Amelioration of desmin network defects by αB-crystallin overexpression confers cardioprotection in a mouse model of dilated cardiomyopathy caused by LMNA gene mutation.

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Abstract

The link between the cytoplasmic desmin intermediate filaments and those of nuclear lamins serves as a major integrator point for the intracellular communication between the nucleus and the cytoplasm in cardiac muscle. We investigated the involvement of desmin in the cardiomyopathy caused by the lamin A/C gene mutation using the LmnaH222P/H222P mouse model of the disease. We demonstrate that in these mouse hearts desmin loses its normal Z disk and intercalated disc localization and presents aggregate formation along with mislocalization of basic intercalated disc protein components, as well as severe structural abnormalities of the intercalated discs and mitochondria. To address the extent by which the observed desmin network defects contribute to the progression of LmnaH222P/H222P cardiomyopathy, we investigated the consequences of desmin-targeted approaches for the disease treatment. We showed that cardiac-specific overexpression of the small heat shock protein αB-Crystallin confers cardioprotection in LmnaH222P/H222P mice by ameliorating desmin network defects and by attenuating the desmin-dependent mislocalization of basic intercalated disc protein components. In addition, αB-Crystallin overexpression rescues the intercalated discs, mitochondrial and nuclear defects of LmnaH222P/H222P hearts, as well as the abnormal activation of ERK1/2. Consistent with that, by generating the LmnaH222P/H222PDes+/- mice, we showed that the genetically decreased endogenous desmin levels have cardioprotective effects in LmnaH222P/H222P hearts since less desmin is available to form dysfunctional aggregates. In conclusion, our results demonstrate that desmin network disruption, disorganization of intercalated discs and mitochondrial defects are a major mechanism contributing to the progression of this LMNA cardiomyopathy and can be ameliorated by αB-Crystallin overexpression.

KEYWORDS: Cytoskeleton; Desmin; LMNA cardiomyopathy; Lamin A/C; αB-Crystallin