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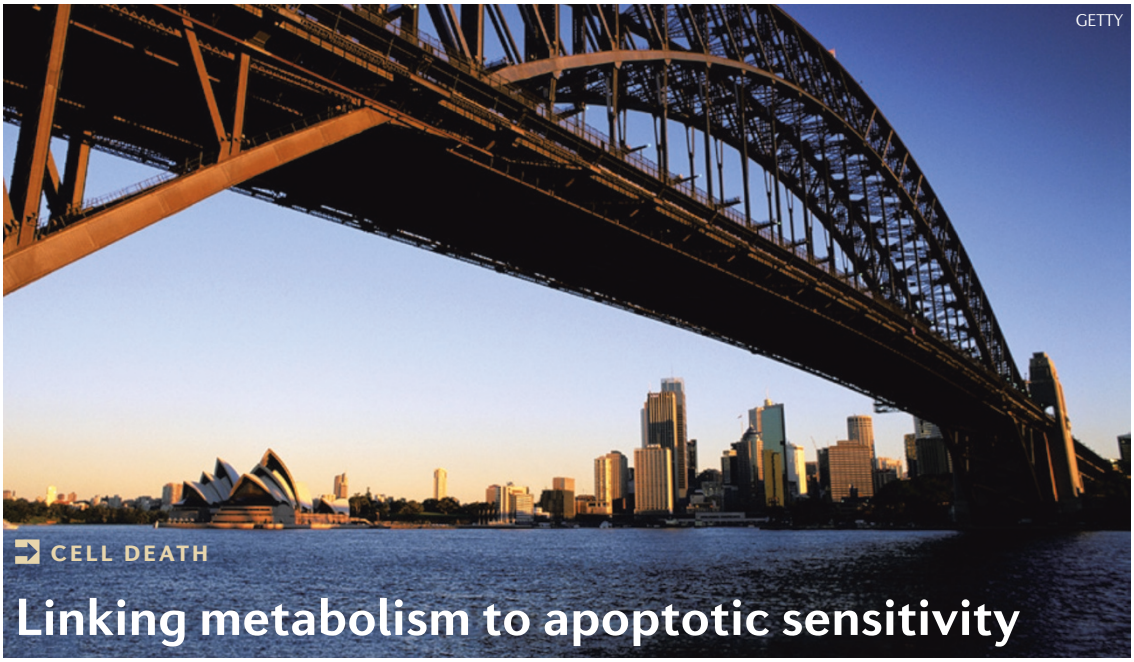

CELL DEATH

Linking metabolism to apoptotic sensitivity

> BCL-XL reduces acetyl CoA levels to inhibit apoptosis.

Studies have suggested that specific metabolites contribute to apoptotic resistance, but the mechanism behind this has been unclear. Yi *et al.* now reveal that the anti-apoptotic protein B-cell lymphoma-extra large (BCL-XL) negatively regulates acetyl CoA levels, and thus acetylation of the amino-terminal α-amine (N^{α}-acetylation), to promote apoptotic resistance.

Protein N^{α}-acetylation is regulated by several *N*-acetyltransferases, including NATA, which consists of the catalytic subunit N^{α}-acetyltransferase 10 (NAA10) and the auxiliary subunit NAA15. As the authors had previously identified the *Drosophila melanogaster* homologue of NAA10, arrest defective 1 (ARD1), as a regulator of apoptosis, they sought to determine whether N^{α}-acetylation links apoptosis and metabolism. Knockdown of *Ard1* in *D. melanogaster* cells, or of *NAA10* or *NAA15* in human cells, conferred apoptotic resistance in response to DNA-damaging agents, suggesting that N^{α}-acetylation is required for apoptosis.

To study this idea further, the authors developed an assay for measuring N^{α}-acetylation, which uses a ligase that adds biotin to proteins that are not acetylated at their N terminus. Thus, a higher level of biotinylated proteins correlates with a lower level of N^{α}-acetylation. Knockdown of *NAA10* or *NAA15* increased the biotinylation of known and predicted N^{α}-acetylation substrates, as determined by western blotting. Furthermore, a 30% reduction in the level of N^{α}-acetylated caspase 2 was observed in NAA15-deficient cells by mass spectrometry, validating the specificity of this assay.

As BCL-XL is known to influence metabolism, the authors used this assay to determine how its expression affects N^{α}-acetylation. BCL-XL overexpression and knockout decreased and increased, respectively, the N^{α}-acetylation levels of several caspases and the pro-apoptotic protein BAX. The authors next asked whether changes in the level of acetyl CoA (a potential donor of acetyl groups) influence N^{α}-acetylation levels in BCL-XL-overexpressing cells. Treatment of these cells with acetate or citrate, which stimulate acetyl CoA production, restored protein N^{α}-acetylation levels. Thus, BCL-XL might block apoptosis by reducing acetyl CoA levels, and thus N^{α}-acetylation.

The authors looked further at the relationship between BCL-XL and acetyl CoA. Acetyl CoA levels were twofold lower when BCL-XL was overexpressed and were increased in cells lacking BCL-XL, suggesting that BCL-XL reduces acetyl CoA levels to inhibit apoptosis. Consistently, increasing the levels of acetyl CoA by acetate or citrate treatment led to increased sensitivity of BCL-XL-overexpressing cells to apoptosis. Although BCL-XL can inhibit apoptosis by binding BAX, acetyl CoA levels were also reduced in cells expressing BCL-XL mutants that cannot bind BAX, suggesting that BCL-XL regulates acetyl CoA levels independently of an interaction with BAX.

The ability of BCL-XL to reduce acetyl CoA levels, and thus N^{α}-acetylation and apoptosis, links metabolism to apoptotic sensitivity and provides an additional, BAX-independent mechanism, through which BCL-XL can inhibit cell death.

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ORIGINAL RESEARCH PAPER Yi, C. *et al.* Metabolic regulation of protein N-alpha-acetylation by Bcl-xL promotes cell survival. *Cell* **146**, 607–620 (2011)