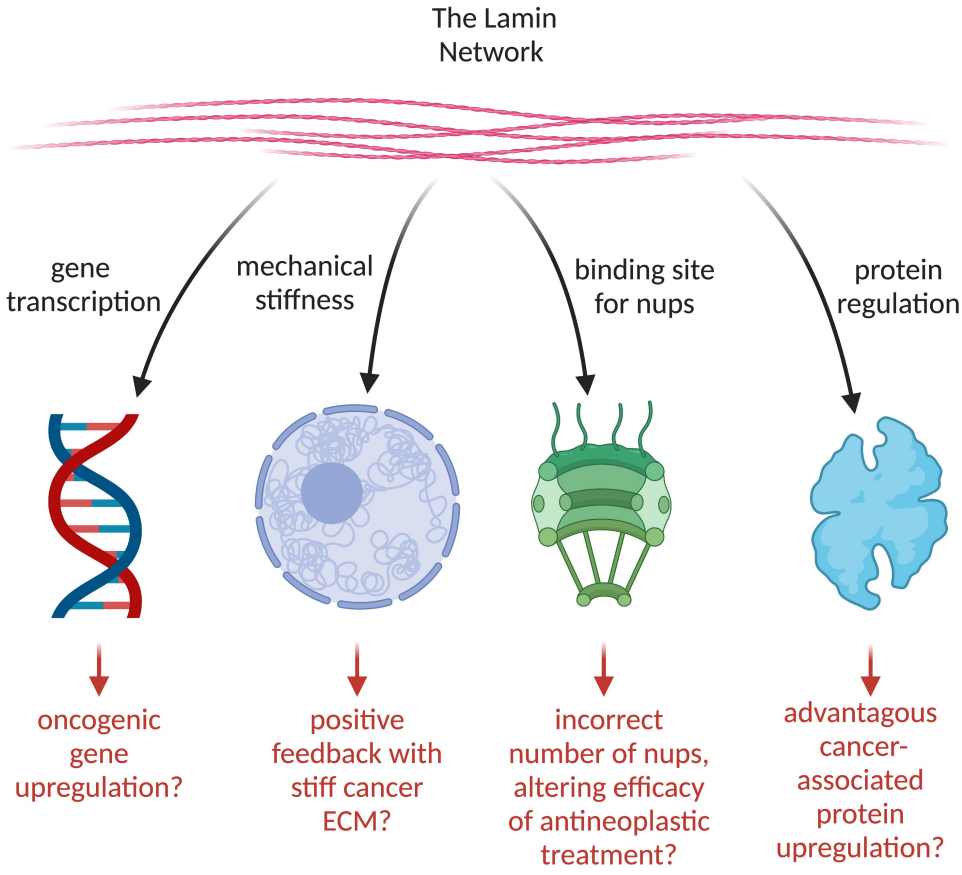

Figure 6. The lamin network is associated with many processes within the cell. The few processes shown have interesting questions that, once well understood, may allow for creation of a new cancer treatment allowing for better patient prognosis with less side effects. Created with BioRender.com.

substrate that the particular cancer resides on, which is naturally done depending on whether the cancer is at the core tumor or the invading edges [19,44]. A future idea would be to modify the lamin levels as part of a treatment to allow for advantageous uptake of particular molecules designed to be antineoplastic.

Additional questions involve other molecules linked to cancer that may be upregulated due to both stiff ECM in cancer, as well as nuclear prestress due to overexpression of lamin. For instance, YAP/TAZ molecules are linked to several solid mass cancers [94]. They also have significant overlap with A-type lamins in roles within the cell, i.e. they aid in cell mechanosensing, gene transcription, and cell proliferation [94–96]. According to Dupont [2016], there is a positive correlation between YAP/TAZ and breast cancer aggression. Attempts to halt growth by reintroducing cancer cells to soft healthy substrate can inactivate YAP/TAZ, but reactivation of these molecules can cause the cancer proliferation to overcome soft tissue inhibitory effects. YAP/TAZ have also been implicated in cancer associated fibroblasts, encouraging a positive feedback system for stiff ECM creation and increased cancer aggression [96]. While there has been evidence that there is a link between A-type lamins and YAP/TAZ, their correlation is not clear cut. YAP molecules generally localize in the nucleus for cells on stiff substrate scenarios (such as in cancers). However, current results regarding overexpressions of A-type lamins also tend to decrease YAP nuclear localization, which appears counterintuitive given that overexpression of lamin A/C tend to give a stiffer nucleus, and are typically seen in cancers with stiff ECM. Additionally, mutations of the gene encoding A-type lamins, *LMNA*, may inhibit nuclear localization of specific YAP proteins reinforcing the idea that A-type lamins help

regulate nuclear traffic. Finding trends of different cancers and how lamin expressions may alter other protein expressions may open a new series of questions. There have been many articles that indicate the YAP/TAZ pathway as being a potential pathway to exploit as a new cancer treatment [97–99], and answering these questions above and their relation to lamin may elucidate exactly how to make this a reality.

Conclusion

A-type lamins and Nups are known to have both direct and indirect consequences in cell proliferation, gene expression, and transcription. Mutant lamins and transport have been well documented in aiding in the likelihood of carcinogenesis. Lamins A/C and Nups are closely related in many nuclear functions, and together affect nucleo-cytoplasmic transport. Dysregulation or mutation in one may severely affect the other's processes. While A-type lamins and Nups have been researched substantially, many important questions related to their combined efforts in cancer, and how to exploit their natural differences within healthy and cancerous cells need to be answered. These divergences from the healthy expressions could be a key to future treatments ensuring cell cytotoxicity only occurs in the neoplasm, not the healthy neighboring cells.

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