

Abstract

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Antioxidant therapy attenuates myocardial telomerase activity reduction in superoxide dismutase-deficient mice.

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OBJECTIVE: Oxidative stress plays a pathological role in the development of heart failure. This study examined telomere biology in heart/muscle-specific manganese superoxide dismutase-deficient mice (H/M-SOD2(-/-)), which develop progressive congestive heart failure and exhibit pathology typical of dilated cardiomyopathy.

METHODS: EUK-8 (25mg/kg/day), a superoxide dismutase and catalase mimetic, was administered to H/M-SOD2(-/-) mice for four weeks beginning at 8 weeks of age. Telomere length, telomerase activity, telomere-associated proteins, and cell death signals were assessed in hearts from control wild-type mice (H/M-Sod2 (lox/ lox)) and H/M-SOD2(-/-) mice either treated or untreated with EUK-8.

RESULTS: While cardiac function was unchanged in these experimental mice, the end-diastolic dimension in H/M-SOD2(-/-) mice was notably dilated and could be significantly reduced by EUK-8 treatment. At the end of the study, no shortening of telomere length was observed in heart tissues from all mice tested, but telomerase activity was decreased in heart tissue from H/M-SOD2(-/-) mice compared to control mice. Protein expression for telomerase reverse transcriptase and telomere repeat binding factor 2 was also downregulated in H/M-SOD2(-/-) heart tissue as was expression of phospho-Akt, insulin-like growth factor, and endothelial nitric oxide synthase. Expression levels of Sirt1, a lifespan modulator, were enhanced while FoxO3a was depressed in H/M-SOD2(-/-) hearts. All of the changes seen in H/M-SOD2(-/-) heart tissue could be inhibited by EUK-8 treatment.

CONCLUSION: Taken together, the results suggest that oxidant stress might affect myocardial telomerase activity and telomere-associated proteins. Telomerase may therefore play a pivotal role in antioxidant defense mechanisms, and may be useful as a novel therapeutic tool for treating human heart failure.

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