Causes and consequences of nuclear envelope alterations in tumour progression

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Abstract

Morphological changes in the size and shape of the nucleus are highly prevalent in cancer, but the underlying molecular mechanisms and the functional relevance remain poorly understood. Nuclear envelope proteins, which can modulate nuclear shape and organization, have emerged as key components in a variety of signalling pathways long implicated in tumourigenesis and metastasis. The expression of nuclear envelope proteins is altered in many cancers, and changes in levels of nuclear envelope proteins lamins A and C are associated with poor prognosis in multiple human cancers. In this review we highlight the role of the nuclear envelope in different processes important for tumour initiation and cancer progression, with a focus on lamins A and C. Lamin A/C controls many cellular processes with key roles in cancer, including cell invasion, stemness, genomic stability, signal transduction, transcriptional regulation, and resistance to mechanical stress. In addition, we discuss potential mechanisms mediating the changes in lamin levels observed in many cancers. A better understanding of cause-and-effect relationships between lamin expression and tumour progression could reveal important mechanisms for coordinated regulation of oncogenic processes, and indicate therapeutic vulnerabilities that could be exploited for improved patient outcome.

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28 **Abbreviations**

29 12-LOX, 12-lipoxygenase; 2D, two-dimensional; 3D, three-dimensional; CDK, cyclin-
30 dependent kinase; CSC, cancer stem cell; ECM, extracellular matrix; EDMD, Emery-
31 Dreifuss muscular dystrophy; EMT, epithelial-mesenchymal transition; ERK1/2,
32 extracellular signal-regulated kinase 1/2; ESCRT, endosomal sorting complex required
33 for transport; GI, gastrointestinal; HGPS, Hutchinson-Gilford progeria syndrome; HSP90,
34 heat shock protein 90; INM, inner nuclear membrane; iPSC, induced pluripotent stem
35 cell; JNK, c-Jun N-terminal kinase; KASH, Klarsicht, ANC-1, and Syne homology;
36 LAP2 α , lamina-associated polypeptide 2 α ; LINC, linker of nucleoskeleton and
37 cytoskeleton; MAPK, Mitogen activated protein kinase; MEF, mouse embryonic
38 fibroblast; MKL1, Megakaryoblastic leukemia protein-1; MMP, matrix metalloproteases;
39 NAT, *N*-acetyltransferase; NE, nuclear envelope; ONM, outer nuclear membrane; PI3K,
40 phosphoinositide 3-kinase; PP2A, protein phosphatase 2A; pRB, retinoblastoma protein;
41 SREBP-1, sterol regulatory element-binding protein 1; SRF, serum response factor;
42 SUN, Sad1 and UNC-84; TGF- β , transforming growth factor- β ; TRF2, telomere repeat-
43 binding protein;

44

45 **Keywords**

46 Lamins, cancer, signal transduction, cell migration, cell mechanics, gene regulation

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Introduction

It has long been recognized that cancer cells exhibit characteristic changes in the size and shape of their nuclei, and these features serve as important biomarkers in the diagnosis and prognosis of cancer patients (de Las Heras and Schirmer, 2014). The broad prevalence of these changes is particularly intriguing, since nuclear abnormalities are common across a vast spectrum of cancer types, regardless of tissue source, mutational spectrum, and signalling dependencies. The frequency of nuclear alterations would thus suggest that changes in nuclear structure may be critically linked to the transformation process; however, the factors driving these nuclear abnormalities, and the associated functional consequences, are still incompletely understood.

Nuclear morphology could be affected by cancer-associated changes in DNA content (aneuploidy) or higher order chromatin organization (Bustin and Misteli, 2016; Reddy and Feinberg, 2013). The composition of the nuclear envelope (NE) that surrounds the DNA can further influence chromatin architecture and mediate changes in nuclear structure (Pombo and Dillon, 2015). In cancer, morphological abnormalities can occur in the NE itself, appearing as irregular folding, deep grooves, and cytoplasmic inclusions, which is in contrast with the generally smooth NE outline of most normal cells (Fischer, 2014). Notably, altered NE morphology is a crucial part of pathologists' assessment of tumour grade, and correlates with prognosis (Bussolati et al., 2014; Bussolati et al., 2008). Some studies even indicate that NE irregularities may be a direct result of oncogene activation, lack of tumour suppressor function, or genomic instability (Boyd et al., 1991; Fischer, 2014; Fischer et al., 1998). Taken together, these findings suggest that changes in the structure and composition of the NE may be regulated events occurring early in the transformation process, and could thus be directly linked to tumourigenesis.

The NE includes the inner and outer nuclear membranes (INM and ONM, respectively) and associated membrane proteins, the underlying network of intermediate filaments, termed the nuclear lamina, and nuclear pore complexes spanning the NE (Hetzer, 2010) (Fig. 1). The lamina consists mainly of A-type lamins (A and C) and B-type lamins (B1 and B2). Lamins A and C, as well as less abundant isoforms, are alternatively spliced from the *LMNA* gene, whereas lamins B1 and B2 are encoded by the *LMNB1* and *LMNB2* genes, respectively. Lamins are type V intermediate filaments composed of a N-terminal head domain, a rod domain, and a long C-terminal tail containing an immunoglobulin-like domain (Ho and Lammerding, 2012). Lamins form homodimers through coiled-coil interactions. Homodimers organize head-to-tail into polymers, and polymers further assemble in anti-parallel fashion into non-polar filaments (Gruenbaum and Medalia, 2015). Intriguingly, mutations in the *LMNA* gene cause a wide range of diseases, collectively termed laminopathies, that include Hutchinson-Gilford progeria syndrome (HGPS), dilated cardiomyopathy, and Emery-Dreifuss muscular dystrophy (EDMD) (Schreiber and Kennedy, 2013). Research aimed at understanding treatment options and disease progression of laminopathies has driven the characterization of many cellular functions for A-type lamins, revealing roles in pathways also known to contribute to tumour progression, such as proliferation and genomic instability. In addition to these signalling pathways, the NE also provides physical strength and stability to protect the nucleus (Isermann and Lammerding, 2013; Lammerding et al., 2006). The structural support generated by lamins is particularly important in cell types subjected to greater mechanical stress, such as in skeletal and cardiac tissues (Isermann and Lammerding, 2013; Swift et al., 2013; Zuela et al., 2016; Zwerger et al., 2013). Thus, alterations in the NE could impact both the physical and biochemical properties of cells during tumour initiation and progression.

Strengthening the potential connection between NE proteins and tumourigenic processes, altered NE protein expression has been detected in many human cancers and can have prognostic significance (reviewed in Denais and Lammerding (2014) and Chow et al. (2012)). For example, decreased expression of lamin A/C is found in many prostate, breast, colon, ovarian, and gastric cancers and is associated with worse prognosis (Belt et al., 2011; Gong et al., 2015; Matsumoto et al., 2015; Saarinen et al., 2015; Wu et al., 2009). Conversely, studies on colorectal and prostate tumours have identified an association between increased expression of lamin A/C and disease progression (Kong et al., 2012; Willis et al., 2008). These studies indicate that the role of A-type lamins in cancer is likely context-dependent, and further studies are required to determine how lamins function in cancer progression in different cell types, mutational backgrounds, and stages of disease. Furthermore, despite the widely documented changes in NE composition in cancer, few studies have been able to directly connect factors initiating alterations in the NE to functional consequences in malignant cell behaviours. Thus, there is a need to understand the cause-and-effect relationships between changes in NE structure and composition and the tumourigenic process. Although many NE proteins are altered in cancer and likely contribute to tumourigenesis and cancer progression, this review focuses mainly on how A-type lamins and their interaction partners could act as a key point of dysregulation in cancer, and promote growth and metastasis through effects on cell structure, signalling, genomic stability, and gene expression.

The nuclear envelope in migration, invasion, and metastasis

Invasive behaviour is one of the hallmarks of cancerous cells (Hanahan and Weinberg, 2011). Cancer cell invasion contributes to the spread of tumour growth to additional tissues, termed metastasis, which is the main cause of morbidity and mortality

in most cancers (Talmadge and Fidler, 2010). During *in vivo* migration, cells navigate through spaces in extracellular matrix (ECM) and cellular environments as small as 2 μm in diameter, which is substantially smaller than the size of the nucleus (Stoitzner et al., 2002; Weigelin et al., 2012). Cells can navigate these tight spaces by remodeling ECM fibers to modify their environment, including through ECM degradation by secreted matrix metalloproteases (MMPs), which are upregulated in many cancers and associated with poor prognosis (Coussens et al., 2002). Alternatively, cells can deform to squeeze through the available space (McGregor et al., 2016). This versatility may have contributed to the failure of MMP inhibitors to improve patient outcome in clinical trials (Coussens et al., 2002). While the dynamic cytoplasm deforms easily to fit through micron-scale spaces, the nucleus is the largest and stiffest cellular organelle, and nuclear deformation can impose a rate-limiting step on migration in 3D environments (McGregor et al., 2016; Wolf et al., 2013). Accordingly, cells migrating in 3D collagen matrices show extensive nuclear deformation when MMP activity is inhibited, and sufficiently small pore sizes can lead to complete stalling of cell movement as the nucleus becomes 'trapped' in the dense network (Wolf et al., 2013). The deformability of the nucleus is largely determined by expression of A-type lamins (Lammerding et al., 2006; Lammerding et al., 2004; Pajerowski et al., 2007; Schape et al., 2009), although changes in B-type lamin expression can also impact nuclear elasticity (Ferrera et al., 2014; Swift et al., 2013). As a result, cells with decreased lamin A/C levels migrate significantly faster through narrow constrictions in microfluidics devices and transwell plates with 3 μm pore sizes (Davidson et al., 2014; Harada et al., 2014; Shin et al., 2013). Consistent with these findings, cells in the periphery of a xenograft tumour model showed more nuclear deformation and lower lamin A expression relative to cells in the tumour core, suggesting that subpopulations of cells with lower lamin A were more efficient at invasion *in vivo* (Harada et al., 2014). The importance of lamin A/C levels in *in*

150 *vivo* cell migration is further exemplified in neutrophils, where maintaining nuclear
151 deformability is critical for passage through narrow capillaries less than one-fifth of the
152 cell diameter (Doerschuk et al., 1993). A-type lamins are normally downregulated during
153 neutrophil differentiation (granulopoiesis), and ectopic expression of lamin A in
154 neutrophil-type cells impairs their ability to pass through micron-scale constrictions
155 (Rowat et al., 2013). These studies demonstrate the importance of lamin A/C-dependent
156 nuclear stiffness in normal physiology and cancer cell invasion.

157 Interestingly, decreased lamin A/C expression may facilitate migration in confined
158 space, but also renders cells more susceptible to physical stress. This is particularly
159 relevant for cancer cells subjected to changing physical conditions, such as increased
160 hydrostatic pressure within the tumour, mechanical stress associated with migration
161 through tight interstitial spaces, and fluid shear stress in the circulatory system.

162 Increased nuclear fragility and NE rupture has been reported in lamin A/C-deficient and
163 lamin mutant models for laminopathies (Broers et al., 2004; De Vos et al., 2011;
164 Lammerding et al., 2004; Vargas et al., 2012). The NE has a critical role in protecting the
165 genome, and loss of NE integrity could damage DNA and potentially lead to cell death
166 (Denais et al., 2016; Raab et al., 2016). Cells expressing less lamin A/C have a general
167 increased sensitivity to mechanical stress, as cells with reduced lamin A/C levels exhibit
168 more cell death in response to mechanical strain (Lammerding et al., 2004), fluid shear
169 stress (Mitchell et al., 2015), and migration through confined spaces (Harada et al.,
170 2014; Raab et al., 2016). However, other studies did not report increased cell death from
171 confined migration (Davidson et al., 2014; Denais et al., 2016; Liu et al., 2015; Rowat et
172 al., 2013), indicating that different cell types or experimental conditions may impact the
173 specific sensitivity to mechanical stress in confined spaces. Recent work from our lab
174 and others has shed additional light on the potential consequences of nuclear
175 deformation in confined migration. Migration through tight spaces *in vitro* and *in vivo*

176 resulted in rupture of the NE in a broad panel of cell types, and the incidence of NE
177 rupture increased dramatically with smaller pore sizes and depletion of lamins (Denais et
178 al., 2016; Harada et al., 2014; Raab et al., 2016). NE rupture was characterized by
179 uncontrolled exchange of material between the nucleus and cytoplasm, chromatin
180 herniation into the cytoplasm, and DNA damage (Denais et al., 2016; Raab et al., 2016).
181 Strikingly, the majority of cells survive these NE rupture events, but survival requires
182 rapid ESCRT (endosomal sorting complex required for transport)-dependent NE repair
183 and intact DNA damage repair machinery (Denais et al., 2016; Raab et al., 2016). In
184 cancer cells, migration-induced DNA damage could further contribute to genomic
185 instability and thereby promote cancer progression. However, nuclear rupture could also
186 be a unique vulnerability of metastasizing cancer cells, such that targeting NE repair and
187 DNA damage repair in these cells could have therapeutic value.

188 In addition to protecting the nuclear content, lamins and associated LINC
189 complex proteins also play important roles in organizing cytoskeletal structure,
190 dynamics, and polarity, which are important for cell migration. Interrupting nucleo-
191 cytoskeletal coupling by disruption of the LINC-complex or lack of A-type lamins results
192 in altered organization of actin, tubulin, and vimentin networks and impaired cell
193 polarization and 2D cell migration, although effects on migration vary across different
194 studies (Broers et al., 2004; Davidson et al., 2014; Houben et al., 2009; Lee et al., 2007;
195 Lombardi et al., 2011; Razafsky et al., 2014). Increased levels of lamin A can also
196 promote migration of colorectal cancer cells through increased expression of T-plastin,
197 which downregulates E-cadherin, a key cell-cell adhesion molecule frequently absent in
198 cancer (Willis et al., 2008).

199 Taken together, these studies indicate that lamin A/C expression may be a
200 double-edged sword: low levels promote cell invasion through increased nuclear
201 deformability, while high levels protect against mechanical forces, such as increased

202 interstitial pressure within the tumour, and some minimum function of lamins is required
203 for proper cell polarization and cytoskeletal organization. In addition, cell viability in
204 response to strain or after rupture may depend on other functions of lamin A/C that
205 impact signalling pathways or DNA damage repair (discussed below). Thus, the effect of
206 A-type lamin levels on migration and metastasis is likely context-dependent, favoring
207 high or low expression in different cancer types or stages of disease.

209 **Lamin A/C and cancer stem cells**

210 A-type lamin expression also has important effects in the context of pluripotent
211 stem cells and differentiation. The association of changes in lamin expression with the
212 progression from a stem cell to a differentiated state was first described during mouse
213 development. Lamin A/C levels are absent in embryonic stem cells, and mice lacking A-
214 type lamins undergo seemingly normal embryonic development (Constantinescu et al.,
215 2006; Stewart and Burke, 1987; Sullivan et al., 1999). However, A-type lamins are
216 required for postnatal growth, and A-type lamin expression increases with differentiation,
217 not appearing in some tissues until after birth (Rober et al., 1989; Sullivan et al., 1999).
218 In adult mouse tissues, cell types that exhibit more stem cell or proliferative properties
219 also retain low lamin A/C levels, which is in contrast to the higher lamin A/C expression
220 detected in most somatic cells and tissues (Broers et al., 1997; Rober et al., 1990; Swift
221 et al., 2013; Takamori et al., 2007). The inverse association between lamin A/C levels
222 and stem cell characteristics is further illustrated in *in vitro* differentiation and stem cell
223 induction assays. Somatic cells treated to induce pluripotency show loss of lamin A/C
224 expression, demonstrating that lamin levels are not static but scale reversibly with the
225 degree of differentiation (Alberio et al., 2005; Bru et al., 2008). Conversely, somatic cells
226 expressing higher levels of lamin A show decreased efficiency in reprogramming to
227 induced pluripotent stem cells (iPSCs), and experimental manipulation to increase or

decrease lamin A levels results in reduced or enhanced induction of iPSCs, respectively, suggesting that levels of lamin A in somatic cell populations reflect varying degrees of plasticity (Zuo et al., 2012). In addition, overexpression of lamin A in normal human fibroblasts results in decreased replicative lifespan (Candelario et al., 2008). Furthermore, overexpression of lamin A/C impairs adipogenic conversion of pre-adipocytes (Boguslavsky et al., 2006), possibly due to the requirement to remodel the nuclear lamina during adipogenesis (Verstraeten et al., 2011). These studies show that lamin A/C expression is not just a marker of differentiation, but also actively contributes to lineage commitment and loss of phenotypic plasticity.

The function of lamin A/C in differentiation can be attributed in part to the ability of lamin A/C to interact with chromatin and influence the structural organization of the nucleus. Interactions between chromatin and lamins change during differentiation and play an important role in lineage determination (Lund et al., 2013; Peric-Hupkes et al., 2010). Increased NE shape fluctuations are an identifying feature of mesenchymal stem cells, and lack of lamin A/C has been shown to increase both nuclear deformations and chromatin dynamics (Bronshtein et al., 2015; Lee et al., 2014; Makhija et al., 2016). Hundreds of genomic regions termed lamina-associated domains (LADs) interact with the lamina and typically exhibit transcriptional repression (Guelen et al., 2008). Artificial tethering to the lamina can downregulate expression of targeted genes, and directing lamin A to promoter regions results in transcriptional repression (Finlan et al., 2008; Lee et al., 2009; Reddy et al., 2008). Transcriptional silencing of chromatin tethered to the lamina is mediated at least in part by epigenetic modifications associated with heterochromatin (reviewed in Gruenbaum and Foisner (2015)), and many proteins involved in epigenetic silencing interact with NE proteins (Guarda et al., 2009; Somech et al., 2005; Zhong et al., 2005). Accordingly, correct expression levels of A-type lamins are required for normal chromatin organization and control of gene expression during

differentiation (Frock et al., 2006; Solovei et al., 2013). Increased lamin A/C levels in differentiated cells could thus solidify phenotypic reprogramming by locking in tissue-specific patterns of heterochromatin at the nuclear periphery; conversely, lamin A/C deficiency is associated with loss of heterochromatin markers (Gonzalo, 2014). It is interesting to consider these mechanisms in the context of epigenetic alterations associated with tumourigenesis (Esteller, 2008; Galiova et al., 2008; Scaffidi and Misteli, 2005).

The involvement of lamin A/C in cellular differentiation and self-renewal is of particular importance when considering the function of lamins in cancer. The cancer stem cell (CSC) model describes a subset of cells in a tumour that have the ability to continually self-renew and to differentiate into a heterogeneous population (Medema, 2013). The phenotypic flexibility and renewal potential from these CSCs, also called tumour-initiating cells, can mediate tumour growth, therapeutic resistance, and completion of the metastatic cascade (Vermeulen et al., 2012), motivating research efforts to define, identify, and treat the stem cell-like population in human cancers. In addition to regulating chromatin organization, the role of lamin A/C in determining cellular plasticity may also involve reprogramming of signalling pathways known to be important for stemness, such as Wnt/ β -catenin, TGF- β , and Notch, which are discussed further in sections below. These pathways are already implicated in stem cell phenotypes in cancer, but studies have yet to address the potential involvement of lamin A/C in the CSC phenotype promoted by these signalling events. Nonetheless, Nardella et al. (2015) demonstrated that depletion of A-type lamins in a neuroblastoma cell line resulted in a cell subpopulation with enhanced stem cell characteristics. The authors suggest that this phenotype was mediated by altered expression of microRNA-101, which results in upregulation of the MYC proto-oncogene, and reveals an inverse correlation between expression of lamin A/C and MYC in human neuroblastoma biopsies (Nardella et al.,

2015). Based on our emerging understanding of lamins and their role in stemness and differentiation, the decreased levels of lamin A/C in human cancers may both reflect and promote CSC qualities for proliferation and differentiation, which can determine tumour growth, metastasis, and response to therapeutics.

As some tumours exhibit increased expression of A-type lamins, it will be interesting to determine whether these tumours still contain a subpopulation of CSCs with lower expression of lamin A/C. Since increased lamin levels could also potentially promote stemness through regulation of signalling and transcription, it will be relevant to determine whether high, rather than low, levels of A-type lamins typify stem cell populations in a particular cancer tissue of origin. Thus, high expression of lamins in such cancers could reflect activation of a stem cell program specific to that tissue. This appears to be the case in colorectal cancer, where the colon stem cell niche stains strongly for lamin A, and increased A-type lamin expression has been associated with aggressive cell behaviour and poor outcome (Willis et al., 2008). In contrast, lamin A/C expression is absent from gastrointestinal (GI) tract stem cells, and a mouse model of GI-specific *Lmna* deletion showed enhanced polyp growth in response to oncogenic stimulus (Wang et al., 2015). These studies highlight the multi-faceted role of lamins in cancers, and demonstrate that the cell type of origin could impact the functional consequences of lamin A/C expression.

A-type lamins in DNA damage and genome stability

The role of the nuclear lamina in physically protecting the nucleus, tethering chromatin, and regulating protein complexes, including components of the DNA damage repair machinery, provides a central position for lamins in the maintenance of genome integrity. Genomic instability is a hallmark feature of most cancers and drives tumour evolution and progression. Maintaining genome integrity has a key role in the

306 suppression of cancer, which is evident in both the tumour suppressor function of DNA
307 damage checkpoint proteins and the existence of hereditary cancers arising from
308 mutations in DNA repair genes (Negrini et al., 2010).

309 The importance of lamins in maintaining genomic stability is apparent in studies
310 of laminopathy disease progression (reviewed in Gonzalo (2014)). Lamin A/C-mutant
311 and -deficient models exhibit misshapen nuclei, loss of heterochromatin markers,
312 accumulation of unrepaired DNA damage, and chromosomal abnormalities (Gonzalo,
313 2014; Hutchison, 2011; Lammerding et al., 2004). There are diverse mechanisms
314 through which lamins can contribute to genomic stability. Lamin A/C stabilizes the
315 interaction of telomere repeat-binding protein 2 (TRF2) with telomeres, which influences
316 length and protection of telomeric DNA at the ends of chromosomes (Wood et al., 2014).
317 Loss of lamin A/C alters positioning of telomeres in the nucleus and results in telomere
318 shortening, which promotes genomic instability (Gonzalez-Suarez et al., 2009; Wood et
319 al., 2014). However, telomere shortening is also considered tumour-suppressive, since
320 telomere maintenance is required for continued DNA replication and cell immortalization,
321 and is often mediated in cancer by activation of the telomerase enzyme (Harley, 2008).
322 TRF2 is a potential oncogene upregulated in some cancers, and TRF2 overexpression
323 can maintain telomere length independently of telomerase through facilitating telomere
324 recombination events, which also foster chromosomal instability (Blanco et al., 2007). It
325 is tempting to speculate that lamin A/C may be required in TRF2-dependent tumours for
326 TRF2 to function in telomere maintenance. Therefore, both increased and decreased
327 lamin A/C expression could potentially contribute to genomic instability through
328 regulation of TRF2. Decreased expression of lamin A/C may also subject cells to
329 increased DNA damage due to enhanced susceptibility to mechanical stress, increased
330 nuclear deformation, and more frequent NE rupture events (Denais et al., 2016; Raab et
331 al., 2016). Furthermore, loss of lamin A/C impacts chromatin organization, gene

silencing, and gene positioning, and may therefore increase DNA translocations, which occur more often in transcriptionally active regions and between chromosomes in close proximity (Chiarle et al., 2011; Parada et al., 2004). Cells with loss or mutation of lamin A/C also show separation of chromatin into nuclear blebs or fragments, which could further promote chromosomal instability (Denais et al., 2016; Hatch et al., 2013; Lammerding et al., 2006; Vigouroux et al., 2001). Interestingly, treatment of laminopathic cells with the *N*-acetyltransferase (NAT) 10 inhibitor, remodelin, restores nuclear shape and decreases DNA damage, supporting the idea that genomic instability could be a direct consequence of altered lamin A/C levels and aberrant nuclear structure in cancer (Larrieu et al., 2014).

Altered lamin levels can also impact the ability of cells to repair DNA damage, potentially accelerating mutagenesis and enhancing tumour initiation and progression. Disruption of lamin A/C increases sensitivity of cells to DNA damaging agents and enhances activation of p53 signalling and p53-dependent senescence (Liu et al., 2005; Singh et al., 2013; Varela et al., 2005). Because p53 is frequently mutated in cancers and therefore unable to suppress growth in response to unrepaired DNA damage, genomic instability caused by altered lamin A/C levels could contribute to tumour progression rather than senescence in cancer cells (Muller and Vousden, 2014). Lamin A/C expression may further impact DNA repair responses through regulation of p53-binding protein-1 (53BP1), a DNA repair protein and potential tumour suppressor (Ward et al., 2003). Mouse embryonic fibroblasts (MEFs) and human fibroblasts both show decreased 53BP1 stability upon lamin A/C deficiency, leading to defects in DNA repair (Gibbs-Seymour et al., 2015; Gonzalez-Suarez et al., 2009; Redwood et al., 2011). Furthermore, 53BP1 interacts with lamin A/C, and depletion of lamin A/C decreases recruitment of remaining 53BP1 to sites of DNA damage and decreases cell viability in response to DNA damage (Gibbs-Seymour et al., 2015). This suggests that loss of lamin

A/C can promote genomic instability through effects on both activity and protein levels of 53BP1.

Lamin A/C also interacts with proteins involved in chromatin remodeling, such as HDAC1 and RBBP4, and altered epigenetic modifications of chromatin can diminish recruitment of components of the DNA repair machinery and contribute to the accumulation of DNA damage (Krishnan et al., 2011; Pegoraro et al., 2009).

Interestingly, depletion of A-type lamins also decreases levels of heat shock protein 90 (HSP90), which is a molecular chaperone implicated in DNA damage repair (Harada et al., 2014). However, as a chaperone protein facilitating protein homeostasis, HSP90 also has pro-tumourigenic effects on survival and growth of cancer cells expressing mutated and oncogenic proteins (Trepel et al., 2010). Thus, lower levels of lamin A/C may be detrimental to the growth of tumours driven by HSP90 client proteins, which may explain the increased lamin A/C levels observed in some cancers. In considering the role of lamin A/C-related signalling networks in cancer therapy, it will be important to determine whether tumours with low lamin A/C levels show enhanced sensitivity to treatment with either DNA damaging agents or inhibitors of DNA repair pathways.

Lamin A/C interplay with oncogenes and tumour suppressors

Recent studies suggest that lamins and other NE proteins can serve as a hub and modulator for numerous important signalling pathways, such as growth factor-induced kinase signalling and the transcriptional regulation of cell cycle progression (Andres and Gonzalez, 2009). Importantly, these pathways also contribute to many of the hallmarks of cancer, including self-sustained proliferation, insensitivity to anti-growth signals, evasion of apoptosis, limitless self-renewal potential, and invasion and metastasis (Fig. 2). We briefly highlight the role of lamins in some of the most relevant pathways below.

pRB/E2F

Inactivation of the retinoblastoma protein (pRB) is a widespread feature of human cancers (Johnson et al., 2016). The tumour suppressor function of pRB is attributed to its role in regulating cell proliferation. pRB binds to the E2F transcription factor, resulting in repression of genes involved in cell cycle progression and DNA replication. The cyclin-dependent kinase (CDK)-mediated phosphorylation of pRB causes release of E2F, increased E2F transcriptional activity, and G1-S cell cycle progression (Giacinti and Giordano, 2006). Recent studies indicate that lamins A/C and the lamina-associated polypeptide 2 α (LAP2 α) exert an additional layer of control on pRB. Lamin A/C tethers pRB either through direct interaction or in complex with LAP2 α , promoting accumulation of hypophosphorylated pRB and delay of cell cycle entry (Dorner et al., 2006; Markiewicz et al., 2002; Van Berlo et al., 2005). Furthermore, in the absence of lamin A/C, pRB is mislocalized and targeted for proteasomal degradation, suggesting that depletion of lamin A/C could promote increased proliferation through loss of the pRB checkpoint (Johnson et al., 2004). Accordingly, lamin A/C-deficient MEFs exhibit increased cell cycle progression, and depletion of lamin A/C in a human lung cancer cell line increased *in vivo* tumour growth rate (Harada et al., 2014; Johnson et al., 2004). In contrast, depleting lamin A/C in primary human diploid fibroblasts results in G₁ arrest, demonstrating cell type-dependent effects of lamin A/C levels on proliferation (Pekovic et al., 2007). The pRB/E2F and p53 tumour suppressor pathways are interconnected, suggesting that mutation of p53 in cancer cells may account for some of the context-dependent effects on proliferation observed with loss of lamin A/C (Muller and Vousden, 2014; Polager and Ginsberg, 2009). Additional NE components may also influence the role of LAP2 α and lamin A/C in pRB regulation, as lack of the INM protein emerin has been associated with diminished ability of pRB to repress transcription (Melcon et al.,

2006). Finally, it is worth noting that multiple studies in cell lines and tissues support an inverse relationship between lamin A/C levels and proliferation, which is consistent with the association of increased lamin A/C with differentiation (Broers et al., 1997; Ivorra et al., 2006; Nitta et al., 2006; Van Berlo et al., 2005). Thus, dysregulation of pRB and increased cell proliferation could be a key consequence of lamin A/C alterations in cancer, particularly in cells lacking functional p53.

Wnt/ β -catenin

The Wnt proto-oncogene is a secreted factor that binds to the Frizzled receptor to promote stabilization of β -catenin, which is followed by β -catenin nuclear translocation and regulation of transcription (reviewed in Clevers and Nusse, 2012). The Wnt/ β -catenin pathway is implicated in promoting CSCs and epithelial-mesenchymal transition (EMT) in cancer, which has driven the development of therapies targeting Wnt pathway (Takebe et al., 2015). Recent studies indicate that several NE proteins interact with β -catenin and can modulate Wnt/ β -catenin signalling. Emerin interacts with β -catenin and represses its activity through negative regulation of nuclear accumulation (Markiewicz et al., 2006). Loss of emerin results in β -catenin nuclear localization and hyperactivation (Markiewicz et al., 2006; Stubenvoll et al., 2015). Lamin A directly interacts with emerin and is required for its NE localization, and lamin A/C has also been identified in complex with β -catenin (Bermeo et al., 2015; Vaughan et al., 2001). However, lamin A/C expression increases nuclear translocation and activity of β -catenin, and lamin A/C mutations inhibit Wnt/ β -catenin activity in mouse models of the segmental aging disease HGPS (Bermeo et al., 2015; Espada et al., 2008; Hernandez et al., 2010). The KASH domain protein, Nesprin-2, also interacts with emerin and β -catenin, and depletion of Nesprin-2 reduces β -catenin nuclear translocation and activity, demonstrating an additional layer of complexity in NE-mediated regulation of β -catenin (Neumann et al.,

2010). Moreover, the Wnt/ β -catenin pathway also modulates expression of NE proteins, as depletion of β -catenin decreases emerin gene expression and increases lamin A/C expression (Tilgner et al., 2009). These studies demonstrate complex, bi-directional interplay between β -catenin and the NE and stimulate further investigation to determine whether alterations in NE-mediated regulation of β -catenin also occur in tumourigenesis, and whether such changes could contribute to maintenance of the CSC population and EMT.

MAPK

Mitogen activated protein kinase (MAPK) signalling kinases phosphorylate both cytoplasmic and nuclear targets to modulate diverse cellular processes related to malignant transformation (Dhillon et al., 2007). Dysregulation of MAPK signalling is a common feature in cancer, often occurring downstream of growth factor signalling or through mutation (Dhillon et al., 2007). Interestingly, loss of lamin A/C or emerin, as well as expression of lamin A/C mutations associated with muscular dystrophy and dilated cardiomyopathy, result in hyperactivation of multiple MAPK signalling branches, namely extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 α MAPK (Emerson et al., 2009; Muchir et al., 2007; Muchir et al., 2012a; Muchir et al., 2012b; Muchir et al., 2009). The molecular mechanism by which lamin A/C and emerin can modulate MAPK signalling remains incompletely understood. A-type lamins interact directly with ERK1/2 and c-fos, resulting in ERK1/2-dependent release of the c-fos transcription factor from lamin A/C and activation of AP1-mediated transcription and proliferation (Gonzalez et al., 2008). Competitive ERK1/2 binding to lamin A may also regulate cell cycle progression through displacement and inactivation of pRB (Rodriguez et al., 2010). Interestingly, lamin A was also found to interact with protein kinase C (PKC) α , which is a serine-threonine kinase implicated in MAPK activation and cancer

progression (Haughian et al., 2009; Martelli et al., 2002; Mauro et al., 2002). Translating these findings to signalling in the context of cancer cells could be an important step in determining the role of lamin A/C alterations in tumour progression. Inhibitors of the MAPK pathway are in clinical trials for cancer treatment, raising the question of whether levels of A-type lamins could have prognostic value for response to MAPK inhibition (Roberts and Der, 2007).

PI3K/Akt

The phosphoinositide 3-kinase (PI3K)/Akt signalling network, which controls cancer cell proliferation, metabolism, and invasion, is the most frequently altered pathway in human cancers, making it a focus for targeted therapeutics (Fruman and Rommel, 2014). Increased PI3K/Akt activity can result from alterations in GTPase or tyrosine kinase signalling inputs, activating PI3K/Akt mutations, or loss of negative regulators, such as the PTEN lipid phosphatase (Engelman, 2009). However, it remains unclear what role lamins play in Akt-mediated cellular responses, particularly in the context of cancer. Interestingly, the heart and muscle of lamin A/C-deficient mice show hyperactivation of mammalian target of rapamycin complex 1 (mTORC1), which is a downstream target of Akt (Ramos et al., 2012). In contrast, increased levels of lamin A/C were found to positively regulate the PI3K/Akt pathway in prostate cancer, where lamin A/C expression has been associated with higher risk tumours (Kong et al., 2012; Skvortsov et al., 2011). Low grade prostate cancers showed very little lamin A/C, suggesting that the pro-tumourigenic function of lamin A/C may arise in cooperation with other changes associated with high grade tumours, rather than as a general feature of prostate cancer.

TGF- β

Transforming growth factor- β (TGF- β) ligands bind to type I and type II receptors to activate Smad-dependent and Smad-independent signalling cascades (Moses and Barcellos-Hoff, 2011). Phosphorylation of Smads results in dimerization and translocation into the nucleus, where they act as co-activators and co-repressors interacting with an extensive collection of transcription factors (Ten Dijke et al., 2002). The outcome of TGF- β signalling is dependent on the transcription factors present and on activation of parallel signalling pathways (Gomis et al., 2006). This allows the TGF- β pathway to assume diverse, context-dependent roles in tissue development and homeostasis, acting as a mediator of EMT, ECM remodeling, apoptosis, and cell cycle arrest (Wu and Hill, 2009). Despite having tumour suppressive effects at the initiation stage of tumourigenesis, TGF- β can drive the progression and metastasis of established tumours and has been pursued as a therapeutic target (Papageorgis, 2015; Siegel et al., 2003; Tang et al., 2003).

Increasing findings suggest that A-type lamins and other NE proteins may play a part in determining the biological outcomes of TGF- β stimulation. Regulation of pRB is a primary mechanism through which TGF- β inhibits proliferation, and the absence of pRB can switch TGF- β signalling effects from growth-inhibitory to tumour-promoting. Dysregulation of pRB in lamin A/C-deficient MEFs diminishes the ability of TGF- β 1 to decrease proliferation, and lamin A/C expression is required for TGF- β -stimulated dephosphorylation of pRB through regulation of protein phosphatase 2A (PP2A) (Van Berlo et al., 2005). Interestingly, lamin A/C levels also impact the kinetics of TGF- β 1-induced Smad phosphorylation, with more rapid, intense, and shorter duration phosphorylation of Smad2/3 occurring in the absence of lamin A/C (Van Berlo et al., 2005). Lamin A/C may further co-ordinate responses to TGF- β signalling through regulation of other lamina-associated proteins, such as MAN1 and Nesprin-2. MAN1, an integral INM protein, binds directly to Smad2 and Smad3, possibly acting as a

competitive inhibitor of formation of the transcriptionally active complex (Lin et al., 2005). Overexpression of MAN1 is sufficient to inhibit induction of both transcriptional activity and proliferation arrest downstream of TGF- β stimulation (Lin et al., 2005). In contrast, Nesprin-2 mediates TGF- β -induced nuclear translocation of Smad2/3 and c-fos (Rashmi et al., 2012). Therefore, the specific composition of the NE can promote or inhibit aspects of the TGF- β signalling program. Interestingly, increasing lamin A expression decreases secretion of TGF- β , demonstrating both upstream and downstream roles for lamins in TGF- β signalling (Evangelisti et al., 2015). Additionally, TGF- β 1 stimulation was found to reduce the levels of lamin A/C in endothelial cells, and to promote proliferation and migration (Qi et al., 2011). Given the wide variety of phenotypes elicited by TGF- β , it will be interesting to determine whether changes in lamin levels can control the switch between the growth-suppressive and tumour-promoting effects of TGF- β in different stages or types of cancer.

MKL1/SRF

Megakaryoblastic leukemia protein-1 (MKL1, also termed MRTF-A or MAL) is a transcription coactivator of serum response factor (SRF) that regulates expression of genes involved in cell motility, growth, and differentiation (Pipes et al., 2006; Scharenberg et al., 2010). MKL1/SRF signalling has key functions in tumour progression, such as mediating TGF- β -induced EMT and promoting cell migration and metastasis (Kircher et al., 2015; Medjkane et al., 2009; Morita et al., 2007). MKL1 is localized in the cytoplasm through binding to G-actin, but mitogenic or mechanical stimulation results in actin polymerization and translocation of MKL1 to the nucleus, where it serves a co-factor for SRF to activate expression of numerous proteins involved in cytoskeletal organization, contractility, and adhesion, including integrins, vinculin, and actin (Olson and Nordheim, 2010). MKL1 is also regulated by nuclear actin dynamics,

and loss of lamin A/C or emerin from the NE impairs nuclear translocation and signalling of MKL1 due to the role of emerin in controlling nuclear actin polymerization (Baarlink et al., 2013; Ho et al., 2013; Holaska et al., 2004). Consequently, the loss of nuclear accumulation of MKL1 and diminished MKL1/SRF signalling further alters cytoskeletal actin dynamics in lamin A/C- and emerin-deficient cells (Ho et al., 2013). Decreased MKL1/SRF transcriptional activity due to the absence of lamin A/C would be predicted to reduce invasive capabilities of tumour cells, suggesting that this pathway may provide selective pressure to retain a critical amount of lamin A/C, and select against *LMNA* gene deletions and dominant mutations.

Additional pathways

In addition to the above pathways, lamin A/C has been shown to influence NF- κ B transcriptional activity (Lammerding et al., 2004), which can have tumour promoting and tumour suppressive effects (Perkins, 2004). Lamin A/C has also been found to influence the YAP transcriptional coactivator (Bertrand et al., 2014; Swift et al., 2013), which is a major downstream effector of the Hippo pathway and increasingly implicated in tumour progression (Moroishi et al., 2015). Furthermore, lamin A/C mutations responsible for HGPS disturb the Notch pathway (Scaffidi and Misteli, 2008), which is another signalling pathway that can have both oncogenic and tumour suppressor functions (Lobry et al., 2011). A-type lamins were also found to interact with the pro-tumourigenic transcription factors, c-Fos and MYC, and the sterol regulatory element-binding protein 1 (SREBP-1) transcription factor, which is a master regulator of pro-tumourigenic lipid metabolism (Guo et al., 2014; Ivorra et al., 2006; Lloyd et al., 2002; Myant et al., 2015). Interestingly, lamins may also impact tumourigenesis by modulating fatty acid metabolism. Lamin A was identified in a yeast two-hybrid screen for interactors of the pro-tumourigenic enzyme 12-lipoxygenase (12-LOX) (Tang et al., 2000). LOX enzymes are implicated in

carcinogenesis by mediating conversion of polyunsaturated fatty acids into metabolites involved in modulating diverse signalling pathways (Shureiqi and Lippman, 2001). 12-LOX has been implicated in promoting survival, growth, and metastasis in many human cancers (Agarwal et al., 2009; Dilly et al., 2013; Honn et al., 1994; Kerjaschki et al., 2011; Klampfl et al., 2012). Further study is required to determine whether the regulation of these pathways by lamin A/C contributes to tumourigenesis and metastasis.

Mechanisms controlling lamin A/C levels in cancer

Mutations in the *LMNA* gene are responsible for the various laminopathies, but genomic analysis of human tumours suggests that *LMNA* mutations, deletions, or copy-number variations are not a common feature of most cancers (Fig. 3). However, it is interesting to note the recent identification of a translocation between the tropomyosin-receptor kinase (TRK) and *LMNA* genes resulting in a fusion product, *LMNA-NTRK1*, in metastatic colorectal cancer and congenital infantile fibrosarcoma (Sartore-Bianchi et al., 2016; Wong et al., 2016). In both cases, most of the *LMNA* gene (exons 1-10 or 1-11) is fused to an intact NTRK1 kinase domain, and tumours responded to tyrosine kinase inhibition. However, the mechanistic role of the *LMNA* portion of the fusion protein in affecting kinase activation, localization, or substrate selection requires further study. Despite the relatively infrequent genomic alterations, changes in lamin A/C expression are common in many cancers at the protein and transcript level, suggesting the involvement of epigenetic, transcriptional, and/or post-translational mechanisms of regulation.

LMNA gene expression

Transcript levels of lamin A/C are governed by epigenetic modifications, transcription factor activity, and microRNAs. The retinoic acid receptor transcription

factors have been shown to act in regulation of lamin A/C (Okumura et al., 2004; Swift et al., 2013), and CpG island promoter hypermethylation is responsible for decreased lamin A/C expression in hematologic cancers and associated with poor prognosis in lymphoma (Agrelo et al., 2005). However, *LMNA* promoter hypermethylation was not detected in other cancer types, suggesting alternative mechanisms for altered lamin A/C levels in these cases (Agrelo et al., 2005; Lee et al., 2012). One such mechanism could be the microRNA miR-9, which represses lamin A, but not lamin C, in the brain (Jung et al., 2012). Altered miR-9 expression occurs in cancer, and miR-9 has multiple targets that may contribute to tumourigenesis (Cekaite et al., 2012; Lu et al., 2014; Ma et al., 2007). For example, expression of the MYC proto-oncogene in breast cancer cells increases miR-9 expression, which in turn promotes invasion and metastasis through downregulation of the cell-cell adhesion protein, E-cadherin (Ma et al., 2010). Therefore, regulation of lamin A/C by miR-9 may be coordinated as part of a larger metastasis-related signalling network. Akt signalling has also been shown to control *LMNA* gene expression, demonstrating that multiple signalling programs could contribute to transcriptional regulation of lamin A/C (Bertacchini et al., 2013).

Although lamins A and C are both expressed from the *LMNA* gene, regulation of splicing can control the relative expression levels of these two proteins. Alternative splicing of the *LMNA* gene contributes to the large variation in tissue-specific differences between expression of lamin A and C (Aljada et al., 2016). Importantly, relative to normal tissues, the ratio of lamin C to lamin A mRNA was found to be elevated in cancers from breast, colon, liver, lung, ovary, thyroid, and prostate (Aljada et al., 2016). Most commonly used antibodies cannot distinguish between lamin A and C, which are identical for the N-terminal 566 amino acids. Nonetheless, differentiating between lamin A and lamin C will be important when determining the relationship between lamin expression and prognosis, as these isoforms may have distinct effects on cancer

618 progression. For example, in epithelial ovarian cancer, downregulation of lamin A, but
619 not lamin C, is associated with metastasis and decreased disease-free survival (Gong et
620 al., 2015). These results reveal that regulation of *LMNA* splicing may play an important
621 role in fine-tuning the properties of the nucleus in different tissues, and may also provide
622 an important point of dysregulation in cancer.

624 Post-translational modifications of lamins A/C

625 The assembly, function, and stability of lamin A/C is also regulated by post-
626 translational modifications. The best characterized lamin post-translational modification
627 is phosphorylation. CDK1- and/or PKC-mediated phosphorylation of lamins disrupts
628 head-to-tail polymer formation promoting lamina disassembly during mitosis (Collas,
629 1999; Peter et al., 1990). There are 61 known lamin A/C phosphorylation sites, with Ser-
630 22, Ser-392, Ser-404, and Ser-406 being key residues for mitotic lamin depolymerization
631 (Simon and Wilson, 2013). Recent studies found that phosphorylation can also modulate
632 lamin assembly and function during interphase (Buxboim et al., 2014; Kochin et al.,
633 2014). Changes in interphase lamin A/C phosphorylation and subsequent degradation in
634 response to substrate stiffness are thought to regulate the stiffness-dependent levels of
635 lamin A/C (Buxboim et al., 2014; Swift et al., 2013). Stiffer matrix and myosin-IIA activity
636 decreases levels of lamin A Ser22 phosphorylation, while cyclin-dependent kinase
637 (CDK)-mediated increases in Ser22 phosphorylation occurred upon reduction of stiffness
638 and nuclear tension (Buxboim et al., 2014).

639 Intriguingly, lamin A is also a nuclear substrate for Akt phosphorylation (Barati et
640 al., 2006; Cenni et al., 2008). Akt-mediated Ser-404 phosphorylation targets prelamin A
641 for degradation, and Akt-mediated degradation of lamin A is important for normal
642 epidermal differentiation (Bertacchini et al., 2013; Cenni et al., 2008; Naeem et al.,
643 2015). Since dysregulated PI3K/Akt signalling is frequently associated with

tumourigenesis, this suggests a potential mechanism for downregulation of lamin A/C in cancer.

Other post-translational modifications that could impact lamin A/C assembly and function are ubiquitination, and acetylation, and the covalent addition of small ubiquitin-like modifier (SUMO) proteins (Simon et al., 2013; Simon and Wilson, 2013; Zhang and Sarge, 2008). Furthermore, the addition of β -O-linked N-acetylglucosamine, termed O-GlcNAcylation, to lamins has long been recognized, but the impact of this modification on lamin functions remains incompletely understood (Ferraro et al., 1989; Simon and Wilson, 2013). An additional mechanism for post-translational modification of lamins is the oxidation of cysteine residues in the tail domain of lamin A, resulting in disulphide bridges in response to oxidative stress (Pekovic et al., 2011). Thus, there are many possible avenues for post-translationally tuning lamin A/C stability and organization, but a functional understanding of these modifications and their consequences is still lacking.

Lamins and the mechanical tumour microenvironment

It is increasingly becoming apparent that the mechanical tissue microenvironment is playing a crucial role in tumourigenesis and tumour progression (Pickup et al., 2014; Wei and Yang, 2016). The tumour microenvironment is composed of various cell types, ECM proteins, blood vessels, lymphatics, and soluble factors that together create a niche that can support or hinder tumour progression (Quail and Joyce, 2013). During tumourigenesis, remodeling the cellular and ECM architecture in the tissue alters the function of tumour and stromal cells, which can conversely further remodel the microenvironment (Yu et al., 2011). In particular, ECM composition and rigidity modulate signalling pathways associated with tumour progression, such as ERK, TGF β , and PI3K, thereby affecting EMT and metastasis (Chaudhuri et al., 2014; Leight et al., 2012; Levental et al., 2009; Paszek et al., 2005; Pickup et al., 2014; Wei and Yang, 2016).

Increased stiffness in the stroma surrounding the tumour was shown to accompany tumour progression in a mouse mammary tumour model, and increasing stiffness *in vitro* is sufficient to convert mammary epithelial cells to an invasive, malignant phenotype (Chaudhuri et al., 2014; Levental et al., 2009; Paszek et al., 2005).

Recent studies suggest that lamins could play important roles both upstream and downstream of this mechanosensitive process (Irianto et al., 2016). Since lamins and emerin play a central role in the mechanoregulation of gene expression, changes in lamin levels could influence how cells interpret and respond to changes in their mechanical environment. (Guilluy et al., 2014; Ho et al., 2013; Lammerding et al., 2005; Lammerding et al., 2004). Conversely, a proteomic analysis of soft and stiff tissues revealed that lamin A/C increases with tissue stiffness, whereas B-type lamins exhibited fairly constant abundance, and that the increase in lamin A/C may contribute to lineage specification in differentiation (Swift et al., 2013). Furthermore, xenograft tumours of U251 glioblastoma cells exhibit higher lamin A/C levels when grown in the stiffer subcutaneous flank compared to the brain, suggesting that A-type lamin levels can adjust to tissue stiffness *in vivo* (Swift et al., 2013). However, it cannot be excluded that lamin A/C levels could be affected by other differences in the properties of these microenvironments, such as levels of tissue-specific growth factors, local metabolite concentrations, or other signaling pathways. In addition to modulating total levels of lamin A/C, the physical properties of the microenvironment can also affect intranuclear lamina organization. For example, with increased substrate stiffness and cell spreading, a lamin A/C conformational epitope in the Ig-domain becomes masked in the basal portion of the NE (Ihalainen et al., 2015), suggesting structural rearrangements within the lamina that could further impact interactions of lamins with chromatin and other binding partners. These studies demonstrate that organization and levels of lamin A/C

are both dynamically regulated in response to the physical microenvironment and can modulate cellular mechanotransduction signalling.

Altered lamin A/C levels could in turn influence the microenvironment, as increased collagen deposition and fibrosis are features of multiple laminopathies, and loss of lamin A/C increases collagen production in MEFs (Arimura et al., 2005; Hernandez et al., 2010; Van Berlo et al., 2005; van Tintelen et al., 2007). This suggests that lamin A/C levels could respond to cancer-associated changes in the microenvironment to influence not only nuclear structure, but also feedback to remodel the tissue structure and microenvironment. Further research is required to understand how changes in lamin A/C contribute to ECM alterations in cancer, and whether the mechanosensitive scaling of lamin A/C remains generally intact in cancer cells and contributes to tumour pathology.

Enhanced stiffness in the tumour microenvironment would be expected to affect lamin A/C levels, which could further promote tumour progression. Importantly, increased tissue rigidity is not a uniform characteristic of tumours and has been shown to vary between subtypes and within single tumours (Acerbi et al., 2015). In breast cancers, increased rigidity is commonly observed at the tumour edge, with high stiffness and greater variability in the invasive front (Acerbi et al., 2015; Plodinec et al., 2012; Provenzano et al., 2006). These findings, along with the ability of increased stiffness to promote EMT-like phenotypes, support the hypothesis that tissue rigidity promotes invasion and metastasis (Pickup et al., 2014; Wei and Yang, 2016). However, invasive breast tumours have more heterogeneity in tissue stiffness than benign tumours, which have a more uniform increase in stiffness over normal tissue (Plodinec et al., 2012). Interestingly, studies of stiffness in mouse mammary tumour models found that increased metastasis was associated with more compliant tumours, and lung metastases display lower stiffness than matched primary tumours (Fenner et al., 2014;

Plodinec et al., 2012). The idea that A-type lamins may be regulated by rigidity in these different environments is particularly exciting when viewed from the perspective of lamin A/C controlling differentiation and plasticity. During tumourigenesis, increased tissue-stiffness could modulate lamin A/C levels and intranuclear distribution, thereby disturbing chromatin organization and gene expression. During metastasis, outgrowth at the secondary site is thought to be the rate-limiting step in the metastatic cascade, and could require a switch from an EMT to a MET phenotype (Luzzi et al., 1998; Tsai and Yang, 2013). Thus, phenotypic flexibility could be the true driver of tumour progression, and may be directly linked to changes in lamin levels and intranuclear organization. In this scenario, it is attractive to imagine that increased rigidity may promote invasion and escape from the primary tumour, but perhaps a softer microenvironment at the secondary site leads to decreased lamin A/C levels that support the enhanced stem cell-associated plasticity required for outgrowth and metastasis (Fig. 4).

Conclusions and future perspectives

Both increased and decreased lamin A/C levels have been associated with poor prognosis in human cancers. This paradox could arise from tissue-specific functions, variation in expression within a single tumour, or dynamic changes in response to biochemical or mechanical signals throughout tumour progression (Fig. 4). Regardless, this discrepancy warrants further investigation to understand in what contexts increased or decreased lamin A/C promotes tumour progression. The infrequency of cancer-associated deletions or mutations in the *LMNA* gene suggests that selective pressures exist for retention of a minimum level of expression or the ability to upregulate lamin A/C for cellular responses to the changing tumour environment. It is still unclear whether lamin A/C levels in cancer are a dynamic representation of conditions in the tumour at a

particular time, and thus a reflection of response to transformed signalling pathways and microenvironmental conditions, or whether altered lamin A/C levels in cancer are uncoupled from normal regulatory mechanisms and can independently initiate oncogenic changes.

The NE participates in complex regulatory loops, and determining the function of lamin A/C in cancer will require studies that can distinguish between the causes and consequences of altered lamin A/C in particular tumour types and disease stages. Lamin A/C influences EMT and stem cell phenotypes, which are interconnected cellular programs and important mediators of metastasis and therapeutic resistance (Mani et al., 2008; Shuang et al., 2014). It will be pertinent to determine whether lamin A/C expression in CSCs and metastatic subpopulations is different compared to the bulk primary tumour, and whether this is associated with specific therapeutic vulnerabilities. The use of inducible systems to modify lamin levels at specific stages of *in vivo* tumour xenograft experiments could be instrumental in answering some of these unresolved questions. Tissue-specific alteration of lamin A/C in transgenic mouse models will also be critical to definitively determine the function of lamin A/C during the full scope of disease progression from normal tissue to tumour initiation and through to metastasis.

One exciting future direction is the potential exploitation of lamin A/C in targeted therapies. It is possible that with a better understanding of lamin A/C regulation and functions, altered lamin levels and organization could serve as biomarkers for response to specific therapeutics. Lamin A/C influences pathways known to have roles in both tumour suppression and tumour progression, such as TGF- β , Notch, HSP90, and NF- κ B. It is intriguing to imagine that changes in lamin A/C levels and/or organization in cancer act to promote a shift towards the tumorigenic functions of these pathways, and therefore modulating lamin A/C expression could be a therapeutic approach for restoration of tumour suppressor function. Additionally, understanding the role of lamin

A/C expression in metastasis could lead to improvements in therapy and patient outcome. For example, cells with lower lamin A/C levels may self-select during invasion in tissue environments due to enhanced nuclear deformability, but are also more susceptible to NE rupture, and may have diminished DNA damage response capabilities. This suggests that inhibiting DNA repair pathways could be an effective strategy to eliminate cells in the process of metastasizing, and tumours with low lamin A/C levels could be particularly susceptible to DNA damaging agents. Thus, while many open questions remain regarding the role of lamins in tumour initiation and progression, rapidly emerging findings suggest that we are entering an exciting area of growth and discovery as lamin A/C is increasingly appreciated as a central node regulating multiple aspects of the tumourigenic process, with important diagnostic, prognostic, and therapeutic applications.

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Figure legends

Figure 1. Overview of nuclear envelope organization and lamin A/C functions. The nuclear envelope (NE) consists of the outer nuclear membrane (ONM), inner nuclear

membrane (INM), nuclear pore complexes (NPC), nuclear lamina, and additional proteins bound to the lamina and INM. The lamina is a meshwork of intermediate filaments beneath the INM composed of A-type and B-type lamins. Lamins can also localize to the nuclear interior (not depicted here). Lamin A/C performs many cellular functions, including providing physical stiffness to protect the nucleus and tethering chromatin into transcriptionally repressed regions at the nuclear periphery. The lamina and associated proteins can also form complexes with signalling molecules to influence nuclear accumulation, stability, and substrate engagement. The nucleus is connected to the cytoskeleton through the linker of nucleoskeleton and cytoskeleton (LINC) complex. The LINC complex is composed of Sad1 and UNC-84 (SUN) domain proteins in the INM that bind to Klarsicht, ANC-1, and Syne homology (KASH) domain proteins that span the ONM and connect to the cytoskeleton, facilitating nuclear positioning and mechanotransduction signalling.

Figure 2. Connections between lamin A/C and pathways known to suppress or promote cancer formation and progression. Lamin A/C participates in many pathways characterized to have oncogenic (red) or tumour suppressor (blue) functions in cancer. Lamin A/C expression influences protein levels or downstream activity to modulate signal transduction, and in many cases interactions between lamin A/C and signalling proteins have also been detected (double lines). It is important to note that many of these functions have been identified in lamin A/C mutant or deletion models for laminopathies, and an understanding of lamin A/C-related signalling in the context of cancer demands further study.

Figure 3. Frequency of mutations and copy-number alterations in the *LMNA* gene in human cancers. The results shown here are based upon data generated by the

TCGA Research Network (<http://cancergenome.nih.gov/>). Data are presented as analyzed by cBioPortal, accessed April 10, 2016 (<http://www.cbioportal.org/>) (Cerami et al., 2012; Gao et al., 2013). Shallow loss determined by copy-number analysis is referred to here as “heterozygous deletion” and deep loss is referred to as “homozygous deletion”. Copy number variations make up the majority of genomic changes in the *LMNA* gene in cancer, whereas mutations are rare. It remains to be determined whether *LMNA* genomic alterations correlate closely with protein levels in cancer, and which transcriptional and/or post-translational mechanisms are important contributors to altered lamin A/C expression in cancer.

Figure 4. Potential roles for lamin A/C in tumour initiation and progression. Both increased and decreased levels of lamin A/C have been observed in cancer and related to patient prognosis. The complexity of lamin A/C functions and signalling networks suggests that the role of lamin A/C in tumour progression may vary with stage of disease, tissue of origin, and mutational landscape of a given tumour. Possible functions for increased and decreased lamin A/C levels during tumour progression are depicted here, and warrant further investigation towards understanding the role of lamin A/C in cancer. Importantly, many of these lamin-related functions could contribute to multiple stages of cancer, but are each shown here only once for simplicity.

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Figure 1

Figure 2

Figure 3

Figure 4

Tumour initiation and outgrowth

Invasion and survival in circulation

Metastatic growth and therapeutic resistance

↑
Increased
lamin A/C

- Proliferative signalling through PI3K/Akt
- Mechanotransduction response to increasing ECM stiffness

- Nuclear positioning for polarized migration
- MKL1-dependent gene expression promotes cytoskeleton dynamics and migration
- Resistance to mechanical stress

- Decreased susceptibility to DNA damaging agents
- Increased stemness through β -catenin activity
- Anti-apoptotic NF- κ B functions promote chemoresistance

↓
Decreased
lamin A/C

- Increased genomic instability
- Decreased pRB-mediated growth suppression
- Hyperactivation of MAPK proliferative signalling

- Increased nuclear deformability for migration through confined spaces
- Modulation of TGF- β signalling to promote EMT over growth suppression

- Increased stem cell characteristics through loss of heterochromatin
- Increased ECM deposition for microenvironment remodelling