Abstract

BACKGROUND: Mutations in the LMNA gene are a common cause (6-8%) of dilated cardiomyopathy (DCM) leading to heart failure, a growing health care problem worldwide. The premature aging disease Hutchinson-Gilford syndrome (HGPS) is also caused by defined mutations in the LMNA gene resulting in activation of a cryptic splice donor site leading to a defective truncated prelamin A protein called progerin. Low levels of progerin are expressed in healthy individuals associated with ageing. Here, we aimed to address the role of progerin in dilated cardiomyopathy.

METHODS AND RESULTS: mRNA expression of progerin was analyzed in heart tissue of DCM (n = 15) and non-failing hearts (n = 10) as control and in blood samples from patients with DCM (n = 56) and healthy controls (n = 10). Sequencing confirmed the expression of progerin mRNA in the human heart. Progerin mRNA levels derived from DCM hearts were significantly upregulated compared to controls (1.27 ± 0.42 vs. 0.81 ± 0.24; p = 0.005). In contrast, progerin mRNA levels in whole blood cells were not significantly different in DCM patients compared to controls. Linear regression analyses revealed that progerin mRNA in the heart is significantly negatively correlated to ejection fraction (r = -0.567, p = 0.003) and positively correlated to left ventricular enddiastolic diameter (r = 0.551, p = 0.004) but not with age of the heart per se. Progerin mRNA levels were not influenced by inflammation in DCM hearts. Immunohistochemistry and Immunofluorescence analysis confirmed increased expression of progerin protein in cell nuclei of DCM hearts associated with increased TUNEL+ apoptotic cells.

CONCLUSION: Our data suggest that progerin is upregulated in human DCM hearts and strongly correlates with left ventricular remodeling. Progerin might be involved in progression of heart failure and myocardial aging.

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