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Muscular dystrophies, dilated cardiomyopathy, lipodystrophy and neuropathy: the nuclear connection

Stephen L. Maidment and Juliet A. Ellis

An understanding of muscle structure and function is central to improving our knowledge of the group of muscle diseases referred to as muscular dystrophies. These diseases involve a progressive weakening and wasting of skeletal muscle, which can be associated with life-threatening cardiac arrhythmias. The vast majority of these diseases arise from defects in either cytoskeletal or structural proteins, resulting in a breakdown of muscle cell integrity. However, mutations in two nuclear proteins – emerin and lamin A/C – have also been demonstrated to give rise to a muscular dystrophy phenotype. In addition, mutations in lamin A/C can give rise to a dilated cardiomyopathy, a lipodystrophy or a neuropathy. It is far from clear how mutations in nuclear proteins can result in a dystrophy, or cause more than one clinically distinct disease. Understanding the functional role of nuclear proteins in causing these diseases will therefore provide novel insights into muscle function, and should hopefully provide new directions for treatment.

For many years, cell pathologists regarded the nucleus as little more than a repository for the genome and attendant mRNA synthesis. However, it has recently emerged that several disease states are caused by defects in proteins specific to the nucleus, thereby initiating interest in the possibility of diverse functionality associated with this organelle. Perhaps not surprisingly, some of the first diseases found to involve nuclear proteins were the disorders of growth and differentiation, resulting from defective tumour suppressor genes, DNA-repair genes or proto-oncogenes (Table 1). Further discussion of the functions of these proteins is

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Table 1. Nuclear proteins associated with disorders of growth and differentiation (tab001jel)[a]

Protein	Location	Disease	Function	Refs
DNA helicases	Nucleoplasm	Xeroderma pigmentosum	Seven proteins involved in DNA repair	92
	Nucleoplasm	Fanconi's anaemia	DNA repair	93
	Nucleoplasm	Bloom syndrome	DNA repair subsequent to recombination	94
Kinase?	Nucleoplasm	Ataxia telangiectasia	Cell cycle regulator	95
Nibrin	Nucleoplasm	Nijmegen breakage syndrome	DNA-repair complex	96
'Treacle' protein	Nucleolus	Treacher–Collins syndrome	Not yet known	97
Retinoblastoma protein	Nucleoplasm	Retinoblastoma	Tumour suppression; controls cell proliferation	12, 98

[a] These diseases represent a few of the many that are known to be associated with disorders of cell growth and differentiation. Most of the genes affected encode products that function in DNA repair or cell cycle events. Mutations in these genes often cause cancer.

beyond the scope of this article, and the reader is referred to reviews listed in Table 1.

In 1994, an Italian research group (Ref. 1) reported the identification of a novel nuclear protein, termed emerin, which was associated with the condition Emery–Dreifuss muscular dystrophy (EDMD). This was an intriguing finding for two reasons: first, it was the only description to date of the involvement of a nuclear protein in a disease that, at least upon superficial examination, did not appear to be concerned directly with gene expression or cell differentiation. Second, muscular dystrophies were traditionally associated with defects in proteins located at the plasma membrane (sarcolemma) of muscle fibres [such as the dystrophin–glycoprotein complex (DGC) (Refs 2, 3)], not nuclear proteins. Clinically, the muscular dystrophies are a large and heterogeneous group of inherited disorders, united by shared pathological features such as progressive skeletal muscle wasting and cardiac conduction defects. The diseases are classified by their mode of inheritance, the age of onset and the specific groups of muscles that are initially affected. At the cellular level, muscle cell integrity is lost as a result of a breakdown in the structure of the sarcolemma. It is easy to propose mechanisms leading to this event when the defective proteins reside in the sarcolemma. However, it is far from clear how the same pathology can arise when the defective protein is located in the nucleus. Fears that this might have been a spurious finding proved groundless when another nuclear protein, lamin A/C, was identified as being the cause of a range of skeletal, cardiac and adipose tissue dystrophies. The term 'laminopathies' was coined to refer to diseases arising from mutations in either the nuclear lamina or its associated proteins. To date eight dystrophy, cardiomyopathy, lipodystrophy or neuropathy diseases have been associated with nuclear proteins (Table 2), and this review focuses on the current understanding of this connection.

Nuclear structure and function

The nucleus comprises several discrete compartments, each with its own complement of proteins (Fig. 1). Dividing the cytoplasm from the nucleoplasm, and therefore responsible for maintaining the biochemical conditions unique to each, is the nuclear envelope, which is composed of two membranes (Ref. 4). The first of these is the outer nuclear membrane, which is continuous with the rough endoplasmic

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Table 2. Nuclear proteins associated with muscular dystrophies, dilated cardiomyopathy, neuropathy or lipodystrophy (tab002jel)

Protein	Location	Disease	Function	Refs
Emerin	Inner nuclear membrane	X-EDMD	Not yet known	1
Lamin A/C	Nuclear lamina and interior	AD-EDMD FPLD LGMD-1B DCM AR-CMT2	Not yet known	39 70 62 67 75
Lamin B	Nuclear lamina and interior	LGMD-1A (candidate)	Not yet known	99
PABP-2	Nucleoplasm	OPMD	mRNA processing; regulation of E-box transcription	77
RSK-2	Nucleoplasm	Coffin–Lowry syndrome	Ribosomal 56 kinase 2; CREB TF activator	100
SMN	Nuclear bodies ('gems')	Spinal muscular atrophy	mRNA processing and transport; ribonucleoprotein formation	101
MAN1	Inner nuclear membrane	Candidate AD Scapuloperoneal MD	Not yet known	102

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMT2, Charcot–Marie–Tooth disorder type 2; CREB, transcription factor that binds cAMP response elements; DCM, dilated cardiomyopathy; EDMD, Emery–Dreifuss muscular dystrophy; FPLD, familial Dunnigan-type partial lipodystrophy; LGMD, limb-girdle muscular dystrophy; MD, muscular dystrophy; OPMD, oculopharyngeal muscular dystrophy; TF, transcription factor; X, X-linked.

reticulum (RER) and, like the latter, is embedded with ribosomes. The second is the inner nuclear membrane, which contains integral membrane proteins; these interact with the underlying nuclear lamina (see below) and contribute to maintaining and regulating nuclear architecture. Together, the two membranes enclose the perinuclear space, which is continuous with the lumen of the RER. The inner and outer nuclear membranes are spanned by occasional nuclear pore complexes; these protein channels, at which the lipid bilayers of the two membranes become confluent, allow regulated passage of molecules between the nucleus and cytoplasm (Ref. 4). The nucleoplasm contains several specialised domains, each associated with particular biological functions, such as transcription, ribosomal RNA synthesis and protein synthesis. This structure is dynamic and protein exchange occurs between the different domains.

Situated immediately beneath the inner nuclear membrane in all multicellular organisms is the nuclear lamina, a dense filamentous network providing structural support at the nuclear periphery, via its interaction with both the nuclear envelope and the underlying chromatin (Ref. 4). The lamina is required for the maintenance of nuclear shape, heterochromatin organisation, nuclear pore complex spacing, DNA replication and regulation of transcription. The principal components of this structure are the nuclear lamins, a family of intermediate-filament-type proteins.

Nuclear lamins

The nuclear lamin filaments are made up of monomeric subunits, which each comprise a central coiled-coil, α-helical rod domain flanked by globular domains on the C- and N-termini (Refs 5, 6). These form parallel dimers that undergo polymerisation, and the polymers

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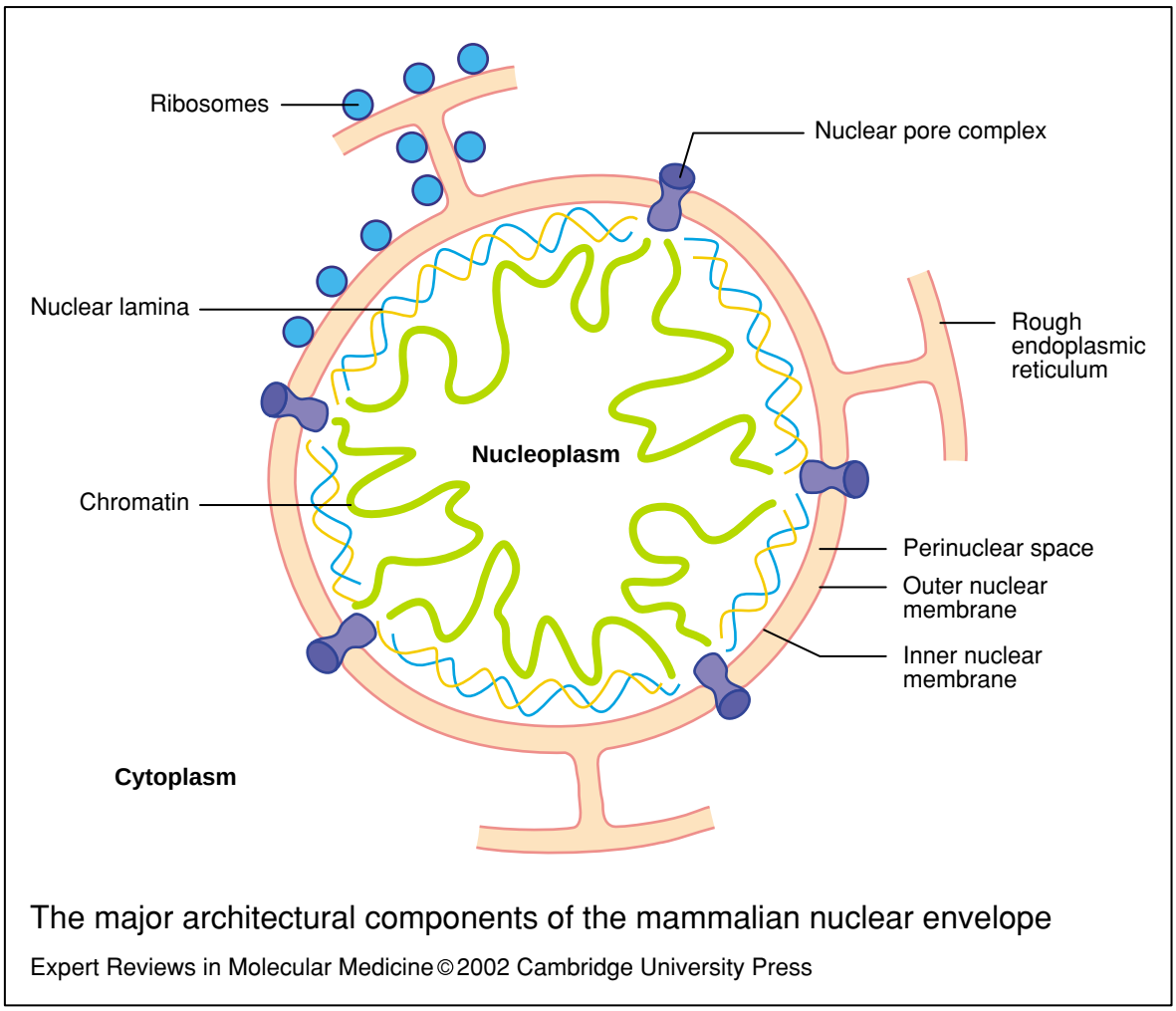

Figure 1. The major architectural components of the mammalian nuclear envelope. The nuclear envelope consists of two membranes: the outer nuclear membrane is contiguous with the rough endoplasmic reticulum and is coated with ribosomes; the inner nuclear membrane contains unique integral membrane proteins. The space between the two membranes is referred to as the perinuclear space. The two membranes (together making up the nuclear envelope) are spanned by nuclear pore complexes, which are involved in regulating the transport of materials between the nucleus and the cytoplasm. The two membranes join at the nuclear pore membrane, which surrounds the nuclear pore complexes. Underlying the inner nuclear membrane is the nuclear lamina, which is a dense filamentous network. Major components of the nuclear lamina are the nuclear lamins A and B, which are a group of filamentous proteins that interact with both inner nuclear membrane proteins and chromatin. The nuclear interior (nucleoplasm) contains soluble proteins **(fig001jel)**.

subsequently co-associate to form the filamentous network of the nuclear lamina. There are three lamin genes in mammals (*LMNA, LMNB1* and *LMNB2*), encoding seven alternatively spliced forms. Lamins are broadly classified as either A- or B-type.

The A-type lamins, of which four are known, are all derived by alternative splicing of the *LMNA* gene located on chromosome 1. The two principal A-type lamins are lamin A and lamin C; the other two are C2 (which is specifically expressed in the testes) and A-Δ10. Lamins A and C share an identical sequence of 566 amino acids from the N-terminus, but differ in that lamin A has a further 98 terminal amino acids whereas lamin C has only 6. This elongated C-terminus of lamin A bears a terminal tetrapeptide sequence known as the CaaX motif (where C is cysteine, a is any amino acid bearing an aliphatic side-chain and X is any amino acid). This motif is the site of post-translational addition of a hydrophobic isoprene (farnesyl) group, which

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allows it to be incorporated into the inner nuclear membrane. Following membrane localisation, the CaaX motif and its contiguous 18 residues are removed by proteolytic cleavage, yielding the mature form of lamin A. The shorter C-terminus extension of lamin C does not undergo these post-translational modifications and its integration into the inner nuclear membrane is dependent upon association with lamin A.

By contrast, the B-type lamins are derived from two genes, *LMNB1* and *LMNB2*, which encode lamin B1 and B2, respectively (Refs 5, 6, 7). There is also a lamin B3, which is a splice variant of B2 and is testis-specific. All B-type lamins have a constitutively farnesylated CaaX sequence and integrate readily within the inner nuclear membrane. The A- and B-type lamins also differ in that all cells constitutively express B-type lamins throughout development, whereas the A-type lamins are developmentally regulated; this phenomenon has been studied in embryonic mice where the lamin A protein is not expressed until midway through gestation (Ref. 8). Furthermore, stem cells in adult organisms, such as those of immuno-haematopoietic lineage or of the gut villus crypts, have been shown not to express A-type lamins until they differentiate (Refs 9, 10). Similarly, many tumour cells have been found to lack A-type lamins, perhaps reflecting a de-differentiated phenotype (Ref. 11).

Lamins occur in the nucleoplasmic interior both as foci and as tubular structures, the localisation of which varies in a cell-cycle-dependent manner (Ref. 7). Intranuclear lamins bind to the tumour suppressor retinoblastoma protein (Rb) (Ref. 12), actin (Ref. 13) and lamina-associated protein 2α (LAP-2α) (Ref. 14), as discussed below. The locality of the nuclear lamins has implicated them in a wide range of nuclear functions such as nuclear growth, maintenance of nuclear shape, DNA replication, chromatin organisation, RNA splicing, cell differentiation, apoptosis and cell-cycle-dependent control of nuclear architecture (Ref. 7). However, a few specific roles have been assigned to individual lamins, as described below.

Integral proteins of the inner nuclear membrane

Approximately 12 integral membrane proteins (Fig. 2) have been described in mammals that partition to the inner nuclear membrane, most likely via a mechanism of selective retention. In this model, membrane proteins destined for the nucleus are post-translationally inserted into the ER and are targeted through the ER network to the nuclear envelope using specific signal sequences (Ref. 15). The outer and inner membranes converge at the nuclear pore membrane (Fig. 1), allowing passage of the membrane proteins from the ER to the inner nuclear membrane. However, only those membrane proteins capable of interacting with entities within the nucleus are retained, becoming uniquely located at the inner nuclear membrane. This model also explains how large protein complexes might form at the nuclear envelope (see below).

The inner nuclear membrane proteins include two related families: the LAP-1 family, comprising LAP-1 A, B and C isoforms; and the LAP-2 family, comprising LAP-2 β, γ, δ and ε isoforms (Ref. 16). LAP-2 has a fifth family member, LAP-2α, which is a soluble nucleoplasmic protein. In addition, there are two related, but distinct, nuclear membrane proteins: emerin (Ref. 1) and MAN1 (Ref. 17).

The LAP families and emerin both contain a single transmembrane domain at the C-terminus, whereas MAN1 possesses two such domains. These proteins are orientated in the inner nuclear membrane with their N-termini projecting into the nucleoplasm (known as type II orientation) (Fig. 2). The nucleoplasmic domains are large and hydrophilic, possessing binding sites for chromatin and other nuclear proteins, as well as potential phosphorylation sites. All the LAP-2 isoforms, emerin and MAN1 share a homologous N-terminal domain, referred to as the 'LEM domain' (for LAP–emerin–MAN) (Ref. 17), which confers the ability to bind to 'barrier to auto-integration factor' (BAF), a DNA-bridging protein of unknown function (Refs 18, 19, 20). LAP-2 and emerin both undergo interphase and cell-cycle-dependent phosphorylation (Refs 21, 22).

Three unrelated multi-membrane-spanning proteins have also been identified: nurim, lamin B receptor (LBR) and a hormonally regulated atypical P-type ATPase termed ring-finger-binding protein (RFBP) (Refs 23, 24, 25). The latter resembles a type IV phospholipid pump, but lacks a domain encoding pump activity. Three proteins have been proposed to connect the inner nuclear membrane to the chromatin network. These are heterochromatin 1 (HP1), which is a component of heterochromatin and

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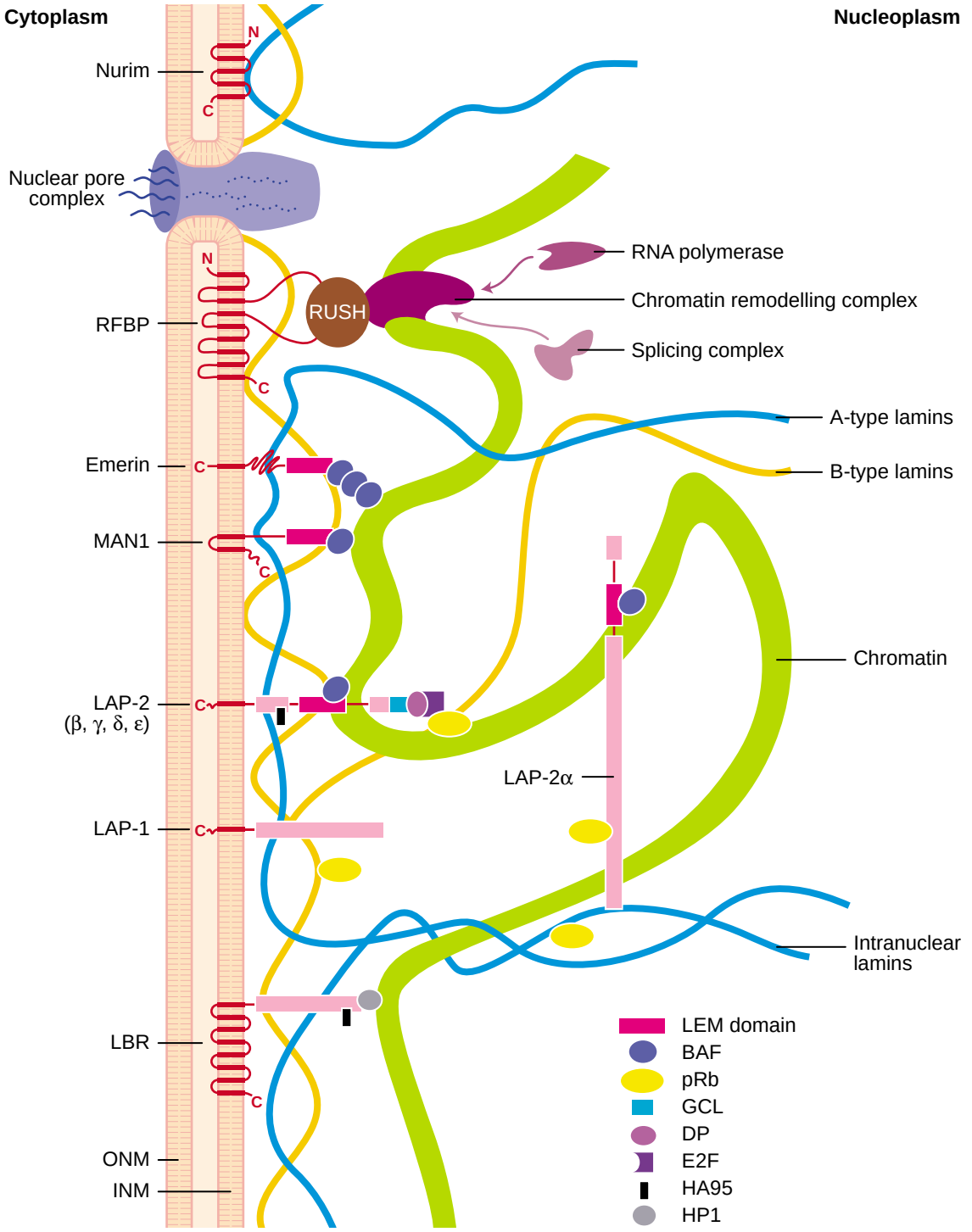

A schematic view of inner nuclear membrane proteins and their binding interactions with the nuclear lamina and nucleoplasmic components

Figure 2. A schematic view of inner nuclear membrane proteins and their binding interactions with the nuclear lamina and nucleoplasmic components (*see next page for legend*) **(fig002jel).**

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Figure 2. A schematic view of inner nuclear membrane proteins and their binding interactions with the nuclear lamina and nucleoplasmic components. The outer and inner nuclear membranes (ONM and INM, respectively) are shown in cross-section, with a nuclear pore complex spanning the two membranes. The exact interactions and organisation of the inner nuclear membrane, nuclear lamina and chromatin are unknown and are hypothetically depicted in this figure. Twelve inner nuclear membrane proteins have been characterised in the mammalian nuclear envelope. These include: the multi-spanning membrane proteins nurim, lamin B receptor (LBR), ring-finger-binding protein (RFBP); the double-spanning membrane protein MAN1; and the single-spanning membrane proteins emerin, lamina-associated protein 2 (LAP-2) isoforms (β, γ, δ, ε) and LAP-1 isoforms (A, B, C). All the LAP-2 isoforms, emerin and MAN1 share a homologous N-terminal domain called the LEM domain, which binds to BAF ('barrier to auto-integration factor'). Interactions occur between the inner nuclear membrane proteins and the A-type lamins (shown in blue) and B-type lamins (shown in orange), which are helical filamentous proteins of the nuclear lamina and nucleoplasm. Intranuclear lamins bind to the soluble LAP-2 isoform LAP-2α. Transcriptional regulators crosslink inner nuclear membrane proteins and chromatin. These include: the retinoblastoma protein pRB; the 'germ-cell-less' protein GCL; the transcription factor E2F; and RNA polymerase, RNA splicing complex and DP protein. Heterochromatin-binding proteins include HP1, BAF and HA95 **(fig002jel)**.

is implicated in gene silencing, BAF and HA95, another heterochromatin-binding protein (Refs 26, 27) (Fig. 2).

A unifying concept is beginning to emerge suggesting that all inner nuclear membrane proteins form large multisubunit complexes that crosslink the nuclear envelope to the chromatin. LBR was the first to be identified as being part of a very large complex, consisting of A- and B-type lamins, a specific kinase (LBR kinase), HP1, and several other proteins of unknown function (Ref. 28). Subsequently, it has been shown that LAP-1 isoforms bind to A-type lamins, the LAP-2β isoform binds to B-type lamins, and the LAP-2α isoform binds to A-type lamins in the nuclear interior (Ref. 6). Emerin forms a complex with lamins A, B and C and with nuclear actin, but the nature of the interactions within the complex are unknown, since lamins independently interact with one another and with actin (Refs 20, 29, 30). However, lamin A is known to be essential for the anchorage of emerin to the nuclear envelope and for the targeting of lamin C to the nuclear lamina (Ref. 31). Recently, further interactions of the LAP-2–lamin complexes with nucleoplasmic proteins involved in transcriptional regulation have been elucidated, as described below.

The laminopathies

EDMD

EDMD (OMIM 31300; 181350; Ref. 31) is the least common of the three major muscular dystrophies, after the Duchenne and Becker types (Refs 2, 3), with an estimated incidence of 1:50 000 (A. Emery, pers. commun.). Initially described as an X-linked recessive disorder (X-EDMD), autosomal recessive and dominant forms are also now recognised (AR- and AD-EDMD, respectively), the dominant form being the most prevalent of the three types.

X-EDMD arises as a consequence of mutations in the *STA* gene, located at chromosome Xq28, which encodes the protein emerin (Ref. 1). This protein occurs ubiquitously at the inner nuclear membrane, and there are controversial reports as to whether it is also located in the intercalated discs of cardiomyocytes (Refs 32, 33). The majority of the emerin mutations are nonsense or frameshifts producing a null phenotype, but about 15% express modified forms of emerin (Refs 29, 34, 35, 36, 37). However, no phenotype–genotype correlation is apparent between these two groups of X-EDMD patients, apart from a single missense mutation that is reported to have a milder phenotype (Ref. 38).

AD-EDMD results from mutations of the *LMNA* gene located at chromosome 1q11-23 (Ref. 39) (Fig. 3). The majority of the mutations are missense (Refs 40, 41, 42, 43, 44), occurring throughout the length of the common region of lamin A and C; therefore, either or both proteins could be responsible for the AD-EDMD phenotype. As for X-EDMD, no phenotype–genotype correlation is apparent in AD-EDMD or AR-EDMD patients.

Dystrophic features (i.e. muscle fibre degeneration) are not a major feature of EDMD. Nevertheless, there is a variation in myofibre (fibres that make up muscle) size, an increase in internal nuclei number and an increase in the number of type 1 (slow) fibres (Ref. 45). Cellular defects are characterised by abnormalities in myonuclear architecture, ranging from marked condensation of chromatin to complete extrusion

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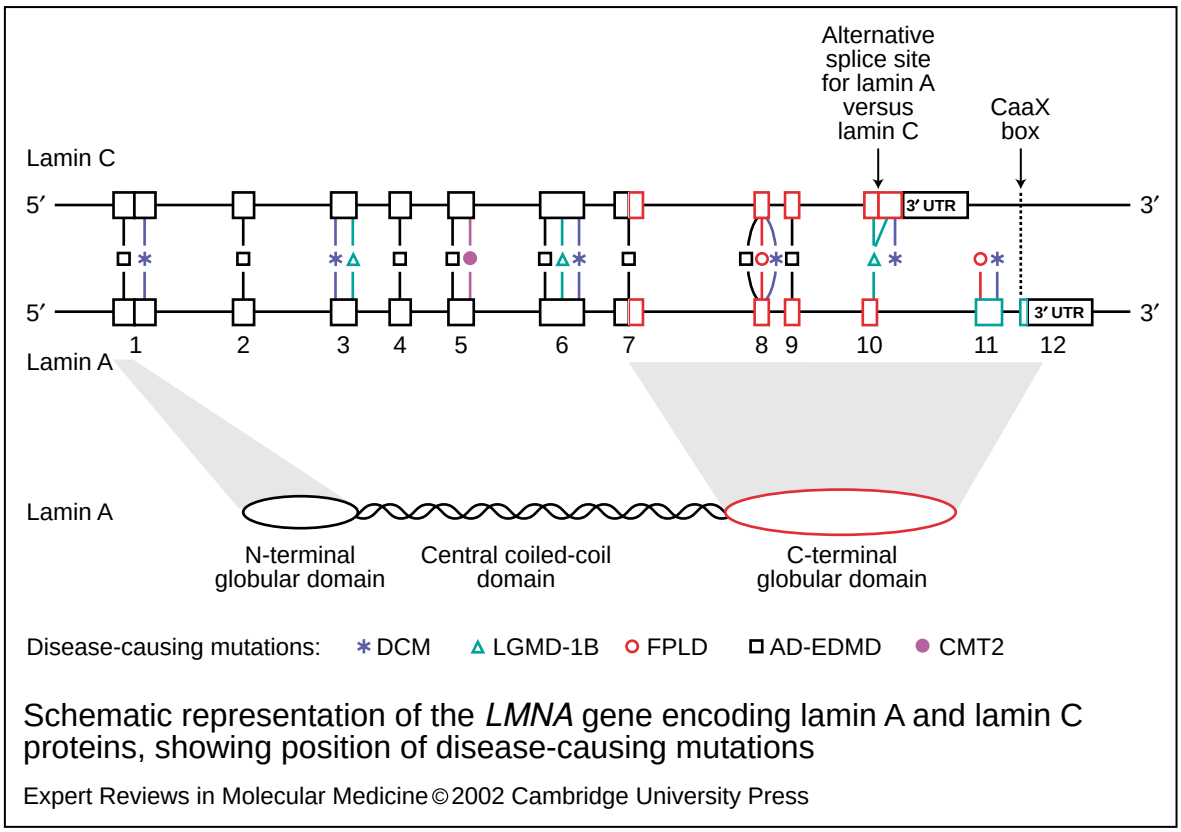

Schematic representation of the *LMNA* gene encoding lamin A and lamin C proteins, showing position of disease-causing mutations

Figure 3. Schematic representation of the *LMNA* gene encoding lamin A and lamin C proteins, showing position of disease-causing mutations. The *LMNA* gene has 12 exons, which are shown here as boxes. The predicted structural motifs of lamin A are shown as two globular domains, one at the N- and one at the C-terminus, with a central coiled-coil region linking the two. Part of exon 1 encodes the N-terminal globular domain, the rest of exon 1 through to part of exon 7 encodes the central helical domain, and the rest of exon 7 to 12 encodes the C-terminus of lamin A. Lamin C has a similar structure, but is shorter at the C-terminus, which is encoded by exons 7 to 10. The elongated C-terminus of lamin A bears a terminal tetrapeptide sequence known as the CaaX motif (where C is cysteine, a is any amino acid bearing an aliphatic side-chain and X is any amino acid). This motif is the site of post-translational addition of a hydrophobic isoprene (farnesyl) group, which allows it to be incorporated into the inner nuclear membrane. Following membrane localisation, the CaaX motif and its contiguous 18 residues are removed by proteolytic cleavage, yielding the mature form of lamin A. The shorter C-terminus of lamin C does not undergo these post-translational modifications and its integration into the inner nuclear membrane is dependent upon association with lamin A. The diagram shows the exons affected by disease rather than the individual mutations, because of space constraints. Mutations causing autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD) occur along the length of the *LMNA* gene. Mutations causing dilated cardiomyopathy (DCM) have been found in exons 1, 3, 6, 8, 10 and 11; mutations linked with familial Dunnigan-type partial lipodystrophy (FPLD) occur in exons 8 and 11; mutations linked with limb-girdle muscular dystrophy 1B (LGMD-1B) occur in exons 3, 6 and 10; and one mutation linked to Charcot–Marie–Tooth disorder type 2 (AR-CMT2) occurs in exon 5. For a more-detailed positioning of mutations see Refs 40, 42, 75. UTR, untranslated region. The diagram is not drawn to scale **(fig003jel)**.

of nuclear components, suggesting muscle cell death might occur by apoptosis (Refs 46, 47, 48). Immunohistochemical investigation of muscle samples from some, but not all, AD-EDMD patients reveals mislocalisation of lamin A/C and re-localisation of emerin to the ER (Refs 30, 49, 50, 51, 52, 53). One research group subsequently demonstrated that it is only lamin C that is unable to assemble at the nuclear envelope (Ref. 30), whereas others have indicated that lamin A or lamin C, or both, can be mislocalised and the distribution of one affects the other (Ref. 52). These observations would seem to imply that only a few proteins of the nuclear scaffold

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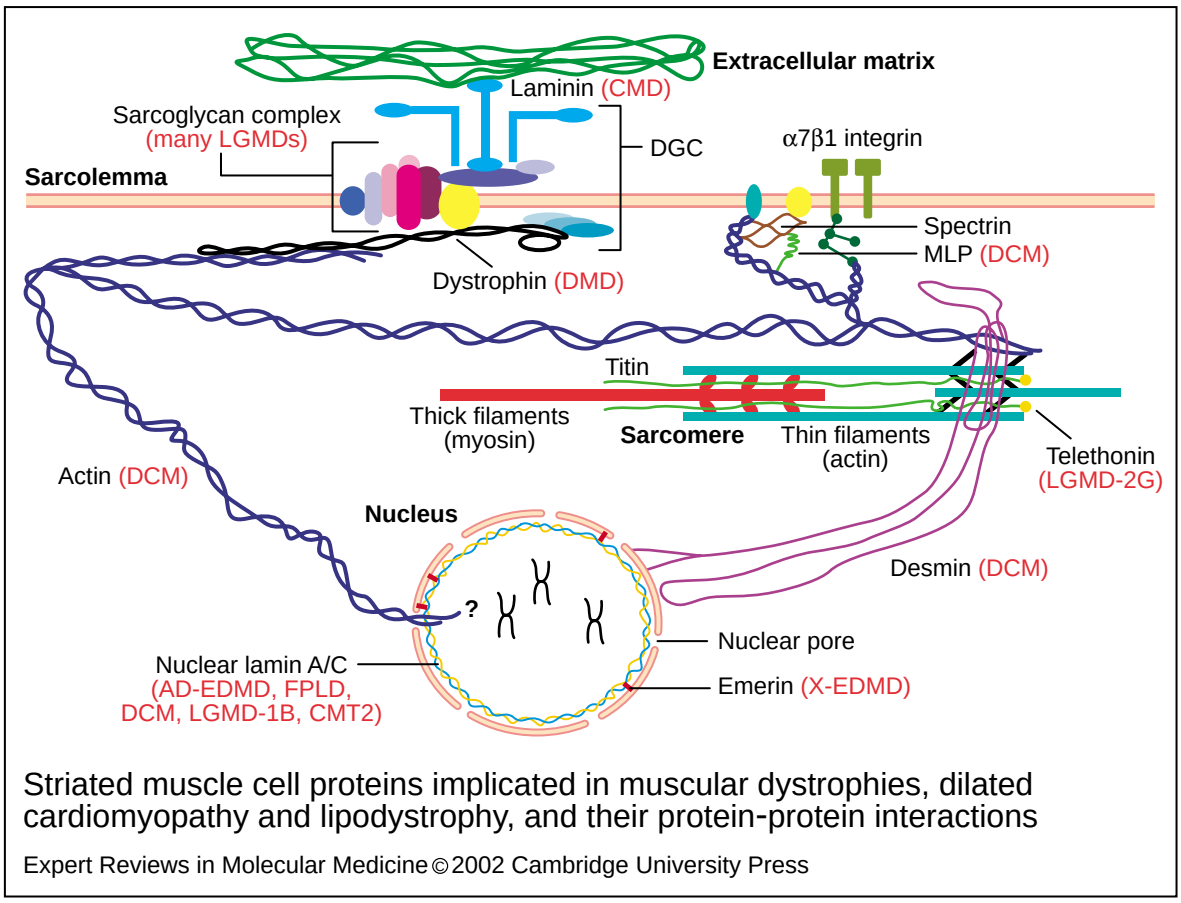

Figure 4. Striated muscle cell proteins implicated in muscular dystrophies, dilated cardiomyopathy and lipodystrophy, and their protein–protein interactions. Myopathies, cardiomyopathy or lipodystrophy known to be caused by particular proteins are indicated in parentheses (red). Spanning the plasma membrane (sarcolemma) of a striated muscle cell (myoblast) is the dystrophin–glycoprotein complex (DGC; bracketed), which provides structural integrity to the cell by crosslinking the cytoskeleton (via actin) to the extracellular matrix (via laminin β1). Mutations in dystrophin cause Duchenne muscular dystrophy (DMD) and mutations in the sarcoglycoproteins cause a variety of limb-girdle muscular dystrophies (LGMD) including 2C, 2D, 2E and 2F. Desmin and actin filaments crosslink the nucleus, sarcomere and sarcolemma. The sarcomere is the structure responsible for muscle contraction, and contains the proteins actin, myosin, titin and telethonin. The muscle LIM protein (MLP; LIM is the term given to a protein–protein interaction domain containing a double zinc finger motif) is a cytoskeletal binding partner of β-spectrin (Ref. 103), itself a cytoskeletal protein. Mutations in lamin A/C can cause LGMD-1B. Other disease abbreviations: AD-EDMD, autosomal dominant Emery–Dreifuss muscular dystrophy; X-EDMD, X-linked EDMD; FPLD, familial Dunnigan-type partial lipodystrophy; CMD, congenital muscular dystrophy; DCM, dilated cardiomyopathy; CMT2, Charcot–Marie–Tooth disorder type 2. The question mark indicates uncertainty as to whether F-actin enters the nucleus from the cytoplasm **(fig004jel)**.

are necessary for maintaining muscle nuclear structural/functional integrity. However, this cannot be the entire picture since only about 10% of myotubes (fused myoblasts) show these abnormalities (Ref. 46). The DGC proteins (Fig. 4) are expressed normally, but the extracellular matrix (ECM) protein laminin β1 shows an age-related secondary reduction in some AD-EDMD cases (Ref. 45). X-EDMD patients expressing modified forms of emerin exhibit a number of molecular abnormalities including a reduction in emerin located at the nuclear membrane, aberrant cell-cycle-dependent phosphorylation of emerin and altered cell-cycle kinetics (Refs 29, 37, 54, 55).

The onset of EDMD is generally within the first decade of life and the progress of the condition is slow, with severe disability rare before adulthood (Ref. 31). Diagnosis is based upon a triad of signs

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and symptoms comprising, initially, contracture of the tendo-calcaneus (Achilles tendon), elbows and neck extensors, leading to a 'toe-walking' gait. Second, there is a slowly progressing muscular wasting, commencing in adolescence and initially following a humero–peroneal pattern, with the biceps and triceps affected first followed by the tibialis anterior and peroneus longus. Finally, there is an associated cardiomyopathy, often manifest as an atrio–ventricular conduction defect that is life-threatening in 40% of cases (Refs 31, 56, 57, 58). Cardiac conduction defects can appear at any age, but usually arise in the teenage years and normally before the age of 30; this is considered to be a primary defect, since abnormal electrocardiograms (ECGs) are seen when the cardiomyopathy is still asymptomatic. The severity of the conduction defect warrants implantation of a cardiac pacemaker, although sudden death has still been reported subsequent to this procedure (Ref. 56). Serum creatine kinase (an indicator of loss in integrity of the plasma membrane) is usually elevated, but not to the remarkable extent seen in the other sarcolemma-related muscular dystrophies. Treatment is palliative, with surgical management of limb and spine contractures in the first instance; however, the progress of the disease is ultimately relentless and sudden heart failure in middle age is the commonest cause of death.

There is considerable intra- and interfamilial phenotype variability in both types of EDMD, but there is a wider range of disease severity in the AD-EDMD patients compared with the X-EDMD patients (4th ENMC EDMD report; listed in 'Further reading, resources and contacts'). In addition, isolated cardiac involvement is more prevalent, and muscle weakness and disease course tends to be more severe in the AD-EDMD than X-EDMD patients. Interestingly, carriers can exhibit cardiopathic symptoms with varying severity, up to and including sudden death. It is therefore important to screen all family members where EDMD is present or suspected.

Limb-girdle muscular dystrophy 1B

Limb-girdle muscular dystrophy (LGMD; OMIM 159001) describes a spectrum of phenotypically similar but pathogenetically distinct disorders of which 13 have been described to date (LGMD-1A to E, and LGMD-2A to H; Refs 59, 60). Of these, LGMD-1B results from mutations in the lamin A/C gene (Refs 61, 62) (Fig. 3). The onset of these disorders can be at any time in the first two decades of life, and they are characterised by initial preferential involvement of the shoulder and pelvic girdle musculature, followed by progressive proximal muscle weakening (more pronounced at the hip than the shoulder). Early signs include waddling gait with toe-walking, exercise intolerance, scapular winging (outward protrusion of the shoulder blades), contracture of the tendo-calcaneus and increased lumbar lordosis (pronounced curvature of the lower spine); furthermore, the patient often experiences painful muscle swelling and calf hypertrophy. The distal musculature eventually becomes affected and, in the case of LGMD-1B, there can be an associated dilated cardiomyopathy (DCM; see below) (Ref. 62). LGMD exhibits a wide clinical spectrum and might be mistakenly diagnosed as Becker-type muscular dystrophy (mild form of Duchenne; see Fig. 4 and Refs 2, 3). Serum creatine kinase levels are 10–120-fold higher than normal, but there is no correlation between these findings and the severity of the disease. To date, only three different mutations have been identified in the *LMNA* gene as causing LGMD-1B (Refs 42, 61, 62). Each is found in a different domain of lamin A/C (see Fig. 3). Molecular and cellular studies have not been reported in LGMD-1B patients.

DCM

DCM has a global incidence of 1:2800 and is a generalised term describing decreased ventricular function, as defined by increased ventricular end-diastolic volume accompanied by a decrease in ejection fraction (the proportion of the total volume of blood in the ventricles at the end of diastole which is actually ejected during systole) to below 50% of normal values (Ref. 63). Patients present with symptoms ranging in severity from arrhythmias to sudden heart death, and the condition can have an environmental aetiology (e.g. alcohol abuse) or be idiopathic. It is now recognised that around 35% of cases of idiopathic DCM are in fact familial and occur either in association with the conditions described above or as a free-standing familial DCM. This kind of familial DCM is virtually impossible to distinguish clinically from other idiopathic DCMs unless there is a family history of a similar condition, or until such time as another family member succumbs.

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Mutations in several genes have been reported to cause DCM, including the cytoskeletal proteins desmin and dystrophin, the plasma membrane protein α-sarcoglycan, the sarcomeric proteins cardiac β-actin and cardiac β-myosin heavy chain, and nuclear lamin A/C (Figs 3, 4); thus the aetiology of DCM has heterogeneous molecular origins (Refs 64, 65, 66). Dystrophin and α-sarcoglycan mutations cause Duchenne and LGMD-2D, respectively, where the cardiomyopathy probably arises as a result of ineffectual force transmission from the sarcomere to the ECM (Ref. 63). In the case of mutations in cardiac β-actin, which localises to the sarcomeres as well as the cytoskeleton, the condition might also result from a force-generation defect.

In families carrying mutations in the *LMNA* gene, the disorder becomes clinically apparent in early middle age, often as an asymptomatic ECG abnormality (Refs 67, 68). The condition progresses from sinoatrial to atrio–ventricular node dysfunction, and finally to full conduction block. For this reason, the condition is sometimes known as DCM with conduction system disease, or DCM-CD. Often the 'dilated' part of the cardiomyopathy is under-represented, and patients with some of the lowest ejection fractions can exhibit the least left-ventricular dilatation. No joint contractures or skeletal muscle involvement are observed in these patients.

The mainstays of treatment are usually cardiac glycosides, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers and other anti-dysrhythmics. Heart transplantation might be indicated in severe cases. To date, too few mutations have been identified to attribute a domain-specific functional abnormality in the *LMNA* gene.

Familial Dunnigan-type partial lipodystrophy

Dunnigan-type, or familial partial lipodystrophy (FPLD; OMIM 151660), is a rare condition (<1 in 15 000 000) and becomes manifest at puberty, suggesting a hormonal component to the development of the disease (Ref. 69). FPLD is characterised by regional changes in the distribution of subcutaneous fat. This is lost from the limbs, gluteal region and trunk, and accumulates in the face, neck, back, axillae and groin, often leading to a misdiagnosis of Cushing-type disorders (conditions resulting from elevated circulating glucocorticoids and characterised by redistribution of body fat). Whole-body magnetic resistance imaging (MRI) studies have indicated that perivisceral, intermuscular and bone-marrow fat are preserved and that intramuscular fat is present in excess. Affected individuals have profound insulin resistance and a reactive hyperinsulinaemia, leading to type II diabetes mellitus later in life that is frequently difficult to control. Early coronary heart disease is a common outcome, but this is most likely due to the hypertriglyceridaemia (elevation of triglycerides in the blood) and diabetes accompanying the condition, rather than the cardiomyopathies described in the disorders discussed above.

FPLD is inherited as an autosomal dominant disorder and affects both sexes equally, although it tends to be more obvious in women because the fat redistribution does not resemble the normal changes seen at puberty. The *LMNA* gene was recently identified as being responsible for this disorder, and individuals homozygous for the condition exhibit a more severe phenotype (Refs 70, 71, 72). Interestingly, Garg et al. reported a mutation in the lamin A-specific tail that resulted in a milder phenotype than that in patients where the mutations affected both lamin A and C proteins (Ref. 73). The few mutations identified all lie in the globular C-terminal domain of the *LMNA* gene (Fig. 3).

Autosomal recessive Charcot–Marie–Tooth disorder type 2

The Charcot–Marie–Tooth (CMT) disorders, also known as 'hereditary motor and sensory neuropathies', are a common group of inherited neuropathies affecting 10–40/100 000 individuals. Clinically, they exhibit electrophysiological and neuropathic symptoms, and are genetically very heterogeneous. They are divided into two main groups based on nerve-conduction velocities: type 1 or CMT1, which are dymyelinating; and type 2 or CMT2, which are axonal in origin (reviewed in Ref. 74).

Mutations in the intermediate-filament protein termed neurofilament (*NF-L* gene; OMIM 162280) and in a microtubule motor protein of the kinesin superfamily (*KIF1Bβ* gene; OMIM 118210) can give rise to autosomal dominant CMT2 (AD-CMT2). Recently, two unrelated families were diagnosed with autosomal recessive CMT2 (AR-CMT2), and both possessed

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the same mutation in exon 5 of the *LMNA* gene (Ref. 75). AR-CMT2 individuals present with symmetrical muscle weakness and wasting (predominantly of the distal lower limbs), foot deformities and walking difficulties associated with reduced or absent tendon reflexes. No DCM-CD or other cardiac abnormality is observed. Confirmation of diagnosis is by the measurement of nerve conduction velocities. Muscle wasting is commonly observed in CMT2, but is usually thought to be secondary to nerve deterioration.

Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD; OMIM 164300), although not a laminopathy in that it is a non-lamina protein that is responsible for the condition, is another example of a muscular dystrophy connected to ubiquitous nuclear function. OPMD can be inherited in either an autosomal dominant or, much more rarely, an autosomal recessive form; the dominant form is particularly prevalent among French Canadians (1 per 1000 births) and Buhakra Jews (1 per 600), although the worldwide incidence is around 1 per 200 000 (Ref. 76). The prevalence of the recessive form has not been calculated.

OPMD results from expansions of a GCG trinucleotide (which codes for alanine) repeat in the gene encoding polyadenylation-binding protein 2 (PABP2) located at chromosome 14q11 (Ref. 77). PABP2 contains six GCG repeats in normal individuals, but this is expanded to nine in 40% of OPMD sufferers and as many as 13 in 1% of cases. PABP2 is expressed in all tissues, but particularly skeletal muscle, and is involved in both the synthesis and truncation of the poly(A) tails of mRNA molecules. PABP2 binds to Ski-interacting protein (SKIP), and co-operatively and synergistically the two proteins activate E-box transcription through the muscle-specific transcription factor MyoD (Ref. 78).

Clinically, the dominant form of OPMD is characterised by the late onset (fifth decade) of a progressive eyelid drooping (ptosis) and progressive swallowing difficulties (dysphagia), followed by other cranial or limb muscle involvement (Ref. 79). In addition, there can be weakness and atrophy of the tongue, and weakness of the facial and proximal arm muscles. Pathological examination of muscle biopsies by transmission electron microscopy reveals characteristic inclusion filaments within 5% of muscle nuclei (Ref. 80). These filaments can be aggregates of the PABP2 protein itself, triggered by the polyalanine expansions, or are caused by the presence of abnormally extended mRNA poly(A) tails due to dysfunctional PABP-2. The recessive form of the disease has a similar, but arguably slightly milder, clinical phenotype, and affected individuals are homozygous for seven GCG repeats. Cardiac involvement is not a characteristic of either type of OPMD.

The nuclear connection: possible molecular mechanisms

The foregoing discussion raises several interesting questions. First, how can mutations in nuclear proteins produce regional myocyte (in EDMD), regional adipocyte (in FPLD) and regional neuronal (in CMT2) degeneration? Second, how can mutations of the *LMNA* gene cause five distinct conditions – namely, EDMD, LGMD-1B, DCM-CD, FPLD and AR-CMT2? From our limited knowledge of the function of the proteins involved, can we formulate molecular mechanisms that can be reconciled with what is known about the pathology of these diseases? Are these conditions actually just one disease that exhibits extensive variable penetrance?

From molecular dysfunction to clinical phenotype

The question of how lamin A/C mutations can give rise to five different clinical conditions has been addressed by studying the distribution of the mutations documented thus far. Many mutations have now been reported for AD-EDMD and these span the length of the *LMNA* gene, although none has been located in the lamin-C-specific tail. By contrast, the number of mutations identified causing FPLD, LGMD-1B, AR-CMT2 and DCM is too small to allow formulation of any meaningful argument for domain-specific loss of functionality. In addition, the situation is complicated by two pedigrees reported by Bonne et al. (Ref. 40) and Brodsky et al. (Ref. 68), where family members with the same mutation in the *LMNA* gene are diagnosed with clinically different phenotypes. Three family members heterozygous for the same mutation (a single nucleotide deletion resulting in a frameshift in the rod domain) displayed LGMD-1B, DCM and AD-EDMD, respectively. This latter finding has led to the proposition that AD-EDMD is a 'full blown'

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condition, of which DCM and LGMD-1B are discrete clinical subsets. A similar story emerges when comparing AR-EDMD patients with AR-CMT2 patients. AR-EDMD is very rare and is normally described as atypical EDMD, which refers to the lack of any cardiomyopathy phenotype in these patients. The few mutations identified as causing AR-EDMD or AR-CMT2 all reside in a linker region between coils 1b and 2a in the central coiled-coil domain of lamin A/C. None of the AR-EDMD patients has undergone peripheral nerve examination. This suggests care is needed in the definition of the clinical phenotypes that share similar features.

Several models have been proposed to try to account for the pathology observed in these diseases. The first model involved the concept of striated-muscle-specific nuclear fragility (Refs 22, 33). Myocytes are long-lived, non-dividing cells, which have to withstand considerable mechanical stresses from the forces of contraction and relaxation imposed upon them. Currently published data suggest that the nuclear membrane of myonuclei lacks lamin B1 (Ref. 33) and therefore LAP-2–lamin-B1 interactions are absent, making it unusually dependent on the presence of emerin–lamin-A/C interactions to maintain nuclear structure. Therefore, the depletion of nuclear membrane components such as emerin or lamin A/C might be more detrimental in this tissue type than in others. Certainly, there are abnormalities of nuclear structure in EDMD – in particular, herniations of the nuclear envelope are visible with transmission electron microscopy. It was postulated that complexes of the inner nuclear membrane and nuclear lamina proteins stabilised the structure of the nucleus with respect to the rest of the cell. In this model, the nuclear membrane complexes structurally and functionally mimic the DGC complex located at the sarcolemma (Ref. 29) (Fig. 4). A nucleocytoskeletal framework exists, consisting of actin and desmin filaments radiating from the nucleus to the cytoskeletal network present under the sarcolemma. The nuclei can therefore be regarded as 'tethered', and any disruption to nuclear architecture might be transmitted, causing effects at the sarcolemma and instigating sarcolemma breakdown. This model is attractive from the viewpoint that a range of cytoskeletal proteins has been shown to cause a DCM (see above), possibly by a similar mechanism. The principal criticisms of this model are, first, that it does not explain the defects seen in the conduction (non-contractile) tissue of the heart, which in this organ is more affected than the contractile tissue, and, second, that it does not easily account for either the lipodystrophic or neuropathic changes seen in FPLD and AR-CMT2, respectively.

A second model arose from a pathological defect observed in all muscular dystrophies, but that currently has no molecular mechanism assigned to it. Normal skeletal muscle undergoes continuous rounds of degeneration–regeneration in response to injury (Ref. 81). This involves the proliferation of muscle stem cells (satellite cells), and their subsequent differentiation to form new myotubes. Satellite cells in dystrophic skeletal muscle display a limited proliferative capacity, and ultimately the regeneration step fails. To explain a defect specific to the satellite cells, one needs to identify proteins or mechanisms that are either specific to this cell type or are non-functional in other cell types because of genetic redundancy. It was proposed that, since there is evidence that emerin and lamin A/C are involved in cell-cycle-dependent processes, they or their unidentified muscle-specific binding partners might be part of such a mechanism. However, although this model might be expanded to incorporate the similar defect observed in adipocytes, it cannot account for the degeneration seen in cardiac or neuronal tissue, since these tissues are non-regenerative.

Tissue-specific effects from tissue-specific gene regulation?

Although both of the above hypotheses have points to recommend them, neither explains the tissue selectivity of the diseases or accounts for all the pathological defects observed. Could it be that mutations in different residues of lamin A/C have a selective effect on the cell types involved? The recent identification of interactions between nuclear lamina components and transcription factors suggests that the tissue specificity of these diseases might arise from subtle changes in tissue-specific gene regulation (Ref. 82). The LAP-2–lamin complexes are able to interact with both the tumour suppressor protein Rb and the 'germ-cell-less' (GCL) protein (a nuclear matrix protein identified in *Drosophila* as being required in the development of the germ-cell lineage) (Ref. 83). Both Rb and GCL proteins interact with E2F transcription factor (Fig. 2),

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which represses transcription of specific genes. The transcriptional repression by Rb correlates with its lamin-binding activity. The interaction between the LEM-domain-containing proteins and the DNA-bridging protein BAF might be a similar mechanism of controlling transcription. Finally, the inner nuclear membrane protein RFBP binds directly to RUSH protein, which is related to SW1/SNF transcription factors. These factors control the remodelling of chromatin (Refs 25, 83). Thus, to explain the tissue selectivity in the laminopathies, different residues of lamin A/C might interact with tissue-specific proteins that have some role in transcription regulation. These, in turn, would control specific downstream gene expression events, the exact event being dependent on the specific tissue affected. The recent publication of the three-dimensional structure of the lamin A/C globular tail revealing that the FPLD-associated mutations cluster within a small surface, whereas muscular dystrophy-associated mutations are distributed throughout the protein core and surface (Ref. 84), supports the theory of tissue-specific lamin A/C interactions.

This model is attractive because it provides a cogent basis for the satisfactory explanation of all the clinical phenotypes described. In addition, human GCL is itself a candidate for Alstrom syndrome, which displays some symptoms (diabetes and cardiomyopathy) that overlap with those seen in DCM and FPLD (Ref. 85). The nuclear-membrane–nuclear-lamina protein complexes regulate nuclear structure, but are also involved in tissue-specific chromatin organisation and transcription. They might provide binding sites for proteins that regulate transcriptional access to chromatin, or play a direct role in regulating transcription or chromatin structure. Heterochromatin normally undergoes regulated movement during the course of the cell cycle, as well as changes in transcriptional repression. Therefore, the model provides an acceptable explanation for the changes in heterochromatin distribution observed in the myonuclei of EDMD patients. Other evidence supporting this hypothesis comes from the observation that ectopic expression of lamin A in myoblast cells induces muscle-specific genes (Ref. 86). FPLD could be incorporated into this model by proposing either that lamin-A/C–Rb complexes bind with adipocyte-specific transcription factors or that the genes regulated by the complexes are adipocyte-specific. Interestingly, adipocytes and myocytes originate from a common mesenchymal stem cell lineage. It has been proposed that mutations in lamin A/C and emerin can selectively influence the development of cells in this lineage by affecting gene expression (Ref. 87).

In conclusion, the nuclear lamina can no longer be viewed as a structure that merely anchors chromatin and nuclear envelope proteins. It is clearly a dynamic entity, and is additionally involved in nucleocytoskeletal interactions, transcriptional repression and cell differentiation. One can therefore postulate with some confidence that mutations in any of the proteins involved in this complex series of interacting molecular pathways could variously result in development of a muscular dystrophy, a cardiomyopathy, lipodystrophy or a neuropathy phenotype (Fig. 4). The precise phenotype could then be dependent on which specific protein domain function is affected, or on single-nucleotide polymorphisms (SNPs), or on unidentified modifying genes.

Clinical implications

The life-threatening cardiac phenotype associated with DCM and EDMD necessitates the screening of all relatives of sufferers, including those that are completely asymptomatic, since there is a high incidence of sudden death within these families. Indeed, in some instances, sudden death can be the only symptom. The conduction defect is traditionally treated with the insertion of a pacemaker device, but sudden death is also reported in individuals subsequent to this treatment (Ref. 58). EDMD/DCM patients can suffer ventricular tachycardia or fibrillation, which a pacemaker can do nothing to prevent and might even induce. A preferred treatment is to insert an implantable cardio defibrillator (ICD), which is able to compensate for the onset of ventricular fibrillation (Ref. 88). In addition, there are now a significant number of patients presenting with EDMD/DCM symptoms without mutations in the emerin or lamin genes, suggesting other genes can also contribute to this phenotype. This group of patients also needs to undergo cardiological examination.

Research in progress

Screening for mutations in other proteins associated with the nuclear lamina is currently under way among families who have normal

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genes encoding emerin or lamin but who exhibit EDMD-like symptoms. Candidate genes include: lamin B1 and B2, LBR, LAP-1C and BAF. Pedigree analysis is being performed in greater depth to elucidate the incidence of families where individual family members exhibit a range of disease types yet carry the same mutation. This would help to resolve whether the LGMD-1B/DCM phenotype arises only as a result of incomplete penetrance of the EDMD phenotype. Triglyceride analysis and insulin measurements are being performed in EDMD/DCM/LGMD-1B patients, as well as those with classical FPLD. Similarly, patients diagnosed with AR-EDMD need to be re-evaluated in the context of AR-CMT2. AR-EDMD patients are very rare and lack any of the cardiopathic symptoms normally associated with EDMD, raising questions about the validity of their clinical diagnosis. In addition, there are several characterised SNPs in the *LMNA* gene, and there is some evidence that these might bias the clinical diagnosis. A common polymorphism (C>T) exists at His566, which is at the splice site of lamin A and lamin C. This polymorphism has been reported to contribute to the variation in fat distribution seen in the general population, with the 'T' allele producing a reduction in fat-cell size (Ref. 89). There are examples of both FPLD and EDMD patients with this polymorphism. The conduction defect observed in EDMD/DCM patients has not been elucidated at the molecular level. Concerted efforts have been initiated to collect hearts from post-mortem subjects, for detailed histological analysis and comparisons.

Lamin-A-type null mice (both homozygous and heterozygous) have been successfully constructed (Ref. 49). Although both types exhibit an EDMD-like phenotype, this is relatively mild in the heterozygous mouse. Neither mice type displayed any FPLD characteristics, but this might be because the mice failed to reach puberty. Aberrant nuclear morphology and emerin mislocalisation to the ER are observed in both mouse types, but these are more severe in the homozygous mouse. Ultrastructural analysis of peripheral nerves revealed neuropathic features in homozygous null mice, but not in heterozygous mice, similar to those found in the human neuropathies (Ref. 75). Knock-in mice are now being constructed, representing mutations found in the *LMNA* gene. The production of a dysfunctional protein, as opposed to no protein at all, might be required to visualise the full clinical phenotypes. In agreement with this concept, it has recently been shown that homozygous null mice for the protein Zmpste24, a possible metalloproteinase, develop muscular dystrophy, DCM and lipodystrophy, as a result of aberrant pre-lamin-A processing (Ref. 90). There have been no successful reports of a knock-out model for X-EDMD. Emerin and one lamin A-type protein are found in *Caenorhabditis elegans*; knocking out lamin A in this organism mislocalised emerin to the ER (Ref. 91). However, the emerin knock-out exhibited no phenotype.

Many investigators are examining the molecular functions of all the nuclear envelope proteins discussed here using in vitro and in vivo model systems. Novel binding partners for the lamins are being sought, and tissue-specific transcriptional pathways are being unravelled. Recently, it has been reported that distinct phenotypes have been observed for both EDMD and DCM mutants, depending upon whether the lamin A or lamin C cDNA carried the mutation (Ref. 50). This implies lamin A and lamin C are functionally non-equivalent. Future research needs to unravel how lamin A and lamin C interact with each other, as well as individually with other nuclear membrane components.

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Reference book

Emery, A.E.H., ed. (1999) Neuromuscular Disorders: Clinical and Molecular Genetics, Wiley and Sons

Electronic Sources

The European Neuro Muscular Centre website summarises diagnostic criteria for many neuromuscular disorders, reports on international workshops and hosts a discussion board.

http://www.enmc.org

A list of mutations found in the *STA* gene can be found in the Emery–Dreifuss Muscular Dystrophy Mutation Database.

http://www.pod-designs.net/emd/

The Online Mendelian Inheritance in Man (OMIM) database (US National Center for Biotechnology Information) is a catalogue of human genes and genetic disorders.

http://www.ncbi.nlm.nih.gov/Omim/

The UK-based Muscular Dystrophy Campaign website provides information about neuromuscular conditions, patient support (such as care and equipment), and activities of the charity.

http://www.muscular-dystrophy.org

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