**CROSS-TALK BETWEEN MITOCHONDRIAL AND ER DEATH PATHWAYS IN THE HEART**

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Alternative gene splicing provides a versatile mechanism by which cells generate proteins with different or even antagonistic properties. Previously we determined the hypoxia-inducible protein Bnip3 is integral component of the mitochondrial death pathway that can signal apoptosis and autophagy but the precise mechanisms that differentially regulates these divergent processes remains cryptic. Herein, we provide novel evidence that inclusion or skipping of exon3 of Bnip3 mRNA by alternative splicing generates proteins with distinct and opposing actions on autophagy and cell survival. Metabolic stress imposed by hypoxia or nutrient deprivation resulted in the synthesis of two Bnip3 mRNA isoforms in post-natal ventricular myocytes in vitro and in vivo. Notably, one Bnip3 mRNA comprised of exons 1 through exon 6 encoded a protein of 26kDa, while a second mRNA generated by the fusion of exon2 and exon4 encoded a truncated Bnip3 protein of 8.2kDa. Sequence analysis revealed the truncated isoform encodes a conserved C-terminus domain that exclusively targets Bnip3 to the endoplasmic reticulum and not mitochondrion. While the 26kDa Bnip3 induced mitochondrial perturbations and autophagy, the spliced variant suppressed Bnip3- induced mitochondrial defects and autophagy. Furthermore, genetic knock-down or mutations within the C-terminus of the spliced variant defective for ER targeting sensitized cardiac myocytes to mitochondrial ROS production and death. To our knowledge our data provide the first direct evidence for a novel survival mechanism whereby the metabolic status of the cell programs autophagy or apoptosis by preferentially targeting Bnip3 isoforms to mitochondria or ER during metabolic stress.