Another Broken Heart
Loss of Lamina-Associated Polypeptide 2α Causes Systolic Dysfunction
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More than one-third of cases of dilated cardiomyopathy (DCM) are caused by inherited mutations, with 5% to 10% of these mutations being linked to the LMNA gene encoding the nuclear envelope proteins lamin A and C.1–3 Whereas geneticists have mostly looked for mutations in genes encoding sarcomeric and cytoskeletal proteins in the past, genes for nuclear envelope associated proteins are proving to be equally important candidate genes for DCM. The subsequent discoveries that mutations in other nuclear envelope proteins that directly bind to lamin A/C, for example, nesprin4 and emerin,5 can also cause DCM has stimulated the interest in exploring the role of lamin and its binding partners in DCM. New insights into the functional mechanisms by which nuclear proteins can cause DCM have come from the identification of a mutation in another lamin A/C binding partner, the nuclear protein lamina-associated polypeptide (LAP)2α, as a cause for DCM in a large kindred6 and subsequent studies in LAP2α-deficient (LAP2α−/−) mice.7 In this issue of Circulation Research, Gotic et al report that young, male, LAP2α−− mouse develop systolic dysfunction and show deregulation of the major cardiac transcription factors GATA4 and myocyte enhancer factor (MEF)2c.8 These findings, taken together with previous reports showing an important role of lamin A/C in regulating gene expression by sequestering or altering the activity of transcription factors,3–11 suggest that (nucleoplasmic) lamins may act as a scaffold for transcription factors and other DNA binding proteins such as LAP2α and, through this complex, modulate gene expression and cell function. This function could be distinct or overlapping with their role in providing nuclear structure and support.12

The nuclear envelope has gained particularly great interest because mutations in its components have been associated with a spectrum of diseases ranging from muscular dystrophy, DCM, familial partial lipodystrophy, peripheral neuropathy, and bone defects to premature aging (reviewed by Woman et al13). Lamins are the major building blocks of the nuclear lamina, a dense protein network underlying the inner nuclear membrane, and of a more diffuse network in the nucleoplasm.14,15 The detailed higher order structure of lamins, their various cellular functions, and the molecular mechanisms underlying nuclear envelope–associated diseases such as DCM remain unclear and are the focus of intense research. Lamins were originally regarded as mere structural proteins providing stability and structural support to the nuclear envelope but are now known to be also involved in chromatin organization, gene regulation, DNA transcription and replication, DNA repair, and overall cellular integrity (reviewed by Verstraeten et al16). Importantly, it is the interaction of lamins with a multitude of integral nuclear membrane proteins, such as emerin, MAN1, LAP2 proteins, lamin B receptor, SUN proteins, and transcription factors such as SREBP-1c, c-Fos and retinoblastoma protein (pRb), that give lamins a pivotal role in the nucleus. LAP2α is the sole member of the LAP2 family that lacks a transmembrane domain and is restricted to the nucleoplasm. Here, LAP2α binds the nucleoplasmic pool of lamins A and C and forms a complex with the cell cycle regulator and tumor suppressor pRb (Figure). Through the LAP2α–lamin A/C–pRb complex, LAP2α modulates pRb and thus controls cell cycle exit and, thereby, the maintenance of progenitor pools.7

The fact that mutations in both lamin A/C and LAP2α result in DCM suggests a major role for the lamin A/C–LAP2α complex in cardiac function. Gotic et al tried to further dissect the cardiac function role of this complex and specifically looked at the role of LAP2α in recently created LAP2α−− mice7 and in a conditional knockout mouse model. In their studies, young male LAP2α−− mice developed ventricular systolic dysfunction characterized by significantly decreased fractional shortening and ejection fraction; 10- to 12-month-old male mice showed similar defects in systolic function without further progression. Interestingly, 3 of 11-old male mice showed cardiac fibrosis. Although these numbers are not quite statistically significant, they could indicate an increased susceptibility to cardiac fibrosis in LAP2α−− mice. In contrast to the male mice, female LAP2α−− mice did not develop any overt phenotype. This finding is reminiscent of LmnaA222P/A222P mice, a model for Emery–Dreifuss muscular dystrophy, where female mice developed a milder phenotype, which suggests yet to be identified sex differences. Because of the systolic dysfunction observed in LAP2α−− mice, Gotic et al studied the
expression of transcription factors crucial in cardiac development and hypertrophic response. MEF2c expression was significantly decreased in newborn LAP2α−/− hearts, although reached normal levels by the age of 10 weeks. GATA4, myocardin A, and STARS (striated muscle activator of Rho signaling) were found to be repressed in old LAP2α−/− hearts only. Brain natriuretic peptide, which is one of the downstream effectors of MEF2c and GATA4, showed a reduced expression in both young and old LAP2α−/− hearts. Because brain natriuretic peptide has an inhibitory effect on fibroblast proliferation and extracellular matrix production, its reduced expression could add to the sporadically observed extensive cardiac fibrosis in male LAP2α−/− hearts. In an attempt to produce a more pronounced cardiac phenotype, the authors subjected LAP2α−/− mice to treatment with a β-adrenergic agonist, isoproterenol, which increases heart rate and contractility. Whereas wild-type animals had a significant increase in systolic left ventricular diameter and end-systolic left ventricular volume after isoproterenol infusion for 7 days, the increase in LAP2α−/− over baseline was not statistically significant. However, absolute differences between wild-type and LAP2α−/− mice were comparable after isoproterenol treatment, indicating that the effect of LAP2α on the β-adrenergic response was rather small. The authors attribute this attenuated stress response to reduced expression of β-adrenergic receptor 2 in LAP2α−/− hearts. Unfortunately, without analysis of the expression for β-adrenergic receptor-1, it is hard to draw definitive conclusions regarding this matter.

The authors recently demonstrated that LAP2α regulates the homeostasis and number of progenitor cells by modulating localization of lamins A/C and affecting pRb activity. To address whether the observed systolic dysfunction in male LAP2α−/− mice was a consequence of loss of LAP2α during early development or later on in life, the authors used a conditional LAP2α−/− mouse that abolishes LAP2α expression in mature cardiomyocytes only. These mice, however, did not develop any overt cardiac phenotype, suggesting that the major role of LAP2α is restricted to early stages of cardiac development or during cardiac homeostasis later on in life. This is consistent with previous findings that LAP2α is primarily involved in the regulation of early progenitor cell proliferation in regenerative tissues in vivo and is only moderately expressed in the adult heart. It would be interesting to test the opposite scenario, ie, whether depletion of LAP2α only in early stages of cardiac development or in progenitor cells is sufficient to cause systolic dysfunction.

A role of LAP2α in cardiac progenitor cells could also have important implications in adult hearts. A recent study provided strong evidence for cardiomyocyte renewal in humans. Evaluation of the integration of carbon-14, generated by nuclear bomb tests during the Cold War, into DNA of cardiomyocyte nuclei showed that approximately half of the cardiomyocytes are exchanged during normal life span. Cardiomyocyte renewal does decrease by age from 1% at the age of 25 to 0.45% at the age of 75. In view of the previously established role of LAP2α in the proliferation of tissue progenitor cells, its absence could negatively affect the cardiac regenerative potential, resulting in heart failure and, eventually, leading to DCM.

In light of these facts, what is the outlook of DCM caused by mutations in nuclear envelope proteins? There is increasing evidence of a major role of defective gene regulation in the development of DCM associated with mutations in nuclear envelope proteins. Emerin-null and LmnaH222P/H222P mice, 2 models of Emery–Dreifuss muscular dystrophy, which is associated with severe DCM in humans, show significant activation of the extracellular signal-regulated kinase 1/2 branch of the mitogen-activated protein kinase pathway before clinical signs or molecular markers of cardiomyopathy become apparent. These findings showed promise for pharmacological interventions to treat or prevent cardiomyopathy in the context of Emery–Dreifuss muscular dystrophy. Indeed, treatment of LmnaH222P/H222P mice with PD98059, an inhibitor of extracellular signal-regulated kinase phosphorylation, delayed the development of left ventricular dilatation. Although, Gotic et al did not address any putative alterations in the mitogen-activated protein kinase pathway directly, significant changes in some major cardiac transcription factors such as GATA4 and MEF2c support a primary role for defective gene regulation in the pathogenesis of DCM. This is consistent with the reduced activation of hypertrophic genes despite severe DCM in lamin A/C–null mice and the recent finding that mice that are haploinsufficient for lamin A/C (Lmna−/−) have an attenuated hypertrophic response and reduced induction of the cardiac hypertrophy gene Egr-1 in response to pressure overload. Although the impaired activation of mechano-sensitive genes Egr-1 and Iex-1 in mouse fibroblasts lacking lamin A and C may suggest that the reduced nuclear stiffness associated with loss of lamin A/C may contribute to this impaired gene activation, it is also likely that transcriptional regulation and nuclear structural support are separate (albeit potentially overlapping) functions of lamins. In the case of nuclear envelope proteins, DCM could arise from defects in either function, depending on the specific nature of the mutation. Mutations that affect both structural and signaling properties, or complete loss of lamin function, would then result in additive effects and more severe DCM, as seen in lamin A/C–null mice. The pathogenic changes in gene expression causing DCM could be manageable with pharmacological interventions. However, it will be more challenging to intervene with the loss of nuclear and cellular integrity causing DCM.
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References


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