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Oral presentation

In vivo evidence that cyclic GMP-dependent protein kinase G type I α mediates an anti-hypertrophic pathway in the heart

Robert M Blanton*, Alexandra Dabreo, Richard H Karas and Michael E Mendelsohn

Address: Molecular Cardiology Research Institute, Tufts-New England Medical Center, Boston, MA, USA

Email: Robert M Blanton* - rblanton@tufts-nemc.org

* Corresponding author

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Protein Kinase G I (PKGI) has been implicated as a negative regulator of pathologic cardiac hypertrophy [1,2], though the specific molecular mechanisms involved are unknown. To test the hypothesis that PKGIα negatively regulates cardiac hypertrophy, we characterized the cardiac phenotype in mice homozygous for a leucine zipper mutant (LZM) form of PKGIα in which critical amino acids in the N-terminal LZ motif have been substituted to disrupt PKGIα LZ binding to specific downstream effector proteins. We characterized the hearts of these LZM mice morphologically, by echocardiography and invasive hemodynamics in the unstressed state, and following pressure overload-induced cardiac hypertrophy. In the unstressed state, male PKG Iα LZM mice develop progressive left ventricular hypertrophy (LV mass/ tibia length) compared with wild type (WT) littermates with LV mass 12.3% greater at 30 weeks of age ($p = 0.05$, n = 10 WT, 9 LZM); and 27% greater at 60 weeks of age ($p < 0.001$, n = 5 WT, 13 LZM). Compared with age matched WT mice, the hearts of 30 week old PKGIα mutants are hypercontractile with decreased end systolic diameter (2.25 mm WT vs 1.95 mm LZM, $p = 0.02$) and increased fractional shortening (36.9% WT vs 42.2% LZM, $p = 0.03$) on echocardiography (n = 9 wt, 9 LZM). Invasive hemodynamic assessment demonstrates that LZM mice also have increased left ventricular systolic pressure (107.0 mmHg WT vs 120.7 mmHg LZM, $p = 0.04$), developed pressure (107.5 mmHg WT vs 119.2 mmHg LZM, $p = 0.05$), and LV dP/dt max (8972 mmHg/s WT vs 9802 mmHg/s LZM, $p = 0.13$).

To evaluate the response to hemodynamic stress, cardiac hypertrophy was induced by transaortic constriction (TAC) in 10–12 week old male WT (n = 21) and LZM (n = 15) mice. TAC resulted in striking and early mortality in the LZM mice (60%) compared to the WT (19%) mice at 21 days post procedure ($p = 0.008$), with evidence of accelerated LV hypertrophy in the mice that died early (LV mass/tibia length 9.8 mg/mm in the early LZM deaths vs 7.2 mg/mm in WT 21 day survivors, $p < 0.001$). Additionally, the LZM early deaths had evidence of congestive heart failure with increased right ventricular mass (RV mass/ tibia length 1.8 mg/mm in LZM early deaths vs 1.2 mg/mm in WT 21 day survivors, $p < 0.05$), and increased lung mass (23.1 mg/mm LZM early deaths vs 12.5 mg/mm in WT 21 day survivors, $p < 0.005$). These findings support that the N-terminal LZ domain of PKGIα is required for PGKIα-mediated suppression of cardiac hypertrophy in both unstressed hearts and those exposed to pressure overload. The early mortality following TAC in the LZM mice also supports a critical role for PKGIα in attenuating pathologic cardiac remodeling, identifying PKGIα as an attractive candidate therapeutic target for prevention of cardiac hypertrophy and failure.

References

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