The Nuclear Envelope: An Intriguing Focal Point for Neurogenetic Disease

Howard J. Worman · William T. Dauer

Published online: 14 August 2014

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Abstract Mutations in genes encoding nuclear envelope proteins cause a wide range of inherited diseases, many of which are neurological. We review the genetic causes and what little is known about pathogenesis of these nuclear envelopopathies that primarily affect striated muscle, peripheral nerve and the central nervous system. We conclude by providing examples of experimental therapeutic approaches to these rare but important neuromuscular diseases.

Key Words Nuclear envelope · lamin · muscular dystrophy · dystonia · leukodystrophy

Introduction

The nuclear envelope has traditionally been viewed simply as a physical barrier separating the nucleus from the cytoplasm in eukaryotic cells. Until approximately the mid 1990s, most research on the nuclear envelope focused on nucleocytoplasmic transport and the disassembly/reassembly of the nuclear envelope during mitosis in cycling cells. In 1994, Toniolo and colleagues [1] identified the gene mutated in X-linked Emery-Dreifuss muscular dystrophy (EDMD) and 2 years later the protein product, emerin, was localized to the nuclear envelope

[2, 3]. This was the first example of a human disease caused by nuclear envelope-localized cellular dysfunction. This discovery was surprising, particularly because of the remarkable tissue specificity resulting from dysfunction of a protein that is widely expressed in the nucleus, “the” central organelle; existing dogma at the time predicted that any disruption of nuclear function would either be lethal or have myriad consequences in many tissues. In fact, this discovery was the first of many mutations in genes encoding nuclear envelope proteins being linked to diseases that specifically disrupt muscle and neural tissue. In this review, we provide an overview of the structure of the nuclear envelope and the neurological disorders caused by mutations in genes encoding some of its protein components. We also consider how current views of nuclear membrane biology inform the development of potential therapeutic strategies.

Nuclear Envelope

The nuclear envelope is composed of the nuclear membranes, nuclear lamina and nuclear pore complexes (Fig. 1). The nuclear membranes are interconnected, and continuous with the rough endoplasmic reticulum (ER), but divided into three morphologically distinct domains. The outer nuclear membrane is directly continuous with the rough ER, and similarly has ribosomes on its outer surface. The inner nuclear membrane is associated with an underlying nuclear lamina (composed of lamin proteins) and is separated from the outer nuclear membrane by the perinuclear space, a continuation of the ER lumen. The “pore membrane” connects the inner and outer nuclear membranes at nuclear pore complexes. Specific integral proteins are concentrated in these nuclear envelope membrane domains in interphase cells. The inner nuclear membrane of mammalian cells appears to contain approximately 80 transmembrane proteins, several of which interact with the nuclear lamina [5]. Three integral proteins

Electronic supplementary material The online version of this article (doi:10.1007/s13311-014-0296-8) contains supplementary material, which is available to authorized users.

H. J. Worman (✉)

Department of Medicine and Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA
e-mail: hjw14@columbia.edu

W. T. Dauer (✉)

Department of Neurology and Department of Cell and Developmental Biology, University of Michigan Medical School, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA
e-mail: dauer@umich.edu

Fig. 1 Schematic diagram of a typical eukaryotic cell with a portion of the nuclear envelope indicated by a *rectangle*. A schematic blow-up of the nuclear envelope to the *right* shows that it is composed the nuclear membranes, nuclear pore complexes, and nuclear lamina. The perinuclear space, a continuation of the ER lumen, separates the inner from out nuclear membranes. Proteins secreted into the ER, such as torsinA (TOR1A), can therefore reach the perinuclear space. KASH domain proteins such as large actin-binding nesprin-2 isoforms concentrate in the outer nuclear membrane by binding to inner nuclear membrane SUN proteins within the perinuclear space. The nuclear lamina is a meshwork of intermediate filaments on the inner aspect of the inner nuclear membrane and is composed of proteins called lamins. The lamina is associated with integral proteins of the inner nuclear membrane, with examples shown being MAN1, lamina-associated polypeptide-1 (LAP1), a SUN protein, lamina-associated polypeptide-2 β (LAP2 2β), lamin B receptor

(LBR), emerlin, and a small nesprin-1 isoform. The general structure of lamins is shown (not to scale) in the lower insert. Lamins have α -helical rod domains that are conserved among all intermediate filament proteins and head and tail domains that vary in sequence among members of intermediate filament protein family. Within the tail domain, lamins contain a nuclear localization signal (NLS) that is recognized for active transport into the nucleus and an immunoglobulin-like fold (Ig fold). Most lamins have a CAAX motif at their carboxyl-termini that acts as a signal to trigger a series of chemical reactions leading to modification of the cysteine by farnesylation and carboxymethylation. Reprinted from *Developmental Cell*, Volume 17 / Issue 5, William T. Dauer and Howard J. Worman, The Nuclear Envelope as a Signaling Node in Development and Disease, Pages 626-638, Copyright 2009, with permission from Elsevier (reference [4]).

have been localized to the mammalian pore membranes [6–9] and these interact with other nuclear pore complex proteins. The outer nuclear membrane generally shares transmembrane proteins with the directly contiguous rough ER. However, a subset of specialized KASH domain proteins that form a protein “bridge” spanning the nuclear envelope uniquely characterize the outer nuclear membrane. These KASH domain proteins (generally referred to as nesprins in mammals) are integral proteins of the outer nuclear membrane. Nesprins bind to cytoskeletal elements in the cytoplasm and project into the perinuclear space, where they interact with inner nuclear membrane spanning proteins termed “SUN” domain proteins [10]

(Fig. 1). This complex of nesprin and SUN proteins that spans the inner and outer membranes, and binds within the perinuclear space, is referred to as the linker of the nucleoskeleton and cytoskeleton (LINC) complex [10]. This complex has an essential role in nuclear positioning and migration [11].

The nuclear lamina is a meshwork of intermediate filament proteins call lamins and is localized primarily on the inner aspect of the inner nuclear membrane [12–16] (Fig. 1). Lamins polymerize to form the lamina and also interact with several transmembrane proteins of the inner nuclear membrane [17]. Among these, lamins interact with SUN proteins; hence, via the LINC complex, the nuclear lamina and

cytoskeleton are connected by a series of protein-protein interactions [10, 11]. In mammals, three genes encode nuclear lamins. Human *LMNA* encodes the “A-type” lamins, lamin A and lamin C, which are expressed in most differentiated somatic cells [18]. These proteins are identical for the first 566 amino acids and differ in their carboxyl-terminal tail domains [13, 15, 18]. Human *LMNB1* encodes lamin B1 and *LMNB2* encodes lamin B2. These “B-type” lamins are expressed in all or most somatic cells [19, 20]. All of these proteins, except lamin C, are posttranslationally modified by farnesylation and carboxymethylation at a carboxyl-terminal cysteine-aliphatic-aliphatic-any (“CAAX”) amino acid motif. While the B-type lamins remain farnesylated, prelamin A, the precursor of lamin A, undergoes proteolytic processing by the zinc metalloproteinase ZMPSTE24. ZMPSTE24 cleaves prelamin A 15 amino acids from the farnesylated cysteine, to produce mature lamin A [21, 22].

The nuclear pore complexes are macromolecular structures associated with the pore membrane, where the inner and outer nuclear membranes join. Passive diffusion and active transport between the nucleus and cytoplasm occurs via nuclear pore complexes. Nuclear pore complex structure and transport mechanisms are active areas of research, the details of which have recently been covered in several excellent reviews (for examples see Hoelz et al. [23], Fernandez-Martinez and Rout [24], Bilokapic and Schwartz [25], and Adams and Wentz [26]). Via direct interactions with chromatin, pore complexes may also function in regulating gene expression [27, 28]. For the purpose of this review, it is essential to recall that the pore complexes are composed of multiple copies of approximately 30 different proteins, many of which are known as nucleoporins. Specific groups of these nucleoporins interact to form distinct repetitive subunits that assemble to form the pore complexes. Whereas overall pore complex structure appears to be highly conserved in all cells, the specific protein composition may vary among cell types and tissues [29].

Muscular Dystrophy

The first human disease linked to mutations in a gene encoding a nuclear envelope protein was X-linked EDMD. Cestan and LeJonne at l'Hôpital de la Salpêtrière published what may have been the first description of this disorder at the beginning of the twentieth century [30]. In 1966, Emery and Dreifuss provided the first complete description of X-linked EDMD in a family from Virginia [31]. Rowland et al. [32] at Columbia University reported an additional case in 1979 and applied the term “Emery-Dreifuss type” muscular dystrophy. Classically, skeletal muscle involvement in EDMD is characterized clinically by slowly progressive muscle weakness and wasting in a scapulo-humeroperoneal distribution and early contractures of the elbows, ankles and posterior neck.

Contractures are usually the first clinical sign, and slowly progressive muscle weakness and wasting typically begin during the second decade. While the severity of the contractures and weakness is quite variable and can limit activity, it is never life threatening. Eventually, however, patients develop dilated cardiomyopathy, typically with early atrioventricular conduction block and later ventricular dysrhythmias. Sudden cardiac death and end-stage heart failure are the life threatening features [33].

Bione et al. [1] used positional cloning to map the gene responsible for X-linked EDMD to distal Xq28. They identified five patients with unique mutations in a gene they called *STA*, now called *EMD*, which were predicted to result in the loss of all or part of the protein. They named the encoded protein emerin, after Alan Emery, and reported that it had a putative single transmembrane segment. Emerin was expressed in most cells examined, not only striated muscle. Subsequently, emerin was localized to the nuclear envelope and shown to be absent from skeletal muscle of affected individuals [2, 3]. Most *EMD* mutations are truncations and lead to lack of protein expression, although some missense mutations have been described [34].

The EDMD phenotype can also be inherited in an autosomal dominant manner. In 1999, Bonne et al. [35] studied five families with autosomal dominant EDMD and identified one nonsense and three missense mutations in *LMNA*, which encodes A-type nuclear lamins. Later that year, Sullivan et al. [35] showed that germline deletion of *Lmna* in mice led to postnatal growth retardation, early lethality and features of cardiomyopathy and regionally localized skeletal muscular dystrophy. Sullivan et al. [35] also showed that A-type lamins were necessary for localization of emerin in the inner nuclear membrane, the first evidence that these proteins interact. Hence, alterations in two interacting proteins in the nuclear envelope were shown to cause the same muscular dystrophy/cardiomyopathy phenotype.

Subsequent to the identification of *EMD* and *LMNA* mutations as genetic causes of EDMD, the phenotypic spectrum of muscle involvement became better understood. The same mutations in *LMNA* that cause classical EDMD can also cause a limb-girdle muscular dystrophy with dilated cardiomyopathy and cardiomyopathy with minimal skeletal muscle involvement [36, 37]. These different clinical phenotypes—or overlapping patterns—may even be present in the same family [38, 39]. A similar variability in clinical phenotype is also characteristic of mutations in *EMD* encoding emerin [40–42]. Mutations in *LMNA* may also produce a syndrome of congenital muscular dystrophy [43, 44]. All of these phenotypes share at least some features with classical EDMD, with heart involvement being the most consistent feature. Intriguingly, mutations in *LMNA* can also cause peripheral neuropathy (see below) and non-neuromuscular disorders, including partial lipodystrophy and progeria syndromes, a discussion of which

is beyond the scope of this review but can be found elsewhere [4, 45, 46].

A remarkable number of additional reports further establish a connection between nuclear membrane alterations and myopathy, most of which are corroborated by mouse genetic studies. Small series and case reports have implicated the disruption of several other genes encoding nuclear envelope proteins as causes of muscular dystrophy/cardiomyopathy and EDMD-like phenotypes. Mutation of the *TMPO* gene has been reported in two brothers with dilated cardiomyopathy [47]. *TMPO* encodes multiple transmembrane and nucleoplasmic isoforms of lamina-associated polypeptide (LAP) 2. This report is consistent with the finding that depletion of the nucleoplasmic alpha isoform of LAP2 causes cardiac dysfunction in mice [48]. Mutations and polymorphisms in *SYNE1* and *SYNE2* genes, which respectively encode the KASH domain proteins nesprin-1 and nesprin-2, have also been reported in patients with muscular dystrophy and cardiomyopathy; disruption of the orthologous genes in mice causes skeletal and cardiac myopathy [49–52]. A mutation in *SYNE1* has also been linked to an autosomal recessive form of arthrogryposis multiplex congenita, a syndrome of congenital joint contractures that results from reduced fetal movement [53]. A mutation in *TOR1AIP1* encoding LAP1 has been described in two affected family members in with muscular dystrophy and cardiomyopathy [54]. LAP1 binds to lamins and emerin and its conditional deletion from muscle in mouse causes profound muscular dystrophy, cardiac dysfunction and early lethality [55, 56]. Heterozygous missense mutations in *TMEM43* encoding an integral inner nuclear membrane protein called LUMA have also been reported in two patients with EDMD-like phenotypes [57].

Despite the remarkable link between nuclear envelope defects and myopathy, it has been extraordinarily challenging to unravel the pathogenic mechanisms underlying this connection. The prevailing hypothesis is that the constant mechanical stress experienced by striated muscle is the key factor responsible for the unique vulnerability of this tissue. According to this notion, abnormalities of the nuclear membrane proteome, particularly to the underlying lamina, result in a more fragile nucleus that is easily disrupted by mechanical stress. Some support for this hypothesis comes from the finding of abnormal mechanical properties in cells with alterations in A-type lamins and emerin [58–61]. Similarly, there is abnormal activation of stress-induced signaling pathways, such as mitogen-activated protein kinase cascades, in striated muscle of mice bearing myopathy-causing *Lmna* mutations [62, 63]. Abnormal nuclear positioning, which can potentially increase susceptibility to damage by mechanical force, also results from pathogenic defects in A-type lamins and emerin [64, 65]. An alternative to the “mechanical stress” hypothesis is the notion that alterations in the nuclear envelope cause pathogenic changes in gene expression that are tissue-specific

[66]. These possibilities are not mutually exclusive, as mechanical forces on the nuclear membrane are well documented to alter gene expression and these concepts are the focus of current research [67]. Finally, while A-type lamins, emerin, nesprins and SUN proteins are expressed to some degree in most terminally differentiated cells, more subtle differences in tissue expression may play a role in determining which organs are affected in disease. For example, there is very little lamin A present in mammalian brain as a result of microRNA regulation [68]. More detailed analysis of tissue-specific and cell-specific expression of nuclear envelope proteins, particularly in striated muscle at different stages of development, will be necessary to better understand why striated muscle is so frequently disrupted in nuclear envelopopathies.

Peripheral Neuropathy

As noted above, mutations in *LMNA* cause several diseases in addition to myopathies [4, 45, 46]. In 2002, De Sandre-Giovannoli et al. [69] reported segregation of a unique homozygous *LMNA* mutation in three Algerian families with autosomal recessive Charcot-Marie-Tooth type 2 disease. The mutation, an arginine to cysteine amino substitution at residue 298 of lamins A and C, has subsequently been reported in affected members from seven different families, all from Algeria [70]. De Sandre-Giovannoli et al. [69] further showed that the sciatic nerves of *Lmna* null mice had reduced axon density, axonal enlargement and nonmyelinated axons. However, mice in which the specific pathogenic mutation has been introduced into *Lmna* do not exhibit peripheral neuropathy [71]. These mice do express elevated levels of peripheral myelin protein 22 in their sciatic nerves, confirming an effect of the mutation in peripheral nerves. Peripheral neuropathy has also been described in connection with other mutations in *LMNA*. These reports come from patients with *LMNA* mutation who develop peripheral neuropathy concurrent with muscular dystrophy/cardiomyopathy [72–75]. The pathophysiological mechanism responsible for peripheral nerve damage caused by nuclear envelope defects remains obscure.

Central Nervous System Disorders

The central nervous system is largely spared in the numerous diseases caused by *LMNA* mutations. One reason for this may be the fact that the lamin A isoform is not significantly expressed in brain (although lamin C is) [68]. In contrast, altered expression of lamin B1, which appears to be expressed in all somatic cells, has been clearly linked to central nervous system disease in humans. In 2000, the group of Fu and Ptáček mapped the gene responsible for adult-onset autosomal

dominant leukodystrophy to chromosome 5q31, and in 2006 reported that duplications in *LMNB1* affected members of four families [76, 77]. Other groups subsequently confirmed this finding [78–80]. Patients with adult-onset autosomal dominant leukodystrophy are normal until adulthood, when they develop a clinical syndrome somewhat similar to chronic progressive multiple sclerosis, with widespread and symmetric loss of myelin in the central nervous system. The *LMNB1* gene duplication leads to increased expression of lamin B1 in brains of affected individuals [77]. The lack of peripheral myelin defects indicates that *LMNB1* duplication may selectively disrupt the function of oligodendrocytes. Fu and colleagues have explored this question, and the pathophysiology of this disease more generally, through the generation of lamin B1 overexpressing mouse models. They first demonstrated that germline overexpression of lamin B1 replicates most major features of the disease. They then demonstrated overexpression of lamin B1 selectively in oligodendrocytes causes a very similar phenotype, including cognitive impairment, epilepsy, motor deficits and abnormalities of myelin that include the downregulation of proteolipid protein, which is a myelin sheath component [81]. Studies *in vitro* on cultured cells confirmed a deleterious effect of lamin B1 in oligodendrocytes, in which overexpression of lamin B1 suppressed oligodendrocyte-specific genes and prematurely arrested oligodendrocyte differentiation [82]. Specific mechanisms controlling the expression levels lamin B1 have been identified. Lamin B1 expression is suppressed by microRNA-23 and overexpression of this microRNA promotes myelination in the mouse central nervous system; these findings further demonstrate a clear connection between lamin B1, a specific microRNA, and the maintenance of myelination [82, 83].

Whereas lamin B1 overexpression clearly leads to a central nervous system demyelinating disease, deletion or missense mutations in the genes encoding B-type lamins have not yet been linked to human neurological disease. In mice, B-type lamins have been shown to be essential for neuronal migration, whereby loss of B-type lamins causes lissencephaly-like defects in cortical development [84–86]. This has led to the prediction that whole-exome sequencing on patients with severe neurological diseases will eventually uncover nonsense and missense mutations in *LMNB1* and *LMNB2* [85].

As noted earlier, the nesprin family of proteins consists of transmembrane proteins that are localized to the outer nuclear membrane, in which they are components of the nucleocytoplasmic connecting LINC complex. Abnormalities of nesprin proteins have been implicated in two central nervous system disorders. In a search for genetic causes of pure cerebellar ataxias, Gros-Louis et al. [87] identified mutations in *SYNE1* in a French-Canadian cohort, a finding that was subsequently extended beyond French-Canadian individuals [88, 89]. *SYNE1* encodes the KASH domain protein nesprin-1, and *SYNE1* mutations cause recessively inherited cerebellar

ataxia. Mouse genetic studies have demonstrated a role for nesprin-1 and related LINC-complex proteins (nesprin-2, SUN1, SUN2) in nuclear positioning during neurogenesis [90]. However, isolated nesprin-1 loss of function does not cause an overt phenotype in mice; the reasons for the differences between the nesprin-1-related mouse and human phenotypes are unclear. A homozygous mutation in *SYNE4*, encoding nesprin-4, a LINC-complex protein with tissue-restrictive expression, including hair cells of the cochlea, has been linked to progressive high-frequency hearing loss in two families of Iraqi Jewish ancestry [91]. The pathogenic mutation creates a truncated form of nesprin-4 that fails to localize normally to the outer nuclear membrane. *Syne4* null mice mimic this phenotype, exhibiting progressive hearing loss concurrent with the selective degeneration of outer hair cells of the cochlea [91]. These outer hair cells have abnormally positioned nuclei, establishing what is arguably the most direct link between improper nuclear positioning and cell viability.

Mutations in genes encoding nucleoporins have been linked to two central nervous system disorders. A recessively inherited missense mutation in the gene encoding NUP62 causes infantile bilateral striatal necrosis [92]. An autosomal, dominantly inherited, missense mutation in the gene encoding Ran binding protein 2 leads to susceptibility to infection-triggered acute necrotizing encephalopathy [93]. Both of these disorders are characterized by the acute development of bilateral necrotic lesions of deep brain tissue. The central nervous system-specific defects induced by mutations in nucleoporin genes can be explained at least in part by emerging research showing that nucleoporin expression may vary from one tissue to another [29].

Finally, the nuclear envelope is a key focus of the cellular defects responsible for DYT1 dystonia. DYT1 dystonia is a neurodevelopmental disorder of childhood characterized by sustained abnormal involuntary movements that cause twisting and turning of the involved body part. DYT1 dystonia is caused by a dominantly inherited single amino acid deletion in the *TOR1A* gene [94]. The encoded protein, the AAA-ATPase torsinA, is normally localized to throughout the endoplasmic reticular/nuclear envelope endomembrane space, but the DYT1 mutation causes torsinA to concentrate abnormally in the perinuclear space of the nuclear envelope [95–97]. The pathogenetic implications of the abnormal localization of torsinA in DYT1 dystonia are addressed in detail in separate review in this issue [98].

Therapeutic Implications

As highlighted by the foregoing discussion, major advances have been made linking neurological diseases to mutations in genes encoding nuclear envelope proteins. However, the

slower progress towards understanding how alterations in nuclear envelope proteins cause disease has hindered the development of therapeutics for these disorders. Drug development has also been slowed by the unavailability of simple “readouts” to identify promising compounds that could have beneficial effects. For example, there is no readily measurable parameter, such as enzymatic activity or ion channel conductance, which has been robustly linked to the pathogenesis of any nuclear envelopopathy.

One approach towards therapeutic development has been to focus on “downstream” abnormalities that occur in organs and tissues that result from disease-related defects in nuclear envelope function. For example, RNA microarray analysis has shown enhanced mitogen-activated protein kinase signaling in skeletal and heart muscle of a mouse model of autosomal EDMD [62, 63, 99]. This led to trials of specific kinase inhibitors that have been shown to improve cardiac and skeletal muscle function as well as prolong survival in these mice [63, 99–102]. Mouse models of autosomal EDMD also have supra-normal activity of the AKT-mTOR pathway in striated muscle, and rapamycin and temsirolimus have been shown to confer beneficial effects [103, 104]. As human striated muscle appears to have the same abnormalities [99, 102, 103], these interventions can potentially be tested in clinical trials.

Abnormal nuclear morphology appears to be a common finding in many of the nuclear envelopopathies [4, 45, 46]. This has led several investigators to search for drugs that reverse nuclear morphological defects, based on the notion that this effect would translate into beneficial effects for the whole organism. This has been demonstrated best by research on progeria syndromes caused by mutation in *LMNA* or the gene encoding ZMPSTE24, the protease responsible for prelamin processing. Fibroblasts with progeria-causing mutations in these genes have abnormal nuclear morphology. Treatment of these cells with a protein farnesyltransferase inhibitor, which blocks farnesylation of prelamin A and a truncated variant that occurs in Hutchinson-Gilford progeria syndrome, partially reverses these nuclear structural defects [105–109]. Treatment of mouse models of these progeria syndromes with farnesyltransferase inhibitors was then shown to have beneficial effects on disease phenotypes [110–112]. A farnesyltransferase inhibitor has even been tested in an open-label pilot clinical trial in children with Hutchinson-Gilford progeria syndrome [113]. The correlation between drug-induced improvement in nuclear morphology in cultured cells and animal pathology in progeria has led to further screens for compounds that reverse nuclear morphological defects in cells lacking A-type lamins [114].

Another approach to drug screening for nuclear envelopopathies is to search for compounds that reverse the abnormal subcellular localization of nuclear membrane proteins that occurs in several of these disorders. As noted above, the pathogenic form of torsinA that causes DYT1 dystonia abnormally concentrates within the perinuclear space. This has led to the development of a

contextual automated three-dimensional imaging assay that can be modified to automatically assess the subcellular localization of pathogenic and related mutant forms of torsinA and torsinA-related molecules [115]. This assay is based on the hypothesis that among compounds identified to normalize the localization of the torsinA DYT1 variant, some will be activators of the ATPase enzymatic activity of the protein. Conceptual support for this notion is based on the facts that 1) the DYT1 dystonia-causing mutation both impairs torsinA ATPase activity and causes abnormal nuclear membrane concentration [95, 116], 2) a similar abnormality of nuclear membrane concentration is seen with an experimental mutation that impairs the ability of torsinA to hydrolyze ATP [95] and 3) torsinA hypofunction has been linked to dystonic-like movements in mouse models [117].

There are also efforts to treat nuclear envelopopathies affecting the neuromuscular system with cell and gene therapy. The current state of the art in using gene therapeutic approaches for the treatment of neurological disease is discussed in detail by Breakefield and colleagues in a separate review in this issue [118]. Gene therapy may be potentially applied to X-linked EDMD, in which emerin is not expressed in most cases. Another potential application of gene therapy is the expression of downstream proteins to correct abnormalities that result from the genetic mutation or modulating proteins that are linked to the unique susceptibility of the tissue in question. For example, levels of LAP1 have been linked to the unique susceptibility of muscle tissue in X-linked EDMD [55], indicating that overexpression of LAP could slow or halt EDMD-related myopathy. However, many of these disorders, such as autosomal dominant EDMD, result from expression of a dominantly acting protein variant. Hence, genetic interventions may need to be devised that not only replace lost activity but also that block the expression of pathogenic proteins. An analogous “natural” example may be the sparing of the brain in Hutchinson-Gilford progeria syndrome because the toxic truncated prelamin A variant is not expressed there [119].

Acknowledgments Dr. Worman is supported by grants from the National Institutes of Health (R01AR048997, R01HD070713, R01NS059352 and R41TR001008), the Muscular Dystrophy Association (MDA294537) and the Los Angeles Thoracic and Cardiovascular Foundation. Dr. Dauer is supported by grants from the National Institutes of Health (R01NS077730), the Bachmann-Strauss Dystonia and Parkinson Foundation, the Dystonia Medical Research Foundation, Tyler’s Hope For a Cure Dystonia Foundation and the Michael J. Fox Foundation.

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