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**URLs**
MCL1
http://ca.expasy.org/uniprot/Q07820

GSK3
http://ca.expasy.org/uniprot/P49841

CELL DEATH

# Delicate decisions

The anti-apoptotic BCL2-family member MCL1 can be induced by a number of growth factors and promote cell survival. However, how growth factors maintain MCL1 levels to prevent apoptosis has been unclear. Maurer *et al.* now report that the control of MCL1 stability by glycogen synthase kinase-3 (GSK3) is an important mechanism for the regulation of apoptosis by growth factors and AKT/protein kinase B (PKB) in haematopoietic cells.

> The intriguing possibility that this PI3K–AKT/PKB–GSK3–MCL1 pathway might also regulate survival in other cell types remains to be investigated.

Mitochondrial outer membrane permeabilization (MOMP) is a central point in the regulation of apoptosis, and leads to the release of cytochrome *c* and other pro-apoptotic proteins that reside in the mitochondrial intermembrane space. Although the phosphatidylinositol-3 kinase (PI3K)–AKT/PKB pathway has been shown to control MOMP, how apoptosis can be prevented is not fully understood.

To characterize the role of GSK3 in growth-factor-withdrawal-induced apoptosis, Maurer *et al.* investigated the function of GSK3 in haematopoietic cells, which undergo apoptosis after IL-3 withdrawal. The induction of apoptosis was also associated with the activation of GSK3β, and by using small-molecule inhibitors, the authors showed that the inhibition of GSK3 prevents IL-3-withdrawal-induced MOMP and apoptosis. Therefore, the inhibition of GSK3 by IL-3 is important for the prevention of apoptosis by the mitochondrial pathway.

But how does GSK3 regulate the apoptotic pathway? MCL1 is required to protect haematopoietic cells from apoptosis, which prompted the authors to investigate a potential interaction between GSK3 and MCL1. The modulation of the half-life of MCL1 by GSK3 activity and the identification of a conserved GSK3 phosphorylation site on MCL1 indicated that MCL1 could be phosphorylated by GSK3. Using mutation analysis, Maurer and colleagues showed that, both *in vitro* and *in vivo,* MCL1 is phosphorylated at Ser159 by GSK3 — this phosphorylation event was induced by IL-3 withdrawal and could be prevented by AKT/PKB or GSK3 inhibitors. Phosphorylated MCL1 was only detected upon inhibition of the proteasome, which indicated that the phosphorylation of MCL1 triggers increased proteasomal degradation.

The expression of an MCL1 phosphorylation-site mutant in IL-3-dependent cells revealed that non-phosphorylated MCL1 was more stable and conferred an increased protection from apoptosis compared with wild-type MCL1. But how does 'rescued' MCL1 — by inhibiting GSK3 after IL-3 depletion — contribute to the inhibition of MOMP? The authors investigated whether MCL1 does so by sequestering one of the obvious candidates, the pro-apoptotic BH3-only protein BIM. Immunoprecipitation studies showed that BIM was only associated with MCL1 in the presence of GSK3 inhibitors and when IL-3 was depleted, which indicated that MCL1 sequesters BIM, therefore preventing it from inducing MOMP.

The authors propose that the regulation of MCL1 by GSK3 is probably an important switch in the delicate life-or-death decisions made by immature haematopoietic cells during their maturation. The intriguing possibility that this PI3K–AKT/PKB–GSK3–MCL1 pathway might also regulate survival in other cell types remains to be investigated.

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**ORIGINAL RESEARCH PAPER** Maurer, U. *et al.* Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1. *Mol. Cell* **21**, 749–760 (2006)