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Review

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.

Contents

Abbreviations: 12LOX, 12-lipoxygenase; 2D, two-dimensional; 3D, three-dimensional; CDK, cyclin-dependent kinase; CSC, cancer stem cell; ECM, extracellular matrix; EDMD, Emery-Dreifuss muscular dystrophy; EMT, epithelial-mesenchymal transition; ERK1/2, extracellular signal-regulated kinase 1/2; ESCRT, endosomal sorting complex required for transport; GI, gastrointestinal; HGPS, Hutchinson-Gilford progeria syndrome; HSP90, heat shock protein 90; INM, inner nuclear membrane; iPSC, induced pluripotent stem cell; JNK, c-Jun N-terminal kinase; KASH, Klarsicht, ANC-1, and Syne homology; LAP2α, lamina-associated polypeptide 2α; LINC, linker of nucleoskeleton and cytoskeleton; MAPK, Mitogen activated protein kinase; MEF, mouse embryonic fibroblast; MKL1, Megakaryoblastic leukemia protein-1; MMP, matrix metalloproteases; NAT, *N*-acetyltransferase; NE, nuclear envelope; ONM, outer nuclear membrane; PI3K, phosphoinositide 3-kinase; PP2A, protein phosphatase 2A; pRB, retinoblastoma protein; SREBP-1, sterol regulatory element-binding protein 1; SRF, serum response factor; SUN, Sad1 and UNC-84; TGF-β, transforming growth factor-β; TRF2, telomere repeat-binding protein.

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1. 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, 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.

2. 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).