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Previews

When BAD Is Good for β Cells

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BAD, a proapoptotic member of the Bcl-2 family of proteins, is regulated by phosphorylation. A recent study (Danial et al., 2008) suggests a phosphorylation-state-dependent bifunctional role of BAD in the regulation of glucose-stimulated insulin secretion and β cell mass.

Interplay between pro- and antiapoptotic members of the Bcl-2 family of proteins regulates apoptosis by controlling mitochondrial cell death signaling and caspase activation. BAD (Bcl-x_L/Bcl-2-associated death promoter homolog, or Bcl antagonist of cell death) was the first proapoptotic member of the Bcl family to be described. BAD alone is a relatively weak inducer of apoptosis requiring binding with other Bcl proteins for full activity. BAD interaction with a multiprotein complex consisting of Bcl-x_L/Bcl-2 and BAK/BAX triggers apoptosis and is determined by the phosphorylation state of BAD. Although the precise mechanisms are not completely understood, the dephosphorylated BAD BH3 domain binds and inhibits antiapoptotic Bcl-x_L and derepresses proapoptotic BAK/BAX. BAK and BAX aggregate in and permeabilize the mitochondrial outer membrane, facilitating release of proapoptotic mitochondrial proteins into the cytoplasm, apoptosome assembly, and activation of cellular executing caspases.

BAD appears to be a multifunctional protein capable of participating in both cellular survival and death pathways. BAD is a substrate for several antiapoptotic kinases, including protein kinase A (PKA) and protein kinase B (PKB or Akt). Serine phosphorylation of BAD and formation of an inactive complex between phospho-BAD and 14-3-3 proteins may be important cellular survival signals. In mouse hepatocytes, phosphorylated BAD regulates glucose metabolism and mitochondrial bioenergetics. *Bad* knockout mice and expression of an unphosphorylated form of BAD have confirmed an unexpected role of phosphorylated BAD in mitochondrial function, specifically regulating glucokinase (GK; hexokinase IV) in hepatocytes (Danial et al., 2003). Phospho-BAD is necessary for the formation of a functional holoenzyme complex with GK, PKA, protein phosphatase 1 (PP1), and Wiskott-Aldrich syndrome protein (WASP)-family verprolin-homologous protein 1 (WAVE1) (Danial et al., 2003).

A recent study (Danial et al., 2008) demonstrated a central role of BAD in the physiological regulation of insulin secretion and β cell mass. In transgenic $Bad^{-/-}$ mice, β cell function and GK activity were impaired. The first phase of glucose-stimulated insulin secretion (GSIS) was inhibited, and responses to other secretagogues were unaffected. Complementary genetic and biochemical strategies were used to inhibit and rescue phospho-BAD function and establish that phosphorylation of the BAD BH3 domain at Ser155 is required for GSIS and binding to GK. In addition to regulating metabolism, BAD phosphorylation may also be an important survival signal in β cells. Phosphorylated BAD levels are elevated in islets from Zucker diabetic fatty rats prior to the onset of diabetes (Jetton et al., 2005), and high-fat feeding increases *Bad* mRNA expression in mouse islets (Danial et al., 2008). The increased β cell proliferation seen in chronic mild hyperglycemia in a rat model was due to both increased survival and neogenesis of β cells rather than proliferation (Jetton et al., 2008), although in a similar glucose-infused mouse model, replication was enhanced but death rates were unchanged (Alonso et al., 2007). Interestingly, a transgenic mouse model for overexpression of Bcl-x_L,a possible competitor of glucokinase for BAD binding, inhibited β cell death but impaired mitochondrial function, resulting in decreased insulin secretion (Zhou et al., 2000). Future studies may be directed at determining whether there is in fact decreased apoptosis in high-fat-fed $Bad^{-/-}$ mouse islets. Their β cells do seem to have a survival advantage despite decreased insulin secretion, reminiscent of Bcl-x_L-overexpressing mice (Zhou et al., 2000). Despite the decreased insulin secretory capacity, the increase in islet number in response to high-fat feeding in $Bad^{-/-}$ mice compensates for the defect. Islet mass compensation was not seen in a transgenic knockin mouse expressing a mutant of BAD (Bad^{3SA}) with enhanced proapoptotic activity, suggesting that the two functions of BAD are separable (Danial et al., 2008).

The direct interaction between BAD and GK may provide additional insights into the pathogenesis of diabetes. In the human form of monogenic diabetes caused by *GK* mutations, mature onset diabetes of the young, type 2 (MODY2), some of the *GK* mutations are functionally intact but still cause mild diabetes. For example, three GK mutants, R36W, A53S, and V367M, have kinetic and thermal stability properties similar to those of wild-type GK (Miller et al., 1999). These have been thought to cause MODY2 by a defect in protein-protein interactions. The mutations are all on the external surface of GK, based on computer modeling, and far from the active site: do they lack a BAD BH3 binding site? These residues (especially R36 and A53 in the amino terminus of GK) could form a potential interaction domain with BAD BH3.

Since apoptosis and cellular metabolism converge at the mitochondrion, this suggests a unifying hypothesis tying together etiologies of insulin resistance and β cell dysfunction leading to type 2 diabetes mellitus (T2DM) (Muoio and Newgard, 2008). A growing list of β cell defects in type 2 diabetes includes altered mitochondrial calcium and morphology, impaired glucose oxidation, and reduced ATP generation along with a relative decrease in functional β cell mass (Wiederkehr and Wollheim, 2008). Muscle cells from obese *fa/fa* rats have reduced

mitofusin-2 expression, consequent mitochondrial fragmentation, and multiple bioenergetic defects that likely decrease insulin effectiveness (Bach et al., 2003). Proapoptotic BAX binds to mitochondrial fission sites, interacts there with mitochondrial fission proteins, and may play a role in apoptotic mitochondrial fragmentation. BAX or BAK is required for mitochondrial fusion in normal fibroblasts and kidney cell lines (Karbowski et al., 2006). Early dysregulation of the BAD-GK complex due to phosphorylation or decreased mitochondrial binding could cause decreased insulin secretion, perhaps in part mediated by reactive oxygen species (ROS) production in the mitochondria leading to further BAX release, stimulating mitochondrial fission in diabetic islets.

T2DM is thought to arise from a lack of functional β cell mass in the face of insulin resistance. Overwork of β cells in a failed attempt to compensate for increased insulin demand could contribute to a defect in the BAD-GK-mitochondrion interaction, setting off a cascade of events leading to further insulin resistance and hyperglycemia (Fridlyand and Philipson, 2004; Muoio and Newgard, 2008). Although increased GSIS might temporarily improve the diabetic state, oxidative stress consequent to overproduction of ROS by both oxidative phosphorylation in mitochondria and elevated proinsulin translation in the endoplasmic reticulum may eventually lead to β cell failure (Fridlyand and Philipson, 2004). Integrating causes of both insulin resistance and β cell failure due to metabolic stress factors would lead to a unifying mechanistic hypothesis for T2DM (Muoio and Newgard, 2008). Treatment interventions targeting muscle mitochondrial function or number could improve insulin resistance pathways, which would reduce the demand for insulin. Simultaneously, functional inhibition of β cells along with incretin agonist therapy might allow recovery from metabolic stress. Together, these approaches in effect could replicate the impressive results in ameliorating or preventing T2DM achieved by intensive exercise and significant weight loss. By establishing BAD as an important metabolic and survival sensor in β cells, Danial and colleagues (2008) have provided exciting new information necessary for improving our understanding of β cell biology and possible mechanisms underlying the pathophysiology of the growing epidemic of diabetes.

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Fly-let Biology and the High Protein/Low Carb Diet

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In *Drosophila*, a simple network of nutrient-sensing neuroendocrine cells, analogs of pancreatic islet α and β cells, regulates carbohydrate metabolism. Work presented in this issue of *Cell Metabolism* (Buch et al., 2008) shows that signals from these cells control expression of a glycogen-specific glucosidase in response to dietary protein and carbohydrate.

The modern, postgenome era is seeing a resurgence of insect physiology, focusing on *Drosophila* as a model system. A key question to address is, how do nutrition and endocrine circuits affect gene expression? This question is of particular interest because dietary status in animals controls life span, metabolic disease, and growth. Recent studies in flies have used microarray analysis to identify genes whose levels of expression change in response to starvation or dietary intake of sugar (Zinke et al., 2002) or protein (Gershman et al., 2007). These studies have identified genes encoding components of known carbohydrate and lipid metabolic pathways and macromolecular synthesis pathways, as well as many uncharacterized