The nuclear envelope at a glance

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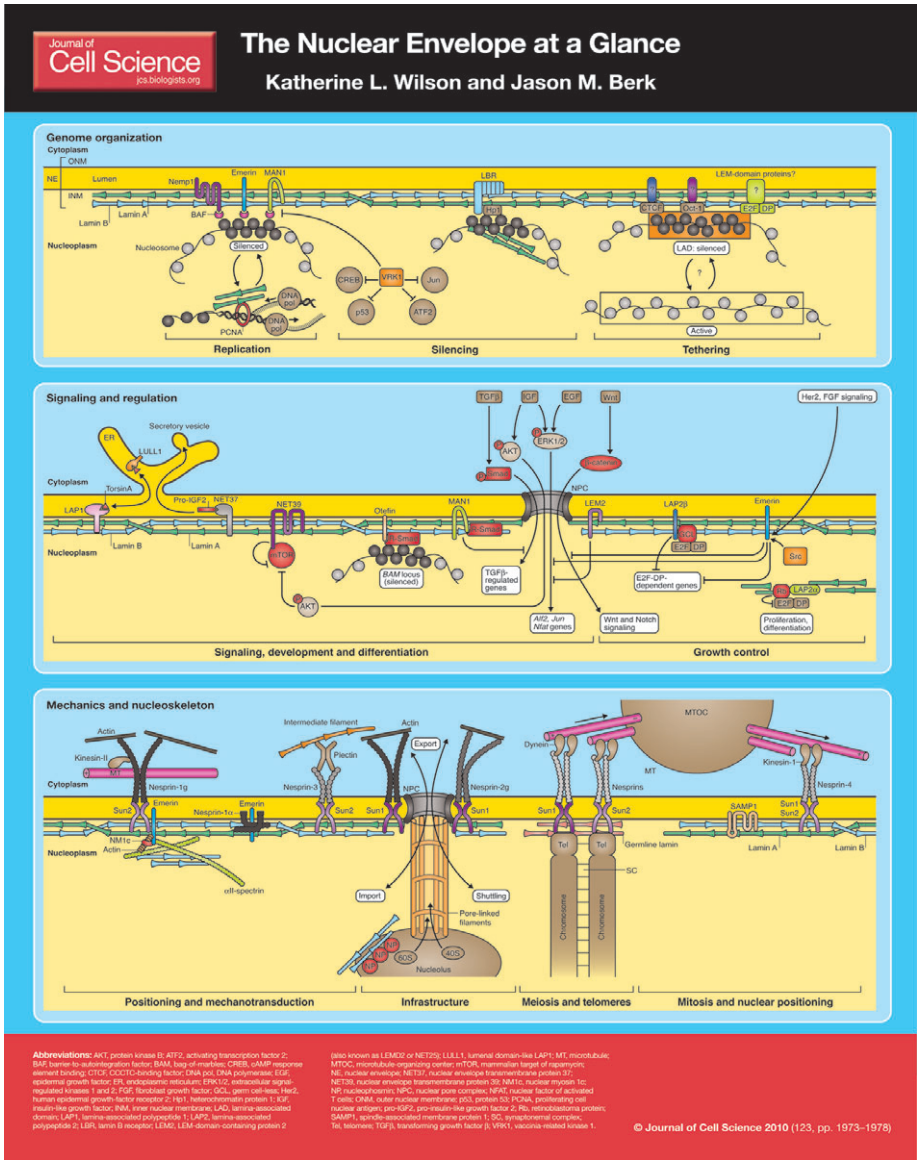
This article is part of a Minifocus on exploring the nucleus. For further reading, please see related articles: 'Integrating one-dimensional and three-dimensional maps of genomes' by Natalia Naumova and Job Dekker (*J. Cell Sci.* **123**, 1979-1988) and 'Connecting the transcription site to the nuclear pore: a multi-tether process regulationg gene expression' by Guennaëlle Dieppois and Françoise Stutz (*J. Cell Sci.* **123**, 1989-1999).

The cell nucleus is the 'mothership' that organizes, protects and regulates the genome. The inner and outer nuclear membranes (INM and ONM, respectively) of the nuclear envelope (NE) have over 60 distinct membrane proteins, whose roles and functional sophistication might rival the cell surface. An appreciation of this functional complexity will be crucial to understand cell biology and to develop treatments for the growing range of human disorders caused by defects in lamins and other components of the NE.

Imagine what would be known about cells today if scientists were aware of only six proteins that localized at the plasma membrane, three of which (by chance) happen to be integrins – we would be unaware of the amazing repertoire of surface proteins that allow cells to network, signal, phagocytose, absorb nutrients, sense and respond to hormones, generate and exploit ion gradients, and so on. Today, such ignorance is almost inconceivable. Yet, until recently, our knowledge of the inner and outer membrane domains of the NE – with its embedded nuclear pore complexes (NPCs) and underlying networks of nuclear intermediate filaments formed by A- and B-type lamins – was precisely this limited.

Early pioneers in nuclear biology discovered major structural proteins, named lamins (Aaronson and Blobel, 1975; Gerace et al., 1978), and a handful of lamin-binding nuclear membrane proteins including the lamin B receptor (LBR) (Worman et al., 1988), MAN1 (Paulin-Levasseur et al., 1996; Lin et al., 2000), lamina-associated polypeptide 1 (LAP1) and LAP2 (Foisner and Gerace, 1993) in vertebrates, and in *Drosophila* two proteins named Otefin (Padan et al., 1990) and Young Arrest (Lopez and Wolfner, 1997). The pace of discovery quickened in 1996 with the realization that a protein named emerin, deficiency in which causes X-linked recessive Emery-Dreifuss muscular dystrophy (Bione et al., 1994), localized at the INM (Manilal et al., 1996; Nagano et al., 1996). The compositional complexity of the NE was subsequently revealed by a proteomic analysis of rat liver nuclei in which 67 new nuclear envelope transmembrane (NET) proteins were identified (Schirmer et al., 2003; Schirmer and Gerace, 2005). Some NE membrane proteins are conserved in metazoans, whereas others are limited to vertebrates or to specific vertebrate tissues, suggesting they have highly specialized roles (Wagner and Krohne, 2007; Gruenbaum et al., 2005).

The idea that NE proteins influence human physiology is inescapably and increasingly supported by disease-gene-mapping studies. Over 20 syndromes in which one or more tissues (e.g. muscle, bone, fat, connective tissue, skin, heart, blood or nervous) are perturbed, brain development is disrupted or accelerated 'aging' occurs, have all been linked to mutations in human genes that encode A- or B-type lamins (*LMNA* or *LMNB1*, *LMNB2*, respectively) or NE membrane proteins that bind lamins, including emerin, LAP2, MAN1, LBR, nesprin-1 (*SYNE1*) or nesprin-2 (*SYNE2*) (Worman and Bonne, 2007; Scaffidi and Misteli, 2008; Wilson and Foisner, 2010). The spectrum of these diseases, collectively known as laminopathies, continues to expand. For example, dystonia, a neurological disease, is caused by mutations in torsin A, a protein in the lumenal space of the NE and endoplasmic reticulum (ER) that monitors oxidative stress and that binds to the related lumenal domains of the INM protein LAP1 and the ER membrane



(See poster insert)

protein LULL1 (Goodchild and Dauer, 2004; Naismith et al., 2009). Each laminopathy inspires new ways to think about how human development and physiology are influenced by specific NE proteins. This article and the accompanying poster illustrate a variety of NE proteins and their roles in genome organization, cell signaling, gene regulation and the nucleoskeleton. Please also see supplementary material Fig. S1 for a 'long view' of the poster and Figs S2-4 for individual poster panels.

Lamin filament networks

A- and B-type lamins form separate, functionally distinct networks of intermediate filaments that concentrate near the NE (the peripheral lamina network); stable lamin structures also exist within the nucleus (the internal lamina) (Bridger et al., 2007; Gruenbaum et al., 2003; Dechat et al., 2008). Almost all characterized INM proteins bind to A- or B-type lamins (or both) directly and are thereby retained at the NE; this is a major mechanism by which lamins contribute to nuclear structure and the functional specialization of the NE. Lamin filaments support two crucial nuclear activities through mechanisms that remain poorly understood: DNA replication [proliferating cell nuclear antigen (PCNA), a processivity factor for DNA polymerase, binds to lamin B (Shumaker et al., 2008)], and transcription (Spann et al., 2002; Shimi et al., 2008). The nucleolus, which lacks lamins, is externally scaffolded by lamin B1, which binds to nucleophosmin and is required for dynamic changes in nucleolar structure (Martin et al., 2009). A-type lamins determine the shape and mechanical stiffness of the nucleus (Dahl et al., 2008) and also influence signaling and gene regulation, for example, by providing binding sites for regulatory proteins, including PKC, Fos and MOK2 (Zastrow et al., 2004; Gonzalez et al., 2008; Gruenbaum et al., 2005; Marmiroli et al., 2009; Harper et al., 2009). A-type lamins contribute to the control of cell proliferation by interacting with LAP2α, retinoblastoma protein (Rb) and inhibitor of growth protein 1 (ING1) (Johnson et al., 2004; Dorner et al., 2007; Han et al., 2008; Naetar and Foisner, 2009). Interestingly, lamin B1, by virtue of its abundance, appears to 'buffer' the cellular response to oxidative stress by binding to and sequestering the transcription factor Oct-1 (Malhas et al., 2009). One consequence of insufficient lamin B1 is that unsequestered (excess of) Oct-1 overactivates mir-31, a small RNA that downregulates the expression of several targets, including the *CDKN2A* locus; this locus encodes both CDKN2B (also known as p16-INK4a), which maintains the Rb checkpoint, and CDKN2A (also known as p14ARF), which activates the p53 pathway (Malhas et al., 2010). Thus A- and B-type lamins also serve non-structural roles in the nucleus.

Genome organization and signaling: major interlinked functions of the NE?

The LAP2, emerin, MAN1 (LEM)-domain family of nuclear proteins appears to have major roles in tethering chromatin, especially silenced chromatin, at the NE (Wagner and Krohne, 2007). All characterized LEM-domain proteins can bind directly to lamins and barrier-to-autointegration factor (BAF), a conserved mobile lamin- and chromatin-binding protein (Margalit et al., 2007a; Montes de Oca et al., 2009). After mitosis, these mutual binding partners (LEM-domain proteins, lamins, BAF) coordinate the reassembly of the NE and lamin networks around chromatin (Margalit et al., 2007a). BAF function is regulated by the conserved kinase VRK1, which causes BAF to release both DNA and LEM-domain proteins (Nichols et al., 2006). This release is important for mitosis (Gorjánácz et al., 2007) and essential to reorganize chromosomes during meiosis (Lancaster et al., 2007).

During interphase, other proteins that are directly phosphorylated and inhibited by VRK1 include the transcription factors p53, Jun, activating transcription factor 2 (ATF2) and cAMP response element binding (CREB) protein (Klerkx et al., 2009). VRK1 promotes the G1-S-phase transition by upregulating the expression of cyclin D1 (Kang et al., 2008). BAF is required to express certain cyclins and for cell-cycle progression in *Drosophila melanogaster* (Furukawa et al., 2003), and facilitates S-phase progression in mammalian cells (Haraguchi et al., 2007). BAF also functions as a tissue-specific transcriptional repressor in *Caenorhabditis elegans* (Margalit et al., 2007b) and during vertebrate eye development (Wang et al., 2002) together with nuclear envelope integral membrane protein 1 (Nemp1), an INM protein (Mamada et al., 2009). BAF can bind histones and associate with specific chromatin regulators (Montes de Oca et al., 2009) but its mechanisms of repression remain unclear.

Signaling cascades can be regulated by INM proteins

Transforming growth factor β (TGFβ) signaling during embryogenesis and vertebrate development is regulated by MAN1, a LEM-domain protein that binds to receptor-regulated Smads (R-Smads) (Pan et al., 2005; Cohen et al., 2007). The *Drosophila* LEM-domain protein Otefin regulates TGFβ signaling and maintains germ-cell fate by binding an R-Smad, and by physically tethering the repressed bag-of-marbles (*bam*) locus at the NE (Jiang et al., 2008). Another LEM-domain protein, emerin, binds directly to β-catenin and inhibits its nuclear accumulation, thereby attenuating Wnt signaling (Markiewicz et al., 2006; Tilgner et al., 2009). Emerin also binds to and feedback-inhibits Lmo7, a signaling transcription factor important in muscle (Holaska et al., 2006). Through unknown mechanisms, the nuclear accumulation of phosphorylated Erk1/2 (also known as mitogen-activated protein kinases 3 and 1, or MAPK3 and MAPK1, respectively) is significantly increased in emerin-null hearts (Muchir et al., 2007) and in emerin-downregulated cells (Muchir et al., 2009), suggesting that emerin also attenuates MAPK signaling. In developing myoblasts, Erk1/2 signaling is inhibited by LEM2 (also known as NET25) (Huber et al., 2009).

Roles in signaling are not exclusive to LEM-domain proteins. Direct binding of mTOR to the recently described INM protein NET39 inhibits the AKT signaling pathway, and insulin-like growth factor 2 (IGF2) production and autocrine signaling (Liu et al., 2009). Intriguingly, the lumenal domain of another INM protein, NET37, has glycosidase activity implicated in the maturation of IGF2; NET37-deficient myoblasts show reduced IGF2 secretion and reduced AKT signaling, suggesting that myogenic differentiation involves inside-out signaling from the nucleoplasm to the NE lumen (Datta et al., 2009). Interestingly, the precursor of heparin-binding epidermal growth factor (HB-EGF), which traffics to the cell surface, can also traffic to the INM (Hieda et al., 2008), but whether this contributes to NE-localized signaling is unknown.

In addition to influencing several signaling cascades, new evidence suggests that emerin and other INM proteins are themselves regulated by signaling. Pathways and kinases that phosphorylate emerin include the human epidermal growth-factor receptor (EGFR)-family member Her2 (also known as Neu) (Bose et al., 2006), fibroblast growth-factor receptor 2IIIb (Luo et al., 2009), protein kinase A (Roberts et al., 2006) and non-receptor tyrosine kinases Src and Abl, which directly phosphorylate emerin and LAP2β (Tifft et al., 2009). These results implicate INM proteins as downstream effectors (and potential regulators) of mitogenic signaling. Differential phosphorylation of emerin might control its binding to chromatin regulators [e.g. BAF, β-catenin, Lmo7, germ cell-less (GCL), Bcl2-associated transcription factor (Btf)] versus structural partners (nesprin-1α, nesprin-2β, Sun1, Sun2, lamins, actin, nuclear myosin 1c), its ability to form specific multiprotein complexes at the

INM (Holaska and Wilson, 2007) or its ability to link mechanical inputs to changes in gene expression, a phenomenon known as mechanotransduction (Lammerding et al., 2005; Holaska, 2008).

Chromatin silencing, tethering and release

In mammals, the ubiquitous transcription factor GCL binds directly to three LEM-domain proteins: LAP2β (Nili et al., 2001), emerin (Holaska et al., 2003) and MAN1 (Mansharamani and Wilson, 2005). In *Drosophila*, GCL is required to silence transcription in the germline (Leatherman et al., 2002). GCL and its interactions with LEM-domain proteins are interesting for several reasons. First, GCL binds the DP subunit of E2F-DP heterodimers and represses the transcription of E2F-DP-dependent genes (de la Luna et al., 1999); the tumor suppressor Rb represses such genes by binding the E2F subunit. Second, GCL appears to require LEM-domain proteins as co-repressors in vivo [as shown for LAP2β and emerin (Nili et al., 2001; Holaska and Wilson, 2006)], and E2F-DP-dependent gene regulation is disrupted in emerin-deficient muscle (Melcon et al., 2006). Third, E2F-DP-binding sites on chromatin were identified as border elements for large (~550 kbp) regions of human chromosomes known as lamina-associated domains (LADs) that contact lamin B1 and emerin (Guelen et al., 2008). Other LAD-border elements included binding sites for CTCF (a chromatin insulator), CpG islands (sites of DNA methylation) and outward-facing promoters (Guelen et al., 2008). There is substantial (80%) overlap between LADs and independently identified large organized chromatin regions (LOCKs) that, when repressed, are enriched in the silencing mark H3K9Me2 (dimethylated histone H3, lysine 9) (Wen et al., 2009). Thus, transcriptional repression in differentiated mammalian cells involves the tethering of specific regions of silenced chromatin to lamins and the NE, consistent with evidence that chromatin located near the NE is typically silenced (Akhtar and Gasser, 2007). Interestingly, developmentally regulated promoters (not the coding or 3′-untranslated regions) have active, positive roles in releasing silent chromatin from the NE to the interior (Meister et al., 2010). In primary human fibroblasts certain chromosomes are relocated either toward or away from the NE within 15 minutes after serum removal; this movement requires nuclear myosin 1c (Mehta et al., 2010).

Conversely, however, some NE-localized genes are expressed (Finlan et al., 2008), revealing large gaps in our understanding of the mechanisms and consequences of chromatin attachment to the NE. For example, LBR binds to B-type lamins and appears to both tether and compact silenced chromatin, in part by binding to heterochromatin protein 1 (Hp1) (Ye et al., 1997; Li et al., 2003) and potentially also to methyl-CpG-binding protein 2 (MeCP2) (Guarda et al., 2009). However, the membrane domain of LBR has sterol reductase activity that is important for cholesterol metabolism during human blood and bone development (Hoffmann et al., 2007). Another INM protein, nurim, is extraordinarily resistant to biochemical extraction, and is homologous both to isoprenylcysteine carboxymethyltransferases (which process CaaX motifs found in lamins and Ras) and to a *Mycobacterium tuberculosis* protein of unknown function (Hofemeister and O'Hare, 2005). These findings illustrate an emerging theme: NE membrane proteins can have unexpected roles in cells, tissues and disease.

During late S phase, heterochromatin detaches from the NE, moves to the nuclear interior for DNA replication and then returns to the NE (Li et al., 1998). One can speculate that this remarkable chain of events involves molecular motors and is regulated by signals that permit the release and subsequent re-attachment of transcriptionally silent (LOCK'd), tethered (LAD'd) chromatin at the NE.

Mechanical and nucleoskeletal roles of NE proteins

Specific proteins embedded in the INM and ONM interact to form structures that span the NE and mechanically link lamin filaments to the cytoskeleton (Lee et al., 2002; Crisp et al., 2006; Starr, 2009). The discovery of these structures, termed linker of nucleoskeleton and cytoskeleton (LINC) complexes (Crisp et al., 2006) was a convergence of studies done in yeast (*S. pombe*), worms (*C. elegans*), flies (*Drosophila*) and cultured mammalian cells, illustrating the value of curiosity-driven research in diverse organisms. KASH-domain proteins (e.g. giant isoforms of nesprin-1 and nesprin-2) embedded in the ONM can bind directly and simultaneously to a cytoskeletal component (e.g. actin filaments, plectin or microtubule-dependent motors) and to the NE-lumenal domain of SUN-domain proteins embedded in the INM (Burke and Roux, 2009). SUN-domain proteins, in turn, bind directly to lamins, forming a basic mechanical unit that spans the NE (Tzur et al., 2006). Sun1 and Sun2 have both overlapping and distinct roles (Lei et al., 2009; Olins et al., 2009). For example, Sun1 concentrates near NPCs and is required to space NPCs; in addition, Sun1 preferentially binds to the precursor form of lamin A, implying roles in lamin A maturation or assembly (Liu et al., 2007; Haque et al., 2010). By contrast, Sun2 is not NPC-associated and binds equally well to both precursor and mature lamin A, consistent with stable anchoring to lamin filaments (Liu et al., 2007). Sun1 and Sun2 also bind directly to emerin, implicating this INM protein as a core LINC complex component (Haque et al., 2010); indeed, in skin fibroblasts, emerin is required to localize the nesprin-2 giant (nesprin-2g) at the ONM (Randles et al., 2010). Interestingly, torsinA – the above-mentioned NE- and ER-lumen protein – is an ATPase that can detach LINC complexes formed by Sun2, nesprin-2 and nesprin-3, but does not affect Sun1 or NPCs (Vander Heyden et al., 2009). This suggests that LINC complexes are actively and selectively remodeled.

Mammals have four known nesprin genes. The genes for nesprin-1 and nesprin-2 (*Syne1* and *Syne2*, respectively) each express numerous protein isoforms, the largest of which are ~1 MDa (known as giant isoforms) (Warren et al., 2005). Most nesprins have multiple spectrin-repeat domains, suggesting that they contribute both stiffness and extensibility to nuclear structure (Dahl et al., 2008). The giant nesprin-1 and nesprin-2 isoforms localize to the ONM, whereas others are found specifically at the INM, or in the nuclear interior, cytoplasm (e.g. in muscle sarcomeres), Golgi membranes or elsewhere (Warren et al., 2005). As nesprin-1α and nesprin-3α were shown to form homodimers (Mislow et al., 2002; Ketema et al., 2007), the poster speculatively depicts all nesprins as homodimers. ONM-localized nesprin-1 and nesprin-2 giants bind directly to F-actin. Interestingly, the nesprin-1 giant can also associate with kinesin-II – a plus-end-directed microtubule motor – during mitosis, and this interaction might be important for cytokinesis (Fan and Beck, 2004). Little is known about how the attachment of LINC complexes to the nucleoskeleton or cytoskeleton is regulated. However, one interesting possibility comes from studies of the postsynaptic neuromuscular junction, where the receptor tyrosine kinase muscle-specific kinase (MuSK) – mutations in which are linked to myasthenia gravis (Stiegler et al., 2009) – associates with the nesprin-1 and nesprin-2 giants (Apel et al., 2000). Smaller INM-localized isoforms, including nesprin-1α and nesprin-2β, predominate in muscle (Randles et al., 2010); they do not bind to actin, but instead bind to lamins and the INM protein emerin (Mislow et al., 2002; Zhang et al., 2005).

Roles for NE proteins in moving enormous cargo

Nesprin-3α (~116 kDa) is an ONM protein that binds to plectin (or to dystonin in neurons) and

thereby links the NE to cytoplasmic intermediate filaments (Wilhelmsen et al., 2005; Young and Kothary, 2008). In keratinocytes, plectin provides a one-step bridge between nesprin-3α at the ONM and integrin α6β4 at the cell surface (Wilhelmsen et al., 2005). The β-isoform of nesprin-3 lacks the plectin/dystonin-binding domain. Nesprin-4 is expressed mainly in secretory epithelia, localizes to the ONM and binds the plus-end-directed microtubule motor kinesin-1; together, nesprin-4 and kinesin-1 are proposed to push the nucleus away from the microtubule organizing center (MTOC) and Golgi complex to achieve a basal position within a polarized cell (Roux et al., 2009). In *C. elegans*, the ONM-localized KASH protein Unc-83 specifically binds to the light chain (KLC-2) of kinesin-1 (Meyerzon et al., 2009), whereas a different KASH protein, ZYG-12, is involved in at least two activities: dynein-mediated nuclear movement during embryogenesis and chromocenter-tethered chromosome movement during meiosis (Penkner et al., 2009; Sato et al., 2009).

Nuclei are actively repositioned in cells by microtubule-dependent motors during development and differentiation [e.g. in neurons (Gros-Louis et al., 2007; Starr, 2009)], and are also repositioned relative to the MTOC each time a motile cell changes direction (Gomes et al., 2005). The highly conserved INM protein SAMP1 is required to anchor the MTOC near the nucleus; SAMP1 also defines a novel membrane that colocalizes with the mitotic spindle (Buch et al., 2009). How SAMP1 is coupled to the MTOC during interphase and the nature of its mitotic role are intriguing questions. During meiosis, the telomeres of paired chromosomes are anchored to the NE by Sun proteins and germ-cell-specific lamins, then dragged long distances along the NE by microtubule-dependent motors in the cytoplasm. These coordinated movements are crucial for chromosome pairing and recombination in *C. elegans* (Penkner et al., 2007), require Sun1 and Sun2 in mammals (Ding et al., 2007; Schmitt et al., 2007) and are conserved in *S. pombe* (Chikashige et al., 2007). Thus, nuclear membrane proteins have ancient roles in nuclear movement and sexual recombination.

Perspectives

Many challenging questions about the nucleus beckon. What are the mechanisms of chromosome- and gene-tethering to the NE? How are these tethers regulated? How do potentially hundreds of different NE membrane proteins influence the genome, cellular signaling pathways and molecular biology? What roles are played by the NE-anchored nucleoskeleton that, in addition to lamins, includes myosins (Louvet and Percipalle, 2009), actin (Gieni and Hendzel, 2009), spectrin (Young and Kothary, 2005), protein 4.1 (Krauss et al., 2003; Kiseleva et al., 2004) and titin (Machado et al., 1998; Zastrow et al., 2006)? With further exploration of the structure and function of NE components, it is certain that more surprises, new insights into cell biology and human physiology, and new targets for molecular medicine await us.

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