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THE ROLE OF TRB3 IN CARDIAC ENDOPLASMIC RETICULUM STRESS

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Objectives TRB-3 (tribbles 3), also called NIPK (neuronal cell death-inducible protein kinase) disrupts insulin signalling by binding to Akt and blocking their activation. TRB3 expression is highly regulated in many cell types, endoplasmic reticulum (ER) stress promotes TRB3 expression in cardiac cells. This work was to examine TRB3 expression and function in cultured cardiac myocytes and in mouse heart.

Methods Cultured HL-1 murine atrial cardiac myocytes were treated with thapsigargin and stimulated with insulin. HL-1 cells were treated with thapsigargin (2 μ M), and 24 h later cells were treated with insulin (10 nM) or control buffer and Akt activation was examined by Western-blotting with an anti-phospho-Akt antibody.

Results Thapsigargin-treated HL-1 cells were resistant to insulin-stimulated Akt activation, and exhibited increased protein levels for GRP78 and CHOP. Some agents induced ER stress increased TRB3 expression in cultured cardiac myocytes while blocking Akt activation in these cells. Experimental myocardial infarction led to increased TRB3 expression in murine heart tissue in the infarct border zone and increased levels of GRP78 protein were detected, pressure overload by transverse aortic constriction in mice resulted in cardiac ER stress, detected increasing levels of GRP78 and CHOP. ER stress may play a role in pathological cardiac remodelling. Transgenic TRB3 mice were also sensitised to infarct expansion and cardiac myocyte apoptosis in the infarct border zone after myocardial infarction.

Conclusions These results demonstrate that TRB3 induction is a significant aspect of the ER stress response in cardiac myocytes. Cardiac ER stress leads to TRB3 induction, Akt inhibition and cardiac myocyte death. Cultured cardiac myocytes exhibited reduced Akt activity dependent on increased expression of TRB3. Experimental myocardial infarction in mice resulted in the induction of TRB3 and other ER stress markers in the infarct border zone. TRB3 antagonises cardiac glucose metabolism and cardiac myocyte survival.