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# **Breaking the scale: how disrupting the karyoplasmic ratio gives cancer cells an advantage for metastatic invasion**

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## **Abstract**

Nuclear size normally scales with the size of the cell, but in cancer this "karyoplasmic ratio" is disrupted. This is particularly so in more metastatic tumors where changes in the karyoplasmic ratio are used in both diagnosis and prognosis for several tumor types. However, the direction of nuclear size changes differs for particular tumor types: for example in breast cancer larger nuclear size correlates with increased metastasis while for lung cancer smaller nuclear size correlates with increased metastasis. Thus there must be tissue-specific drivers of the nuclear size changes, but proteins thus far linked to nuclear size regulation are widely expressed. Notably, for these tumor types ploidy changes have been excluded as the basis for nuclear size changes and so the increased metastasis is more likely to have a basis in the nuclear morphology change itself. We review what is known about nuclear size regulation and postulate how such nuclear size changes can increase metastasis and why the directionality can differ for particular tumor types.

**Keywords:** cancer, karyoplasmic ratio, lamin, NET, nuclear size

**Abbreviations used:** endoplasmic reticulum (ER), inner nuclear membrane (INM), Linker of Nucleoskeleton and Cytoskeleton (LINC), nuclear envelope (NE), nuclear envelope transmembrane protein (NET), outer nuclear membrane (ONM)

## Introduction

Breaking the microscope's 1  $\mu\text{m}$  resolution barrier in the mid-1800s revealed phenotypic and morphological changes in cell nuclei during cancer progression. An early description of these changes published in 1860 by Lionel S. Beale (King's College London) reported alteration of nuclear size and shape in the sputum of a patient with cancer of the pharynx (1). Eighty years later George Papanicolaou developed a stain to visualize cytoplasmic and nuclear structural features for the diagnosis/staging of cervical cancer, setting a standard tool still used today. Though subsequent advances added many other nuclear features to fine-tune diagnoses such as chromatin organization and numbers and sizes of nucleoli, the nuclear size and shape changes are the most microscopically evident characteristics in tumor progression and are highly characteristic for a given tumor type; hence, size is used prognostically for stage and progression of each tumor type (2). It is notable that in many tumor types where nuclear size is used prognostically the size changes have been shown to be independent of ploidy changes (3). Changes in ploidy greatly expand the number of indirect mechanisms that could lead to increased metastasis that would include increasing the burden of proper mitotic segregation. In this short review/hypothesis paper we will only focus on the types of cancer where ploidy has been excluded as a factor in nuclear size changes and thus where the size change itself is more likely to contribute to the increase in metastatic potential. Determining the function and mechanism of these nuclear size changes in cancer, is nonetheless made complicated because they tend to be tissue-specific in degree and direction — *e.g.* smaller nuclei indicate increased metastasis in osteosarcoma and lung carcinoma (4,5) while larger nuclei indicate increased metastasis in breast, prostate, liver, ovarian, pancreatic and colorectal cancers and small-cell cervical, epidermal squamous, papillary thyroid and urinary bladder carcinomas (6–15).

Nuclear size varies in different cell types and through differentiation, but the karyoplasmic ratio — of nucleoplasmic to cytoplasmic volume — is generally maintained for most cell types. Thus, nuclear size generally scales with cell size (16). The karyoplasmic ratio is maintained during the cell cycle (17,18) during which the nucleus typically increases several fold in volume and a general mechanism for this size scaling is conserved to yeast (19,20). This scaling of the karyoplasmic ratio has broken in more metastatic cancer cells, raising the question whether the scaling disruption or the nuclear size change itself contributes an advantage to the tumor? With the many functions now known for the nuclear envelope (NE), advantages could range from changes in gene regulation/signaling to mechanical nuclear aspects enabling faster migration or the easier squeezing through cell junctions to invade different tissues.

### **Possible mechanisms of nuclear size regulation through the NE**

The NE is comprised of outer (ONM) and inner (INM) nuclear membranes and associated proteins (21,22). The membranes are separated by a lumen and connected where nuclear pore complexes (NPCs), comprised of ~30 core proteins, are inserted (23,24). NPCs contain only three transmembrane proteins, but there are hundreds of other Nuclear Envelope Transmembrane proteins (NETs) in both membranes (25–28). Functions of ONM NETs are just beginning to be discovered, but many connect to cytoplasmic filaments (27,29–32) while others function in cell cycle regulation (33–35). Thus far many INM NETs characterized make connections important for genome organization, gene regulation, and signalling (36–43). INM NETs also connect to a polymer of the type V intermediate filament nuclear lamins that confers structural stability to the nucleus (22,29,44). The NE disassembles in mitosis of higher eukaryotes and the reassembled daughter nuclei are much smaller. This is because at the end of S-phase the genome has doubled to 4N, the chromatin is decondensed and the nucleus is filled with proteins and

RNA whereas the reforming NE surrounds a 2N genome that is highly condensed. In general the nucleus volume increases around 2 fold through the cell cycle (45).

As the NE is the outer shell that delimits the nucleus, many NE proteins could be limiting for nuclear size. These range from NPC transport functions to the lamin scaffolding to the connections to cytoplasmic filaments or proteins involved in lipid synthesis. Such proteins could be under a feedback regulatory mechanism for amounts synthesized or a timed mechanism that links nuclear size increases during the cell cycle to the length of a particular stage. Thus changes to gene expression and cell proliferation in cancer cells might underlie nuclear size changes. Notably, such changes in gene expression could themselves be influenced by nuclear size changes if this alters the relative amount of peripheral heterochromatin and gene silencing (Fig. 1A).

It is also possible that a completely independent sensor mechanism maintains the karyoplasmic ratio, for example sensing a change in tension between chromatin contacts and the NE on one side and connections with cytoplasmic filaments on the other. If this were the case then changes in cancer cells to NE-chromatin or NE-cytoplasmic filament interactions might underlie nuclear size changes. Such changes could also explain nuclear shape changes and NE blebbing that often accompanies the size changes in cancer cells (Fig.1B).

A third mechanism might involve post-translational modifications, particularly phosphorylation cascades that often go awry in cancer cells. Such modifications are important for both the stability of the lamin polymer and for NE-chromatin interactions. Indeed, mitotic disassembly of the lamin polymer is coupled with hyperphosphorylation of both lamins and NETs to break the interactions between them and their interactions with chromatin (Fig. 1C).

## **Factors found to regulate nuclear size**

## *Lamins*

Lamins are good candidates to regulate nuclear size as they form an intermediate filament polymer, the nuclear lamina, that provides the main mechanical stability to the nucleus (46–48). Moreover, lamins are also the most abundant NE proteins at ~9 million copies per mammalian cell nucleus (49). Thus their limitation might be predicted to restrict nuclear growth. Accordingly, lamins influence nuclear size in *Xenopus laevis* embryos in a manner that depends on import of lamin B3 and this lamin is reported to be required for NE growth during egg development (50). Both *Xenopus* and mammalian studies have concluded that lamins are essential for nuclear scaling during interphase and their limitation leads to failure in nuclear growth (51–53). Notably, from the standpoint of a limiting function, several NPC proteins have also been linked to cancer and nuclear size regulation (54). Lamins could also contribute to nuclear shape changes in cancer cells as their loss or mutation in several heritable diseases yields defects in nuclear morphology (55,56).

Despite these results, it is unlikely that, apart from being limiting for growth, lamins could control nuclear size on their own as both the total amount of lamin protein and the relative amounts of different lamin subtypes in the nuclear lamina change during development (57–59). A-type lamins, encoded by the *LMNA* gene, are present in the earliest embryonic stages from maternal protein, but new protein is not expressed at these stages so that it disappears for most embryonic stages and reappears later in tissue differentiation (60,61).

The change in lamina constitution in development is interesting in light of changes observed in lamina constitution in some cancer types. The general tendency observed is that B-type lamins continue to be expressed in tumors while A-type lamins are down-regulated (62–64). Because A-type lamins appear later in development, this led to the idea that their loss reflects retro-differentiation or de-differentiation and so might drive or at least reflect the return to a more proliferative and undifferentiated state (65). However, research

in this direction was dropped when it was observed that for some cancer types such as colorectal cancer the more metastatic tumors had increased A-type lamin levels (66). Though at the time this appeared to kill the retro-/de-differentiation theory, subsequent work found that in colonic crypt epithelia the earliest progenitor cell lineages at the base of the crypts in fact express lamin A and this disappears as cells differentiate and migrate up the sides of the crypt. Then in the more differentiated cells at the top of the crypts lamin A becomes expressed again (66). Thus, the less differentiated more proliferative cell likely gives rise to the more metastatic tumor. This study additionally revealed a potential mechanism for lamin A in metastasis: that lamin A functions inside the nucleus can influence the expression of genes encoding proteins that contribute to actin bundling and dynamics such as they showed for T-plastin (66). The effects on actin dynamics could explain how a lamin A-expressing tumor could lead to metastasis and tumor spread as cell mobility would be increased and, indeed, other studies with lamin A knockout cells found that in the absence of lamin A cells migrated into a scratch wound more slowly (47,67). Interestingly, while this beautifully explains how lamin A-expressing tumors can be more metastatic, it leaves us even more in the dark to understand the contribution of loss of lamin A in most cancer types to tumorigenesis.

### *Perinuclear structures*

Connections between the nucleus and the cytoskeleton contribute to both the overall mechanical stability of the cell and its migratory capacity (46–48). Such connections could in theory — particularly in context of the principles of tensegrity (68,69) — enable all major cytoplasmic filament systems to contribute to nuclear size regulation and impact on cell migration as actin microfilaments, microtubules and intermediate filaments all connect to the NE (27,30,70). One recent report identified formins, an actin nucleating family, as players in nuclear protection during confined migration: when formins



were knocked down nuclei tended to rupture more when migrating through confined channels compared to wild-type cells (71). This kind of function, however, cannot account for tissue specific phenotypes found in different cancer types. In contrast, the proteins that connect the nucleoskeleton to the cytoskeleton have been directly linked to nuclear size regulation and some NETs that contribute to such connecting complexes are tissue-specific. The core proteins involved in this connection are SUN-domain containing proteins of the INM and KASH-domain containing proteins of the ONM. Together these form the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex (29) that also supports mechanosignal transduction to the nucleus (67,72). SYNE/nesprins are a family of KASH-domain containing proteins and disruption of LINC using a dominant-negative nesprin mutant leads to nuclear size defects (73). Moreover two nesprins in particular, Nesprin-2 and Nesprin-3, are proposed to form a cytoplasmic cage around the nucleus to contribute to its mechanical support (73). As for lamins, nesprins also contribute to nuclear shape, so that mutations in nesprins have been linked to Emery-Dreifuss muscular dystrophy where aberrant NE organization is observed (74). Thus, in theory, alteration of the expression of nesprins in cancer could lead to changes in cytoskeleton and nuclear stiffness and elasticity, nuclear shape, and nuclear size and accordingly enable extravasation of tumor cells during metastatic spread. These functions are particularly interesting in that analysis of patient sequences in the TCGA cancer database (75) revealed relatively high mutation frequencies in this family with mutations in *SYNE1* (encoding nesprin 1) reaching 26% in Stomach Adenocarcinoma, 24% in Skin Cutaneous Melanoma and 21% in Colon Adenocarcinoma. Other nesprins were also highly mutated in specific tumor types with *SYNE2* (encoding nesprin 2) mutated in 20% of Liver Hepatocellular Carcinoma patients and more than 10% in at least four different cancer types. Interestingly, *SYNE3* (encoding nesprin 3) was only highly mutated in Pancreatic Adenocarcinoma, at 24% of patients, with the next highest mutation frequency being at just 3% in Lung Adenocarcinoma, indicating

considerable tissue-specificity even just amongst this protein family in its potential relationship to cancer. Notably, several different cancers had much lower levels of mutations in SYNE/nesprin proteins, often as much as 100-fold lower (Fig. 2).

Tissue-specific NETs also contribute to these complexes. NET5/Samp1 is not detected in most tissues, but has distinct splice variants in brain and muscle (76). NET5 was found in TAN-lines, nucleo-cytoskeletal connections involved in nuclear migration (77). NET5 was also found to be important for associations between the nucleus and the centrosome that organizes microtubules (31).

### *Nuclear Envelope Transmembrane proteins (NETs)*

Both the nesprins and SUN proteins are NETs and, just like these two protein families largely segregate between the ONM and INM, so do other NETs. There are now many hundreds of NETs that have been identified in the NE by proteomics and most of which are tissue-restricted in expression (26,28,36,38), suggesting they might contribute to the tumor tissue-type specificity of nuclear size effects in cancer. Over 50 NETs have been characterized by super resolution microscopy for their accumulation in the ONM or INM, with a strong majority favoring the INM (78). Some ONM NETs, like nesprins, contribute to mediation of interactions with cytoplasmic filaments. Others are involved in cell cycle regulation, for example NET4/Tmem53 activates a stress-induced p38 kinase pathway that results in cell cycle withdrawal when its levels are perturbed (33). Another ONM NET affecting the cell cycle, NET31/Tmem209, is able to alter cancer cell growth when overexpressed in lung cancer cells and interestingly is up regulated in lung cancer cells and normal testis that contains highly proliferative cells (79). As loss of proliferation controls is a hallmark of cancer cells, these NETs could also be highly relevant to metastatic tumors, though they have thus far not been linked to nuclear size regulation. Very little is known about most other ONM NETs.

Many INM NETs interact with lamins and chromatin and play important roles in gene/chromosome positioning, chromatin organization and epigenetics, and genome regulation (34,36,80–82). Though most of general radial chromosome positioning is based on gene density (83), each tissue also has a subset of genes and chromosomes that reposition during differentiation in a tissue-specific manner (40,41,84,85). The general positioning trends appear to be driven by heterochromatin interactions with lamins and the NET lamin B receptor (LBR) that binds directly to heterochromatin protein 1 (HP1) (80). In general, the periphery tends to be a more silencing environment based on expression profiles and epigenetic marks of genome-wide identified genes that reside there (86). The more tissue-specific gene and chromosome repositionings are directed by tissue-specific NETs. For example, liver NETs NET45/Dak and NET47/TM7SF2 are important for positioning to the NE of chromosome 5 in liver cells (76) and muscle NETs NET39/PPAPDC3, Tmem38A, and WFS1 are important for positioning to the NE of several genes that need to be tightly shut down in a temporal fashion later in muscle differentiation though they are needed in earlier stages (36). Interestingly, there are also many genes that reposition to the more repressive environment of the NE in tissue differentiation that support cell proliferation and must be shut down because most differentiated cells no longer cycle (36–38). Thus, alteration of the normal expression patterns for such NETs in cancer could support metastasis by increasing expression of proliferative genes.

Though little is known about most NETs to determine their likelihood of contributing to cancer progression or metastasis, analysis of NETs identified in NE proteomic studies for changes in different tumour types using the TCGA cancer database (75) revealed that many tend to be lost or inappropriately expressed in a variety of tissue-specific tumor types. One example is the NET LPCAT3, a protein expressed relatively widely, but not in ovary. Its expression profile changes drastically in certain cancer types, with it being

strongly upregulated in ovarian cancer but down-regulated in lung cancer (3,87). The tissue-specific differences characteristic of each tumor type may be explained by such changes in these tissue specific NETs during cancer progression.

### **What advantages can nuclear size changes confer to cancer cells?**

The central conundrum that faces us is how can both nuclear size increases and decreases promote increased metastasis in different tumor types? A smaller nuclear size could obviously convey the advantage of being able to squeeze through junctions between cells during invasion of other tissues, but one might expect that a larger nuclear size would hinder this. This apparent contradiction might be resolved when considering that the NE connects to both cytoplasmic filaments on one side and chromatin on the other side. The largest molecules in the cell are the chromosomes that reach gigadalton masses and dwarf even actin stress fibers in total size. Several studies have shown that chromatin connections to the NE are similarly important as the intermediate filament lamin polymer for nuclear shape and mechanical stability (88,89). If the increase in nuclear size is associated with a reduction of dense chromatin (particularly at the periphery, then the strength of heterochromatin interactions with the NE might diminish to enable the even larger nucleus to distort and squeeze between cell-cell junctions for invasion (Fig. 3A). It is interesting that there is precedent for a third type of change where in neutrophil differentiation an increase in NE-chromatin connections and compacted chromatin drives formation of a 5-lobed nucleus that resembles sausage links (90). As each lobe/ link is very thin, this could also facilitate squeezing through tight junctions.

Notably, the neutrophil nuclear lobulation is also driven by changes in nucleocytoplasmic connections associated with increased lamin B2 levels and reduced lamin A levels (91). Several studies have shown that lamin A contributes more to nuclear strength and stability than other lamin subtypes and in vitro binding assays revealed lamin B2 to

have the weakest and least stable interactions (46,92). Such connections might provide an even simpler explanation if both nuclear size increases and decreases are associated with changes in cytoplasmic filament connections that facilitate cell migration. The separate findings that altering levels of lamins and LINC components affects cell migration in wound healing assays (47) indicates the likelihood of this possibility. Furthermore, tissue-specific NETs that contribute to lamin-LINC-cytoplasmic filament connections could confer the tumor type specificity for this nexus. Importantly, such disruption of the even larger chromatin-lamin-LINC-cytoplasmic filament nexus could additionally weaken the mechanical stability of the nucleus to explain the changes in nuclear shape that include blebbing at the NE that often accompany nuclear size changes (Fig. 3B).

A larger nuclear size accompanied by a reduced heterochromatin interaction with the nuclear periphery might also enable faster proliferation for metastasis, not just through changes in gene expression or post-translational modifications as mentioned above, but also by having less late-replicating peripheral heterochromatin and having to break fewer genome-NE contacts when replicating the genome. Changes in such contacts could also influence overall genome stability whether due to loss of lamin A or a tissue-specific NET. Notably, lamins also bind pRb and can affect proliferation by sequestering or releasing pRb (35,93). Similarly, several NETs bind transcriptional regulators and Smads are sequestered by the NET MAN1 away from target genes in the nucleoplasm such that altering MAN1 can yield bone disorders (94–96). Thus both lamins and tissue-specific NETs can influence metastasis through effects on proliferation that could parallel nuclear size changes from the same proteins.

## **Conclusions**

It is clear that characteristic nuclear size changes correlate with particular tumor types; however, it remains unproven whether these changes are secondary to driver changes in the cancers or if they directly influence the cancer progression and metastasis. There are many ways noted above that both the size change itself or associated changes in NE-chromatin or NE-cytoplasmic filament connections can provide advantages to cancer cells. These range from migratory aspects of metastasis such as increased cell migration and an enhanced ability to squeeze through cell junctions in invading other tissues to an increased proliferative capacity and altered gene expression. Despite the obvious logic of this, the NE is extremely under-investigated in cancer research and so there are no conclusive studies demonstrating a role of nuclear size regulation in promoting cancer progression or metastasis. Similarly, there is little data available regarding the three mechanisms (limiting, mechanical sensor, post-translational modification) suggested to underlie the loss in nuclear size control. That to date the strongest supporting studies have all to do with a limiting function most probably only reflects the complexity of NE building blocks as the proteins identified with such functions are all widely expressed and most nuclear size changes in cancer are specific to a particular tumor type. We postulate that many of the tissue-specific NETs will be found to play critical roles in such tumor type specific characteristic changes in the karyoplasmic ratio. Due to their tissue-specificity such NETs would be fantastic targets for cancer therapies as their specificity should reduce toxic side effects in treatment while, being more directly linked to the metastasis, they might significantly improve survival of more metastatic tumors.

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## References

1. Beale LS. Examination of sputum from a case of cancer of the pharynx and the adjacent parts. *Arch Med Lond*. 1860;2(44).
2. Zink D, Fischer AH, Nickerson J a. Nuclear structure in cancer cells. *Nat Rev Cancer* [Internet]. 2004 Sep [cited 2014 Aug 19];4(9):677–87. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15343274>
3. de Las Heras JI, Schirmer EC. The Nuclear Envelope and Cancer: A Diagnostic Perspective and Historical Overview. In: *Cancer Biology and the Nuclear Envelope* [Internet]. 2014. p. 571–91. Available from: <http://link.springer.com/10.1007/978-1-4899-8032-8>
4. de Andrea CE, Petrilli AS, Jesus-Garcia R, Bleggi-Torres LF, Alves MTS. Large and round tumor nuclei in osteosarcoma: Good clinical outcome. *Int J Clin Exp Pathol*. 2011;4(2):169–74.
5. Ladekarl M, Boek-Hansen T, Henrik-Nielsen R, Mouritzen C, Henriques U, Sorensen FB. Objective malignancy grading of squamous cell carcinoma of the lung: Stereologic estimates of mean nuclear size are of prognostic value, independent of clinical stage of disease. *Cancer*. 1995;76(5):797–802.
6. Abdalla FBE, Markus R, Buhmeida A, Boder J, Syrjanen K, Collan Y. Estrogen receptor, progesterone receptor, and nuclear size features in female breast cancer in libya: correlation with clinical features and survival. *Anticancer Res* [Internet]. 2012;32:3485–93. Available from: <http://www.hubmed.org/display.cgi?uids=22843935>
7. Nandakumar V, Kelbauskas L, Hernandez KF, Lintecum KM, Senechal P, Bussey KJ, et al. Isotropic 3D nuclear morphometry of normal, fibrocystic and malignant breast epithelial cells reveals new structural alterations. *PLoS One*. 2012;7(1).
8. Tan PH, Goh BB, Chiang G, Bay BH. Correlation of nuclear morphometry with pathologic parameters in ductal carcinoma in situ of the breast. *Mod Pathol*. 2001;14(10):937–41.
9. Rashid F, Ul Haque A. Frequencies of different nuclear morphological features in prostate adenocarcinoma. *Ann Diagn Pathol* [Internet]. 2011;15(6):414–21. Available from: <http://dx.doi.org/10.1016/j.anndiagpath.2011.06.002>
10. Giorgadze T, Kanhere R, Pang C, Ganote C, Miller LE, Tabaczka P, et al. Small cell carcinoma of the cervix in liquid-based Pap test: Utilization of split-sample immunocytochemical and molecular analysis. *Diagn Cytopathol*. 2012;40(3):214–9.
11. Malhotra S, Kazlouskaya V, Andres C, Gui J, Elston D. Diagnostic cellular abnormalities in neoplastic and non-neoplastic lesions of the epidermis: A morphological and statistical study. *J Cutan Pathol*. 2013;40(4):371–8.
12. Yan J, Zhuo S, Chen G, Wu X, Zhou D, Xie S, et al. Preclinical study of using multiphoton microscopy to diagnose liver cancer and differentiate benign and malignant liver lesions. Vol. 17, *Journal of Biomedical Optics*. 2012. p. 26004.
13. Zeimet AG, Fiegl H, Goebel G, Kopp F, Allasia C, Reimer D, et al. DNA ploidy, nuclear size, proliferation index and DNA-hypomethylation in ovarian cancer. *Gynecol Oncol*. 2011;121(1):24–31.
14. Taira T, Kawahara A, Yamaguchi T, Abe H, Ishida Y, Okabe Y, et al. Morphometric image analysis of pancreatic disease by ThinPrep liquid-based cytology. *Diagn Cytopathol*. 2012;40(11):970–5.
15. Helander K, Hofer PA, Holmberg G. Karyometric investigations on urinary bladder carcinoma, correlated to histopathological grading. *Virchows Arch A Pathol Anat Histopathol*. 1984;403(2):117–25.
16. Chan YM, Marshall WF. Scaling properties of cell and organelle size. 2010;6(2):88–96.
17. Cavalier-Smith T. Economy, speed and size matter: Evolutionary forces driving nuclear genome miniaturization and expansion. *Ann Bot*. 2005;95(1):147–75.
18. Edens LJ, White KH, Jevtic P, Li X, Levy DL. Nuclear size regulation: From single cells to development and disease. *Trends Cell Biol* [Internet]. 2013;23(4):151–9. Available from: <http://dx.doi.org/10.1016/j.tcb.2012.11.004>

19. Neumann FR, Nurse P. Nuclear size control in fission yeast. *J Cell Biol.* 2007;179(4):593–600.
20. Jorgensen P, Edgington NP, Schneider BL, Rupes I, Tyers M, Futcher B. The Size of the Nucleus Increases as Yeast Cells Grow Paul. *Mol Biol Cell.* 2007;18(8):3523–3532.
21. CALLAN HG, RANDALL JT, TOMLIN SG. An electron microscope study of the nuclear membrane. *Nature.* 1949 Feb;163(4138):280.
22. Prunuske AJ, Ullman KS. The nuclear envelope : form and reformation. 2006;108–16.
23. Suntharalingam M, Wenthe SR. Peering through the pore: Nuclear pore complex structure, assembly, and function. *Dev Cell.* 2003;4(6):775–89.
24. Grossman E, Medalia O, Zwerger M. Functional architecture of the nuclear pore complex. *Annu Rev Biophys [Internet].* 2012;41:557–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22577827>
25. Schirmer EC, Florens L, Guan T, Yates JR, Gerace L. Nuclear membrane proteins with potential disease links found by subtractive proteomics. *Science [Internet].* 2003;301(5638):1380–2. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12958361>
26. Korfali N, Wilkie GS, Swanson SK, Srsen V, Batrakou DG, Fairley E a L, et al. The leukocyte nuclear envelope proteome varies with cell activation and contains novel transmembrane proteins that affect genome architecture. *Mol Cell Proteomics.* 2010;9:2571–85.
27. Wilkie GS, Korfali N, Swanson SK, Malik P, Srsen V, Batrakou DG, et al. Several novel nuclear envelope transmembrane proteins identified in skeletal muscle have cytoskeletal associations. *Mol Cell Proteomics [Internet].* 2011;10(1):M110.003129. Available from: <http://www.mcponline.org/cgi/doi/10.1074/mcp.M110.003129>
28. Korfali N, Wilkie GS, Swanson SK, Srsen V, de Las Heras J, Batrakou DG, et al. The nuclear envelope proteome differs notably between tissues. *Nucleus [Internet].* 2012;3(6):552–64. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3515538&tool=pmcentrez&rendertype=abstract>
29. Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, et al. Coupling of the nucleus and cytoplasm: Role of the LINC complex. *J Cell Biol.* 2006;172(1):41–53.
30. Wilhelmsen K, Litjens SHM, Kuikman I, Tshimbalanga N, Janssen H, Van Bout I Den, et al. Nesprin-3, a novel outer nuclear membrane protein, associates with the cytoskeletal linker protein plectin. *J Cell Biol.* 2005;171(5):799–810.
31. Buch C, Lindberg R, Figueroa R, Gudise S, Onischenko E, Hallberg E. An integral protein of the inner nuclear membrane localizes to the mitotic spindle in mammalian cells. *J Cell Sci.* 2009;122:2100–7.
32. Pfisterer K, Jayo A, Parsons M. Control of nuclear organization by F-actin binding proteins. *Nucleus [Internet].* 2017;8(2):126–33. Available from: <http://dx.doi.org/10.1080/19491034.2016.1267093>
33. Korfali N, Srsen V, Waterfall M, Batrakou DG, Pekovic V, Hutchison CJ, et al. A flow cytometry-based screen of nuclear envelope transmembrane proteins identifies NET4/Tmem53 as involved in stress-dependent cell cycle withdrawal. *PLoS One [Internet].* 2011 Jan [cited 2014 Aug 11];6(4):e18762. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3077400&tool=pmcentrez&rendertype=abstract>
34. Srsen V, Korfali N, Schirmer EC. Nuclear envelope influences on cell-cycle progression. *Biochem Soc Trans [Internet].* 2011 Dec [cited 2014 Aug 12];39(6):1742–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22103518>
35. Johnson BR, Nitta RT, Frock RL, Mounkes L, Barbie DA, Stewart CL, et al. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci U S A [Internet].* 2004;101(26):9677–82. Available from: <http://www.pnas.org/content/101/26/9677.full>
36. Robson MI, de las Heras JI, Czapiewski R, Lê Thành P, Booth DG, Kelly DA, et al. Tissue-Specific Gene Repositioning by Muscle Nuclear Membrane Proteins Enhances Repression of Critical Developmental Genes during Myogenesis. *Mol Cell.* 2016;62(6):834–47.
37. Robson MI, de las Heras JI, Czapiewski R, Sivakumar A, Kerr ARW, Schirmer E. Constrained release of lamina-associated enhancers and genes from the nuclear envelope during T-cell activation facilitates their association in chromosome compartments. *Genome Res [Internet].* 2017;44(0):gr.212308.116. Available from: <http://genome.cshlp.org/lookup/doi/10.1101/gr.212308.116>
38. De Las Heras JI, Zuleger N, Batrakou DG, Czapiewski R, Kerr ARW, Schirmer EC. Tissue-specific NETs alter genome organization and regulation even in a heterologous system. *Nucleus [Internet].* 2017;8(1):81–97. Available from: <http://dx.doi.org/10.1080/19491034.2016.1261230>
39. Czapiewski R, Robson MI, Schirmer EC. Anchoring a Leviathan: How the nuclear membrane tethers the genome. *Front Genet.* 2016;7(MAY):1–13.
40. Parada LA, McQueen PG, Misteli T. Tissue-specific spatial organization of genomes. *Genome Biol [Internet].* 2004;5(7):R44. Available from: <http://genomebiology.biomedcentral.com.acces.bibl.ulaval.ca/articles/10.1186/gb-2004-5-7-r44>



41. Kim SH, McQueen PG, Lichtman MK, Shevach EM, Parada LA, Misteli T. Spatial genome organization during T-cell differentiation. *Cytogenet Genome Res.* 2004;105(2–4):292–301.
42. Holaska JM, Rais-Bahrami S, Wilson KL. Lmo7 is an emerin-binding protein that regulates the transcription of emerin and many other muscle-relevant genes. *Hum Mol Genet* [Internet]. 2006 Dec 1 [cited 2014 Aug 11];15(23):3459–72. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17067998>
43. Markiewicz E, Tilgner K, Barker N, Wetering M Van De, Clevers H, Dorobek M, et al. The inner nuclear membrane protein Emerin regulates  $\beta$ -catenin activity by restricting its accumulation in the nucleus. 2006;(June):3275–85.
44. Meinke P, Schirmer EC. LINC'ing form and function at the nuclear envelope. *FEBS Lett.* 2015;589(19):2514–21.
45. Fidorra J, Mielke T, Booz J, Feinendegen LE. Cellular and Nuclear Volume of Human Cells During the Cell Cycle. 1981;214(215):205–14.
46. Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, et al. Lamin A / C deficiency causes Tema Grupo defective nuclear mechanics and mechanotransduction. *J Clin Invest.* 2004;113(3):370–8.
47. Lee JSH, Hale CM, Panorchan P, Khatau SB, George JP, Tseng Y, et al. Nuclear lamin A/C deficiency induces defects in cell mechanics, polarization, and migration. *Biophys J* [Internet]. 2007;93(7):2542–52. Available from: <http://www.sciencedirect.com/science/article/pii/S0006349507715084>
48. Broers JL V, Peeters EAG, Kuijpers HJH, Ender J, Bouten CVC, Oomens CWJ, et al. Decreased mechanical stiffness in LMNA-/- cells is caused by defective nucleo-cytoskeletal integrity: Implications for the development of laminopathies. *Hum Mol Genet.* 2004;13(21):2567–80.
49. Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J, Chen W, et al. Corrigendum: Global quantification of mammalian gene expression control. 2011;473:337–42.
50. Jevtic P, Levy DL. Nuclear size scaling during xenopus early development contributes to midblastula transition timing. *Curr Biol.* 2015;25(1):45–52.
51. Newport JW, Wilson KL, Dunphy WG. A lamin-independent pathway for nuclear envelope assembly. *J Cell Biol.* 1990;111(6 PART 1):2247–59.
52. Jenkins H, Höfken T, Lyon C, Lane BE, Stick R, Hutchison CJ. Nuclei that lack a lamina accumulate karyophilic proteins and assemble a nuclear matrix. *J Cell Sci.* 1993;106 ( Pt 1):275–85.
53. Jevtić P, Edens LJ, Li X, Nguyen T, Chen P, Levy DL. Concentration-dependent effects of nuclear lamins on nuclear size in xenopus and mammalian cells. *J Biol Chem.* 2015;290(46):27557–71.
54. Simon DN, Rout MP. Cancer and the Nuclear Pore Complex. In: Schirmer EC, de las Heras JI, editors. *Cancer Biology and the Nuclear Envelope: Recent Advances May Elucidate Past Paradoxes* [Internet]. New York, NY: Springer New York; 2014. p. 285–307. Available from: [http://dx.doi.org/10.1007/978-1-4899-8032-8\\_13](http://dx.doi.org/10.1007/978-1-4899-8032-8_13)
55. Schirmer EC, Guan T, Gerace L. Involvement of the lamin rod domain in heterotypic lamin interactions important for nuclear organization. *J Cell Biol.* 2001;152(3):479–89.
56. Liu J, Rolef Ben-Shahar T, Riemer D, Treinin M, Spann P, Weber K, et al. Essential roles for *Caenorhabditis elegans* lamin gene in nuclear organization, cell cycle progression, and spatial organization of nuclear pore complexes. *Mol Biol Cell* [Internet]. 2000;11(11):3937–47. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11071918>
57. Stick R, Hausen P. Changes in the nuclear lamina composition during early development of *Xenopus laevis*. *Cell.* 1985;41(1):191–200.
58. Lehner CF, Stick R, Eppenberger HM, Migg E a. Differential expression of nuclear lamin proteins during chicken development. *J Cell Biol.* 1987;105(1):577–87.
59. Röber R a, Weber K, Osborn M. Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: a developmental study. *Development.* 1989;105(2):365–78.
60. Benavente R, Krohne G, Franke WW. Cell type-specific expression of nuclear lamina proteins during development of *Xenopus laevis*. *Cell.* 1985;41(1):177–90.
61. Broers JL V, Machiels BM, Kuijpers HJH, Smedts F, Van Den Kieboom R, Raymond Y, et al. A- and B-type lamins are differentially expressed in normal human tissues. *Histochem Cell Biol.* 1997;107(6):505–17.
62. Venables RS, McLean S, Luny D, Moteleb E, Morley S, Quinlan R a, et al. Expression of individual lamins in basal cell carcinomas of the skin. *Br J Cancer* [Internet]. 2001;84(4):512–9. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2363768&tool=pmcentrez&rendertype=abstract>
63. Kaufmann SH, Mabry M, Jasti R, Lines CC, Shaper JH. Differential Expression of Nuclear Envelope Lamins A and C in Human Lung Cancer Cell Lines Differential Expression of Nuclear Envelope Lamins A and C in Human Lung. 1991;581–6.
64. Agrelo R, Setien F, Espada J, Artiga MJ, Rodriguez M, Pérez-Rosado A, et al. Inactivation of the

Lamin A/C gene by CpG island promoter hypermethylation in hematologic malignancies, and its association with poor survival in nodal diffuse large B-cell lymphoma. *J Clin Oncol*. 2005;23(17):3940–7.

65. Kuzmina SN, Buldyaeva T V, Akopov SB, Zbarsky IB. Protein patterns of the nuclear matrix in differently proliferating and malignant cells. *Mol Cell Biochem*. 1984;58(1–2):183–6.
66. Willis ND, Cox TR, Rahman-Casañs SF, Smits K, Przyborski SA, van den Brandt P, et al. Lamin A/C is a risk biomarker in colorectal cancer. *PLoS One*. 2008;3(8).
67. Ho CY, Jaalouk DE, Vartiainen MK, Lammerding J. Lamin A/C and emerin regulate MKL1/SRF activity by modulating actin dynamics. *Nature*. 2013;497(7450):1–13.
68. Maniotis AJ, Chen CS, Ingber DE. Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure. *Proc Natl Acad Sci U S A* [Internet]. 1997;94(3):849–54. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9023345>
69. Wang N, Tytell JD, Ingber DE. Mechanotransduction at a distance: mechanically coupling the extracellular matrix with the nucleus. *Nat Rev Mol Cell Biol* [Internet]. 2009;10(1):75–82. Available from: <http://www.nature.com/doi/10.1038/nrm2594>
70. Roux KJ, Crisp ML, Liu Q, Kim D, Kozlov S, Stewart CL, et al. Nesprin 4 is an outer nuclear membrane protein that can induce kinesin-mediated cell polarization. 2009;2–7.
71. Skau CT, Fischer RS, Gurel P, Thiam HR, Tubbs A, Baird MA, et al. FMN2 Makes Perinuclear Actin to Protect Nuclei during Confined Migration and Promote Metastasis. *Cell*. 2016;167(6):1571–1585.e18.
72. Swift J, Ivanovska IL, Buxboim A, Harada T, Dingal PCDP, Pinter J, et al. Nuclear Lamin-A Scales with Tissue Stiffness and Enhances Matrix-Directed Differentiation. *Science* (80- ) [Internet]. 2013;341(6149):1240104–1240104. Available from: <http://www.sciencemag.org/cgi/doi/10.1126/science.1240104>
73. Lu W, Schneider M, Neumann S, Jaeger VM, Taranum S, Munck M, et al. Nesprin interchain associations control nuclear size. *Cell Mol Life Sci*. 2012;69(20):3493–509.
74. Zhang Q, Bethmann C, Worth NF, Davies JD, Wasner C, Feuer A, et al. Nesprin-1 and -2 are involved in the pathogenesis of Emery - Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. *Hum Mol Genet*. 2007;16(23):2816–33.
75. Index @ Cancergenome.Nih.Gov [Internet]. Available from: <http://cancergenome.nih.gov/>
76. Zuleger N, Boyle S, Kelly DA, de las Heras JI, Lazou V, Korfali N, et al. Specific nuclear envelope transmembrane proteins can promote the location of chromosomes to and from the nuclear periphery. *Genome Biol* [Internet]. 2013;14(2):R14. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4053941&tool=pmcentrez&rendertype=abstract>
77. Borrego-Pinto J, Jegou T, Osorio DS, Aurade F, Gorjanacz M, Koch B, et al. Samp1 is a component of TAN lines and is required for nuclear movement. *J Cell Sci* [Internet]. 2012;125(5):1099–105. Available from: <http://jcs.biologists.org/cgi/doi/10.1242/jcs.087049>
78. Malik P, Korfali N, Srsen V, Lazou V, Batrakou DG, Zuleger N, et al. Cell-specific and lamin-dependent targeting of novel transmembrane proteins in the nuclear envelope. *Cell Mol Life Sci*. 2010;67:1353–69.
79. Fujitomo T, Daigo Y, Matsuda K, Ueda K, Nakamura Y. Critical function for nuclear envelope protein TMEM209 in human pulmonary carcinogenesis. *Cancer Res*. 2012;72(16):4110–8.
80. Solovei I, Wang AS, Thanisch K, Schmidt CS, Krebs S, Zwerger M, et al. LBR and Lamin A / C Sequentially Tether Peripheral Heterochromatin and Inversely Regulate Differentiation. *Cell* [Internet]. 2011;152(3):584–98. Available from: <http://dx.doi.org/10.1016/j.cell.2013.01.009>
81. Schirmer EC, Foisner R. Proteins that associate with lamins: Many faces, many functions. *Exp Cell Res*. 2007;313(10):2167–79.
82. Mattout-Drubezki a., Gruenbaum Y. Dynamic interactions of nuclear lamina proteins with chromatin and transcriptional machinery. *Cell Mol Life Sci*. 2003;60(10):2053–63.
83. Croft JA, Bridger JM, Boyle S, Perry P, Teague P, Bickmore WA. Differences in the localization and morphology of chromosomes in the human nucleus. *J Cell Biol*. 1999;145(6):1119–31.
84. Szczerbal I, Foster HA, Bridger JM. The spatial repositioning of adipogenesis genes is correlated with their expression status in a porcine mesenchymal stem cell adipogenesis model system. *Chromosoma*. 2009;118(5):647–63.
85. Morey C, Da Silva NR, Kmita M, Duboule D, Bickmore W a. Ectopic nuclear reorganisation driven by a Hoxb1 transgene transposed into Hoxd. *J Cell Sci* [Internet]. 2008;121(Pt 5):571–7. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2258412&tool=pmcentrez&rendertype=abstract>
86. Akhtar W, Jong J De, Pindyurin A V, Pagie L, Meuleman W, Ridder J De, et al. Resource Chromatin Position Effects Assayed by Thousands of Reporters Integrated in Parallel. *Cell* [Internet]. 2013;154(4):914–27. Available from: <http://dx.doi.org/10.1016/j.cell.2013.07.018>

87. de Las Heras JI, Batrakou DG, Schirmer EC. Cancer biology and the nuclear envelope: a convoluted relationship. *Semin Cancer Biol* [Internet]. 2013 Apr [cited 2014 Aug 12];23(2):125–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22311402>
88. Thorpe SD, Lee DA, Lee DA, Thorpe SD, Lee DA. Dynamic regulation of nuclear architecture and mechanics — a rheostatic role for the nucleus in tailoring cellular mechanosensitivity the nucleus in tailoring cellular mechanosensitivity. *Nucleus* [Internet]. 2017;8(3):287–300. Available from: <https://doi.org/10.1080/19491034.2017.1285988>
89. Thorpe SD, Charpentier M, Thorpe D, Charpentier M, Thorpe SD. Highlight on the dynamic organization of the nucleus Highlight on the dynamic organization of the nucleus. 2017;1034(July). Available from: <http://dx.doi.org/10.1080/19491034.2016.1243634>
90. Olins AL, Buendia B, Herrmann H, Lichter P, Olins DE. Retinoic acid induction of nuclear envelope-limited chromatin sheets in HL-60. *Exp Cell Res*. 1998;245(1):91–104.
91. Olins AL, Hoang T V., Zwerger M, Herrmann H, Zentgraf H, Noegel AA, et al. The LINC-less granulocyte nucleus. *Eur J Cell Biol*. 2009;88(4):203–14.
92. Schirmer EC, Gerace L. The stability of the nuclear lamina polymer changes with the composition of lamin subtypes according to their individual binding strengths. *J Biol Chem*. 2004;279(41):42811–7.
93. Berlo JH Van, Voncken JW, Kubben N, Broers JL V, Duisters R. A-type lamins are essential for TGF- $\beta$  1 induced PP2A to dephosphorylate transcription factors. 2005;14(19):2839–49.
94. Pan D, Estévez-Salmerón LD, Stroschein SL, Zhu X, He J, Zhou S, et al. The integral inner nuclear membrane protein MAN1 physically interacts with the R-smad proteins to repress signaling by the transforming growth factor- $\beta$  superfamily of cytokines. *J Biol Chem*. 2005;280(16):15992–6001.
95. Ishimura A, Ng JK, Taira M, Young SG, Osada S-I. Man1, an inner nuclear membrane protein, regulates vascular remodeling by modulating transforming growth factor beta signaling. *Development* [Internet]. 2006;133(19):3919–28. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16943282>
96. Osada S, Ohmori S, Taira M. XMAN1 , an inner nuclear membrane protein , antagonizes BMP signaling by interacting with Smad1 in *Xenopus* embryos. 2003;1783–94.

## Figure legends

FIG 1 Potential mechanisms of nuclear size regulation. A. Control of levels for scaffolding proteins regulating nuclear size. Reduction of scaffolding proteins such as lamins through gene misregulation could be limiting for nuclear size increases (left). At the same time, upregulation of such proteins could promote nuclear growth (right). B. Sensor mechanism regulating the karyoplasmic ratio. The sensor might sense alterations of tension between the NE and chromatin and/or the cytoskeleton and alter nuclear size accordingly. C. Post-translational modifications occurring on NE proteins. Similar to how hyperphosphorylation of lamins triggers their disassembly in mitosis, modifying proteins at the NE to break connections could alter nuclear size.

FIG 2 Alteration of *SYNE* genes encoding nesprins, members of the LINC complex, in different cancer types. Accumulation of mutations in *SYNE* genes differs for each gene and for each tumor type. For example, *SYNE3* is only highly mutated in Pancreatic Adenocarcinoma while *SYNE1* and *SYNE2* are highly mutated in a larger, but partly distinct, set of cancers. Blca: Bladder Urothelial Carcinoma; Brca: Breast Invasive Carcinoma; Coadread: Colon Adenocarcinoma; Gmb: Glioblastoma Multiforme; Hnsc: Head and Neck Squamous Cell Carcinoma; Kich: Kidney Chromophobe; Kirc: Kidney Renal Clear Cell Carcinoma; Luad: Lung Adenocarcinoma; Lusc: Lung Squamous Cell Carcinoma; Ov: Ovarian Serous Cystadenocarcinoma; Paad: Pancreatic Adenocarcinoma; Stad: Stomach Adenocarcinoma; Thca: Thyroid Carcinoma.

FIG 3 Advantages to cancer cells of nuclear size changes. A. Smaller nuclei with more compact chromatin could more readily squeeze between tight cell-cell junctions to invade a tissue (top). If a bigger nucleus has fewer interactions with chromatin and/or more euchromatin, this might enable greater malleability for the nucleus to change shape to squeeze between cell-cell junctions (bottom). B. Alterations of lamin and LINC complex connections. Loss of lamins can weaken the mechanical properties of the nucleus, allowing easier deformability in squeezing through cell-cell junctions and so increasing metastasis (upper panels). The connections between the nucleoskeleton and cytoplasmic filaments also affect cell migration in wound healing assays and so their disruption could result in an increased speed for migration of the cancer cell (bottom panels). Note that in this case both changes to larger and smaller nuclear size could alter nuclear migration properties.

Fig 1

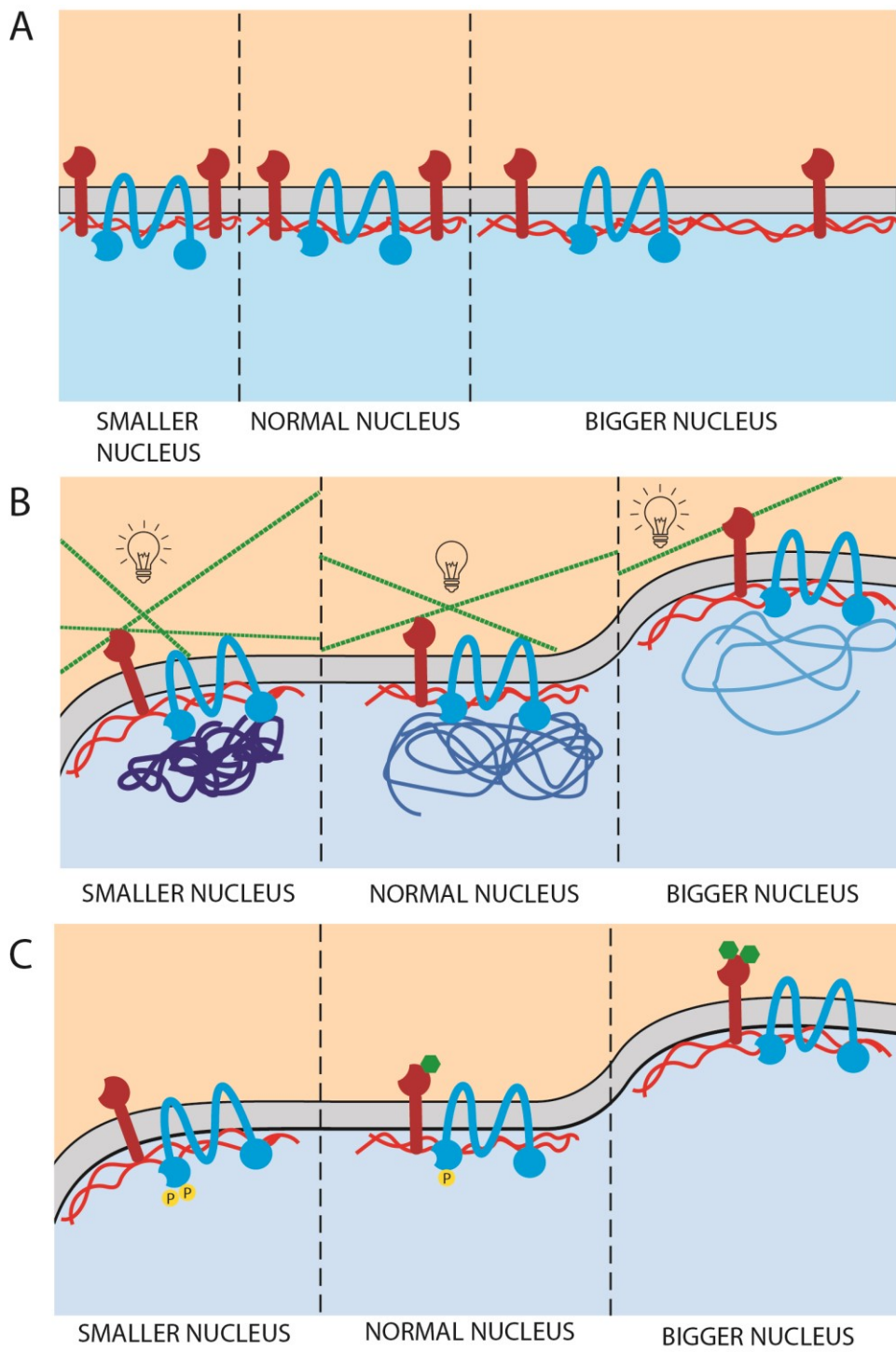


Fig 2

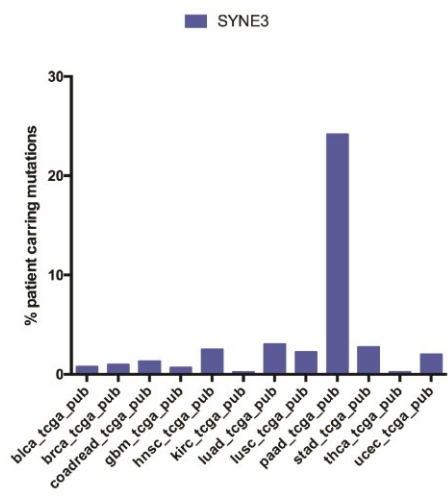
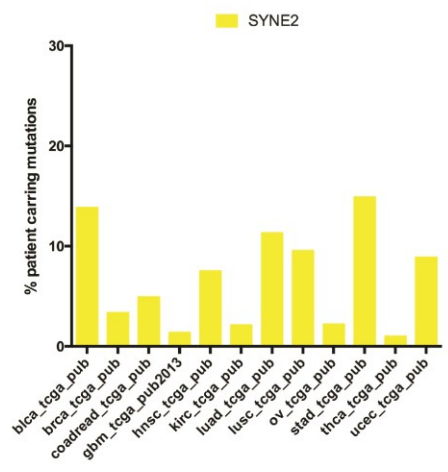
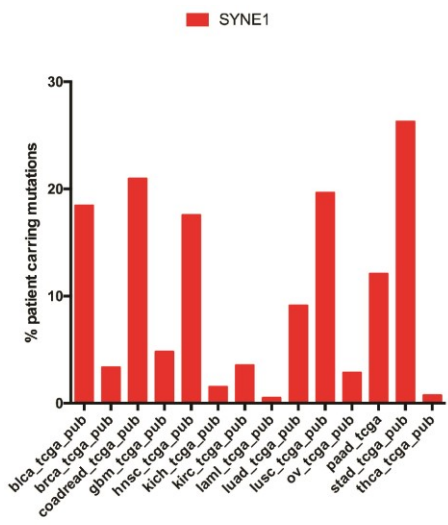
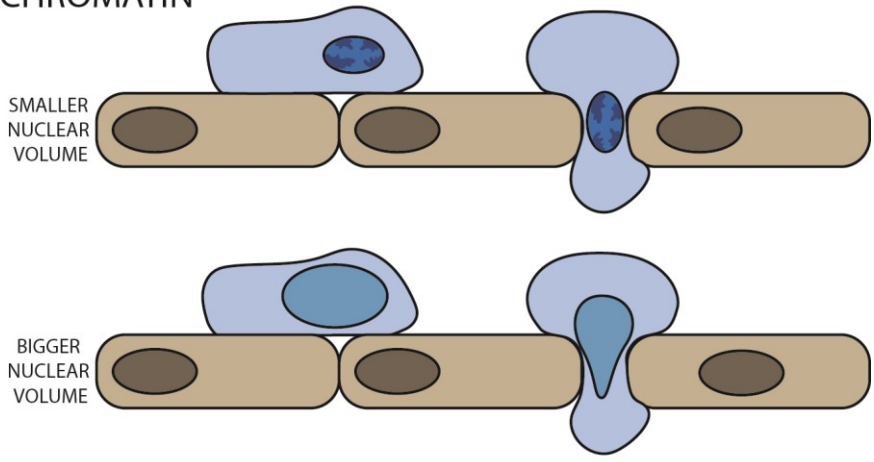
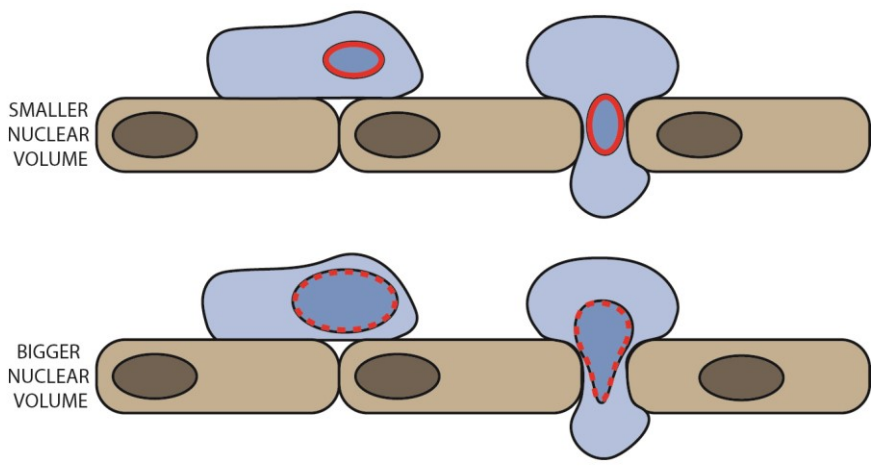


Fig 3

A CHROMATIN



B LAMIN



MIGRATION

