Lamin Processing Comes of Age

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Lamins are the evolutionary progenitors of cytoskeletal intermediate filament (IF) proteins. In mammalian cells, IF proteins are almost ubiquitously expressed with approximately 60 different members known to date (Fuchs and Weber, 1994).

Lamins are characterized by an additional heptad repeat motif of 42 amino acids in the rod domain. By their α-helical rod domain, lamin forms coiled coil dimers that further polymerize in a head-to-tail fashion to form the lamina, a network lining the nucleoplasmatic side of the inner nuclear membrane (Aebi et al., 1986). Lamins are not only present in the nuclear lamina but are also found in the nucleoplasm, being part of intranuclear tubes and present as scaffold proteins. Here, they are thought to play an important role in maintenance of the structural integrity of the nucleus, in DNA replication, in transcription repression, and in apoptosis (for a review see Fuchs and Weber, 1994; Broers et al., 1997; Wilson et al., 2001; Hutchison and Worman, 2004).

Within the IF gene family, two main types of lamins are currently distinguished, the type A and the type B lamins. B-type lamins, represented by lamin B1, B2, and B3, are the initial building blocks of the nuclear lamina and are ubiquitously expressed in all mammalian cells. By contrast, expression of A-type lamins is almost undetectable in cells with a low degree of differentiation and/or in highly proliferating cells. By means of alternative splicing, the lamin A/C (LMNA) gene encodes at least four different A-type lamin protein members, lamin A, lamin A/C10, lamin C, and lamin C2 (Broers et al., 1997; Hutchison and Worman, 2004).

Mutations in the LMNA gene are associated with a broad spectrum of disorders that are collectively called laminopathies. The associated phenotypes include Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, dilated cardiomyopathy with conduction defect, Charcot–Marie–Tooth disease, Dunnigan-type familial partial lipodystrophy, mandibulo-acral dysplasia and Hutchinson–Gilford progeria (for a review see Broers et al., 2004; Hutchinson and Worman, 2004). Why so many different phenotypes can be associated with mutations in a single gene is presently poorly understood.

It is clear now that an intricate series of enzymatic modifications is required for the production of a normal lamin A. Prelamin A is farnesylated on its C-terminus and subsequently hydrolyzed. The zinc metalloprotease ZMPSTE24 is required for the final step. Its lack is therefore associated with the presence of abnormal amounts of (farnesylated) prelamin A in the nucleus, which is thought to be toxic to the cell (Klicic et al., 1999). Absence of ZMPSTE24 apparently does not affect the alternative splicing product, lamin C. Thus, it is not surprising that homozygous mutations in the ZMPSTE24 gene were found to cause laminopathies (Agarwal et al., 2003; Navarro et al., 2004). What is surprising, however, is that all ZMPSTE24 gene mutations in humans and mice are associated with progeroid disorders. Initially, mandibulo-acral dysplasia (MAD), a disorder that is very similar to the more well-known Hutchinson–Gilford progeria syndrome (HGPS), was the only associated disease. Homozygous and compound heterozygous mutations in ZMPSTE24 were found in patients with typical MAD (Agarwal et al., 2003).

HGPS, on the other hand, is so far apparently exclusively associated with heterozygous and compound heterozygous mutations in LMNA (for a review see Pollex and Hegele, 2004). The heterozygous mutation affects splicing of the LMNA gene so that a truncated prelamin A lacking 50 C-terminal amino acids is generated that cannot be processed. As it still contains the CAAX box, it is farnesylated. A toxic action of this truncated protein was postulated to account for the apparent dominant inheritance of HGPS (Fong et al., 2004).

Restrictive dermopathy (RD), also referred to as tight skin contracture syndrome, is a rare disorder that can be considered as a lethal form of HGPS. It is characterized by intrauterine growth retardation, tight and rigid skin with erosions, prominent superficial vasculature and epidermal hyperkeratosis, characteristic facial features (small mouth, small pinched nose and microglossia), sparse to absent eyelashes and eyebrows, mineralization defects of the skull, thin dysplastic clavicles, pulmonary hypoplasia, multiple joint contractures, and an early neonatal lethal course. Interestingly, Navarro et al. (2004) recently reported that RD was associated with heterozygous mutations in ZMPSTE24 and quite convincingly demonstrated defective lamin processing in their patients. Digenic inheritance was postulated as a possible explanation for the fact that heterozygous parents were healthy, whereas their equally heterozygous children had RD and defective lamin A processing, but Navarro et al. were not able to detect homozygous or compound heterozygous mutations in ZMPSTE24, nor were they and others able to demonstrate...
digenic inheritance (Navarro et al, 2004; own data, not yet published).

Although this problem has now apparently been solved, other questions immediately arise. In this issue of the JID, Moulsom et al report their finding of homozygous and compound heterozygous mutations in the ZMPSTE24 gene in RD (Moulsom et al, this issue). They further state that it is quite likely that compound heterozygous mutations were missed in the report by Navarro et al. Moulsom et al clearly demonstrate defective lamin A pre-processing and nuclear abnormalities as the characteristic hallmarks found in all other laminopathies, thus providing the first definitive proof that RD is a laminopathy. Furthermore, they confirm recessive inheritance of RD, which is invaluable for genetic counseling but also for our understanding of the pathogenesis of RD and related disorders.

An essential finding in their report deserves special attention because it may cast some doubt on the supposition that prelamin A is toxic. The nuclear localization of emerin, an inner nuclear membrane protein, is normal in RD fibroblasts. It is probably kept in its normal position by prelamin A, that is incorporated into the nuclear lamina and can apparently function normally as far as its binding to emerin is concerned. Although this does not prove that prelamin A is not toxic, it does, however, raise significant doubts regarding its supposed toxicity. Thus, the current explanation for the apparently dominant nature of mutations in HGPS may not be true. Instead, we think that it is far more likely that, like MAD and RD, HGPS is recessive and that the mutations in the other allele have simply not been detected.

In support of this notion, a recent report by Capanni et al (2005) shows that increased amounts of prelamin A are present not only in HGPS, but also in MAD and familial partial lipodystrophy of the Dunnigan type, another laminopathy. If prelamin A were toxic, one would expect more uniformity within this phenotypic spectrum. Rather than being toxic, however, prelamin A may bind the SREBP1 protein and limit its translocation to the nuclear interior, thereby interfering with fat metabolism by lowering PPAR-γ expression. The lipodystrophy that is common to all of these phenotypes may well result from this phenomenon. The progeroid phenotype of MAD, RD, and HGPS, on the other hand, seems to be the consequence of the absence of a functional lamin A network per se, as the mutations causing Dunnigan-type lipodystrophy and the various muscular dystrophies do not affect lamin structure (Krimm et al, 2002).

Still, a very significant question remains. What causes the phenotypic variation within the group of the progeroid laminopathies? As mutations in genes known to interact with lamin A have so far not been found in any of these disorders, the most plausible explanation for the observed phenotypic variability might be to postulate the putative presence of other hitherto undetected genetic defects interacting with lamin deficiency. Thus, the detection of novel genes involved in laminopathies and the functional characterization of their protein products will be one of the most important missions for researchers in the near future.

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References