Reversal of laminopathies: the curious case of SUN1
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Mutations in the LMNA gene are associated with a spectrum of human dystrophic diseases termed the “nuclear laminopathies.” We recently found that the accumulation of the inner nuclear envelope protein SUN1 is pathogenic in progeric and dystrophic laminopathies. This conclusion arose from the unexpected observation that the deletion of Sun1, instead of accelerating aging, actually ameliorated the progeric and dystrophic phenotypes in Lmna-deficient mice. In human cells, knocking down SUN1 corrected the nuclear aberrancies and the senescent tendencies of HGPS (Hutchinson-Gilford progeria syndrome) skin fibroblasts. Here we offer additional comments on the contributions of SUN1 and the process of normal protein turnover to cellular aging.

Nuclear lamin A is a component of the nuclear lamina associated with the nucleoplasmic surface of the inner nuclear membrane (INM).1,2 Mutations in the LMNA gene cause a spectrum of human dystrophic diseases, including cardiomyopathy, neurodystrophy, lipodystrophy and premature aging, collectively termed the “nuclear laminopathies.”1,3-5 Since the 1980s, an increasing understanding of nuclear lamin functions has emerged; however, questions remain regarding the causality between mutations in lamin A and various tissue-specific debilitating disorders.1,3-5-10 The SUN-domain proteins interact like “braces” on the INM that bridge the connection with the actin cytoskeleton (i.e., Syne1 and Syne2) isoforms localize to the outer nuclear membrane where they connect the nucleoskeleton and cytoskeleton via an N-terminal actin binding domain.11,12

Mammals have four SUN-domain proteins, SUN1, SUN2, SUN3 and SPAG4. Mammals have four SUN-domain proteins, SUN1, SUN2, SUN3 and SPAG4. SUN1 and SUN2 are in the INM like proteins that translocate to telo-meres in the prophase of meiotic cells.11,12

Keywords: SUN1, nuclear envelope, progeria, lamin, aging
Abbreviations: SUN, Sad1-UNC-84 homology; HGPS, Hutchinson-Gilford progeria syndrome; EDMD, Emery-Dreifuss muscular dystrophy

Extra View to: CY Chen, YH Chi, RA Mutalif, MF Starost, TG Myers, SA Anderson, CL Stewart, KT Jeang. Accumulation of the inner nuclear envelope protein Sun1 is pathogenic in progeric and dystrophic laminopathies. Cell 2012; 149: 565-77

http://dx.doi.org/10.1016/j.cell.2012.01.059; PMID: 22541428; http://dx.doi.org/10.4161/nucl.21714

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1. Chi YH, Chen C-Y, Mutalif R, Anderson SA, Starost TG, Myers TG, Jeang KT. Accumulation of the inner nuclear envelope protein Sun1 is pathogenic in progeric and dystrophic laminopathies. Cell 2012; 149: 565-77

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is a metalloprotease of prelamin A). The pathologic phenotype of Zmpste24−/− mice, which arises from failed processing of prelamin A, was found to be alleviated by the additional knock out of p53 (i.e., Zmpste24−/−p53−/− mouse). Increased proliferation of human HGPS cells was also seen when p53 was inactivated by the human papillomavirus (HPV) E6 protein. In other words, the genetic findings appear to be mechanistically distinct from Sun1 deletion-mediated increase in the longevity of Lmna−−/− deficient mice which occurs in a p53 wild type setting.13,14 What are the explanations for the increased longevity of Sun1−/− Lmna−−/− and Sun1−/− LmnaΔv mice? By analyzing Sun1 expression in mouse embryonic fibroblasts (MEFs), we found that Lmna−−/− and LmnaΔv, but not wild type, cells showed significant over accumulation of SUN1 protein in the nuclear envelope (NE) and the Golgi apparatus. This over accumulation arises from reduced protein turnover, not increased gene transcription. Moreover, the mislocation of INM protein SUN1 into the Golgi triggers nuclear envelope rupture, a phenotype that is commonly seen in Lmna−−/− MEFs. Similar to the findings in Lmna−−/− MEFs, increased SUN1 expression was also found in human HGPS cells, suggesting that a common pathogenic event in Lmna−−/−, LmnaΔv, and HGPS cells converges at SUN1 protein misaccumulation.

Because Lmna−−/−, LmnaSun1−/−, LmnaΔv or LmnaΔvSun1−/− mice do not express wild type lamin A, a previous explanation for lamin A-associated dystrophic or progeric diseases was that they occur in these mice because of loss in lamin A function.8,9 On the other hand, our new SUN1 observations add another wrinkle to the aging question.8 SUN1 mislocation and its over accumulation suggest that laminopathies may also in part be caused through an organelle storage disorder-like mechanism. Thus a part of the pathologic impetus of laminopathies may arise, like other age-dependent degenerative diseases such as lysosomal storage diseases (e.g., Fabry, Tay-Sachs, Gaucher, Niemann-Pick, Pompe and Krabbe) and ER storage diseases (e.g., cystic fibrosis, α-antitrypsin deficiency, hereditary hypothyroidism, and progeria type I, II, and IV deficiency), by the “over stuffing” of misaccumulated material in subcellular organelles (e.g., lysosomes, ER, Golgi or nuclear envelope) that elicits stress signals unfavorable to normal cellular physiology.12,20 A feature common to the above metabolic disorders is that the affected individual is normal at birth, but manifests progressive symptoms as they age. Unlike early passaged Lmna−−/− deficient MEFs, in multiply passaged human HGPS fibroblasts, a major accumulation of SUN1 in the Golgi was not seen.16 This could be because the over accumulation of SUN1 is potently toxic in HGPS cells; hence, all such late passaged cells are eliminated due to non-viability. On the other hand, although there was no Golgi over accumulation, multiply-passaged HGPS cells do show significant over accumulation of SUN1 in the NE. If SUN1-Golgi over accumulated cells are eliminated while SUN1-NE over accumulated counterparts persist, this would suggest that the latter mislocation creates a milder, more tolerated phenotype and could represent a form of “NE storage disease.” Indeed, as frequently noted, HGPS patients are born normal, but quickly develop age- associated changes including alopecia, atherosclerosis, osteodystrophy and severe hipo-dystrophy between 12 and 18 mo;16 these changes become more severe as the individuals age. An intriguing question from our work is why does SUN1 over accumulate in the NE and Golgi? A full answer awaits better characterization of SUN1 sequence determinants for localization in and trafficking to the NE, Golgi and ER.16 Nevertheless, we envision that the following processes may be relevant. In anterograde transport, proteins synthesized in the ER exit to transport vesicles that bud from the ER and congregate at the ER-Golgi intermediate compartment (ERGIC).18 By vesicles or tubules they are delivered to the cis-Golgi and then move (by vesicular transport or cisternal maturation) through the Golgi cisternae to the trans-Golgi network (TGN). Secretory proteins that fail to exit the ER result in protein accumulation and pathological ER storage. Consequently, retrograde (Golgi-to-ER) transport retrieves ER residents and other constituents that cycle between these two compartments.29 Furthermore, because the NE is composed of two lipid membranes that are continuous with the ER, one view is that INM proteins synthesized in the ER are transported along the rough ER, through the nuclear pore complex to arrive at the inner nuclear membrane.13 SUN1 accumulation in HGPS and the Golgi represents two opposite destinations of ER retrograde and anterograde trafficking (Fig. 1). Although yet unknown, SUN1 may undergo post-translational modifications through its lamin A dependent interactions in the NE. In the absence of lamin A, SUN1 may not be modified properly and thus cannot achieve normal turnover; and this could explain its proclivity for over accumulation. Possibly, over accumulated SUN1 may aggregate into a conformation that favors ER-Golgi anterograde transport into the Golgi. In the case of HGPS, which heterozygously expresses one wild type allele of lamin A and one mutant allele of lamin A, Lmna−−/−, the single wild type copy of lamin A may produce enough functional lamin A protein to sufficiently direct the appropriate localization of SUN1 to the NE.

Why do other INM proteins not over accumulate? Perhaps they do. HGPS cells show characteristic NPC clustering,20 Emerin mislocalization20 and LAP2 loss,20 although SUN2 localization seems to be normal.16,21 What governs (mis)localization is not fully understood, but we hypothesize that the INM proteins may distribute non-randomly and may occupy discrete “territories” in the inner nuclear membrane similar to the concept of “chromosome territories.”22 Thus, the INM proteins may migrate to designated loci of the INM for various nuclear functions; and lamin A may be one of several determinants that govern these movements. In the absence of functional lamin A, these INM proteins may disseminate freely in various context-dependent manners.

What these new findings mean for therapeutic treatment of HGPS-like diseases remains to be verified. Currently, one line of thought is that HGPS arises from a dominant mutant form of prelamin A protein (named LAD50 or progerin) that contains a CaaX motif which can
be durably farnesylated. Farnesylated progerin is considered to be pathogenic, and thus farnesyltransferase inhibitors (FTIs) that were originally developed to block the farnesylation of Ras onco-gene for the treatment of cancer has been applied with the goal of treating HGPS. Using a FTI, R115777 (Tipifarnib; also known as Zarnestra), Mallampalli, et al. demonstrated that FTI treatment of cells reversed the abnormal nuclear morphology associated with progerin. On the other hand other investigators have not always replicated the same outcome. If the mislocation and misaccumulation in cells of INM proteins such as SUN1 are further contributors to the pathology of HGPS-like diseases, then FTI treatments are unlikely to correct these additional causes. Interestingly, treatment of HGPS cells with rapamycin, an mTOR inhibitor and a strong immunosuppressant that is also a potent inducer of the autophagy pathway, was found to alleviate in part the pathologies of HGPS cells such as nuclear blebbing and cellular senescence (Fig. 1). This result makes mechanistic sense if rapamycin treatment enhances cellular degradation of over accumulated and mislocated nuclear envelope proteins like LAΔ9 and SUN1 through its induction of autophagy (Fig. 1). Interestingly, rapamycin treatment of wild type mice has been shown to prolong their life span by 14%, suggesting that physiological aging and its consequences may also be influenced by age-dependent inefficiencies in normal protein degradation/turnover. The salient observation from our new study is that the elimination of an INM protein, SUN1, ameliorates cellular and organ pathologies of premature aging in mice. A correlative interpretation of our work is that aging (whether premature or physiological) is a consequence of the improper disposal of accumulated cellular proteins that occur with extreme robustness in the Lmna-deficient mice. If aging is a result of abnormal protein turnover, then treatments for premature aging HGPS-like diseases should consider alleviating pathogenic upstream (i.e., treating progerin) as well as downstream (i.e., SUN1 misaccumulation) events. Without addressing downstream protein misaccumulation, therapeutic resolution of progeria or EDMD pathologies are unlikely to be achieved.

Acknowledgments
Our work was supported by NIAID intramural funds, the NHRI, Taiwan (NHRI 04A1-CSPP1-014), and NSC, Taiwan (NSC 98-2320-B-140-009-MY3).
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