P023 Bcl-2 regulates β-cell metabolism and Ca^{2+} homeostasis

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Anti-apoptotic Bcl-2 interacts with mitochondrial proteins such as adenine nucleotide translocase and voltage-dependent anion channel, suggesting that Bcl-2 might influence mitochondrial physiology. Bcl-2 in the ER can protect cells by controlling Ca^{2+} release. This provides tantalizing links between Bcl-2 and 'everyday' cell function. Using small molecule Bcl-2 inhibitors we therefore studied the moment-to-moment roles of endogenous Bcl-2 in primary mouse and MIN6 β-cells. Inhibition of Bcl-2 induced caspase-3 activation and β-cell death. Prior to cell death, we observed pronounced release of Ca^{2+} from the ER and large cytosolic Ca^{2+} fluctuations. Blocking the ER IP_3R and RyR Ca^{2+} channels attenuated cell death and cleaved caspase-3 levels. The cytosolic Ca^{2+} signals were rapidly reversible, suggesting a physiological basis. Removing extracellular Ca^{2+}, blocking voltage-gated Ca^{2+} channels or opening K_{ATP} channels with diazoxide all prevented the Ca^{2+} rises. Moreover, 80 μM Bcl-2 inhibitor hyperpolarized β-cell mitochondria as effectively as 10 mM glucose and respiratory chain inhibition with NaN_3 blocked the Ca^{2+} signals. Acute inhibition of Bcl-2 therefore activates β-cell mitochondrial metabolism and voltage-gated Ca^{2+} influx in a manner that in many ways resembles the β-cell response to glucose. Our findings provide compelling evidence that Bcl-2 controls β-cell Ca^{2+} homeostasis and mitochondrial energetics. This likely constitutes part of the mechanisms by which Bcl-2 regulates cell death, and intriguingly also suggests Bcl-2 as a putative player in the context of β-cell glucose signaling.