CELL BIOLOGY

A BID for the pathway

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Cells have many ways of coping with damage to their DNA, but how are these all coordinated? It seems that BID — a regulator of programmed cell death — stands at the crossroads of several damage-response pathways.

Exposure to DNA-damaging agents can cause mutations, developmental abnormalities or cancer, and cells have developed numerous ways to minimize these effects. Such mechanisms include cell-cycle checkpoints to prohibit damaged cells from dividing while the cell deals with the damage; processes to repair the DNA; and programmed cell death (apoptosis). Although it makes sense that there should be coordinated regulation of these different processes, they have mostly been studied as independent pathways. A new link between these mechanisms comes from work reported in *Cell* by Zinkel *et al.*[1] and Kamer *et al.*[2] demonstrating an unexpected role for the protein BID, a known regulator of apoptosis, in the control of cell-cycle progression following DNA damage.

Apoptosis can be initiated by external signals from other cells — TNF-α, for instance, which is released by certain immune cells to kill infected cells — or by internal warnings resulting from DNA damage or other cellular stresses. Regardless of the stimulus, the death process is controlled by one of several signalling pathways, all of which include one or more members of the BCL-2 family of proteins. The binding of external factors to their cognate 'death receptors' on the cell surface leads to the cleavage and activation of BID[3] — a BCL-2 family member. BID, in turn, activates BAX and BAK, both of which are BCL-2 proteins that then trigger apoptosis (Fig. 1)[4]. By contrast, DNA damage causes activation of the ATM or ATR protein kinases (enzymes that phosphorylate certain target proteins), and this activation leads to a rise in p53 protein levels[5]. This protein can switch on a number of target genes, including those encoding the BCL-2 family members BAX, PUMA and NOXA, each of which contributes to apoptosis in specific cell types[6]. In certain cell types or physiological settings, however, the induction of p53 protein, instead of initiating apoptosis, causes arrest of the cell cycle at the G1 phase. Moreover, other targets of ATM and ATR also contribute to cell-cycle arrest in the S and G2/M phases[5].

Previously, the p53-dependent activation of the genes encoding BAX, PUMA and NOXA was thought to be the main link between DNA damage and the control of apoptosis. Now, Zinkel *et al.*[1] and Kamer *et al.*[2] show that another pathway links the control of apoptosis to that of the cell-cycle arrest following DNA damage. Both groups found that BID is phosphorylated in an ATM-dependent manner after DNA damage and that some of the BID protein then moves into the nucleus. Unexpectedly, both groups also found that arrest of the cell cycle in S phase in response to DNA damage requires BID phosphorylation. Moreover, the domains of the BID protein responsible for control of the cell cycle are distinct from that involved in its apoptotic function. These observations add BID to a surprisingly long list of proteins that are phosphorylated by ATM or ATR to control the progression through the cell cycle after DNA damage (Fig. 1). Furthermore, Zinkel *et al.*[1] demonstrate that cells lacking BID suffer more chromosomal aberrations after DNA damage than those that have BID, raising the possibility that this protein participates in repair of the DNA as well as in cell-cycle control and apoptosis.

Although the two papers agree in several aspects, there are some apparent discrepancies and some findings that require further clarification. The importance of BID and its phosphorylation by ATM in influencing cell survival following DNA damage varied in different experiments in the two papers. These discrepancies may have resulted from differences in cell types, agents or doses used, but they need to be explained if we are to understand the physiological roles of this branch of the ATM pathway. Furthermore, there were inconsistencies between the two studies regarding which DNA damaging agents activate the ATM–BID pathway. For example, Zinkel *et al.*[1] found that ATM was required for BID phosphorylation following exposure to many different types of agents, including hydroxyurea and ultraviolet light, whereas Kamer *et al.*[2] observed BID phosphorylation and ATM-dependence only after treatment with agents that introduce breaks in DNA strands, such as ionizing irradiation and the drug etoposide. The specificity of ATM-dependence for responses to ionizing irradiation would be consistent with a large amount of data in the literature[5].

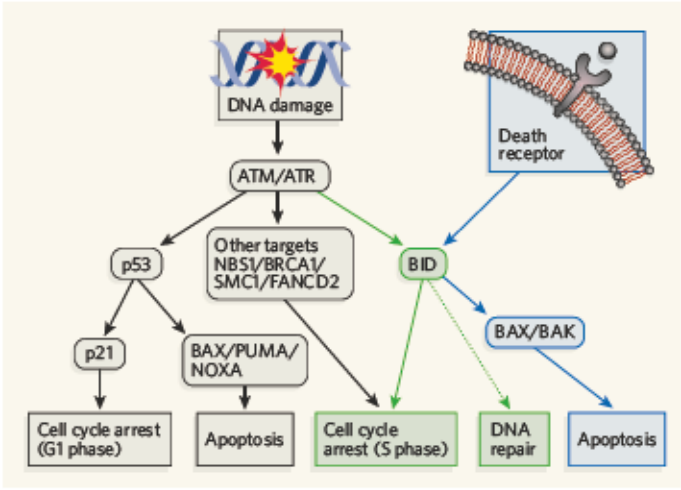

Figure 1 | BID linking two pathways. Zinkel *et al.*[1] and Kamer *et al.*[2] find an unexpected role for BID in the ATM pathway that responds to DNA damage (new steps in green). Following DNA damage, ATM and ATR are activated and, through p53, can cause either cell-cycle arrest at the G1 stage or apoptosis. ATM and ATR also activate several other protein targets, causing the cell cycle to stall in the S phase. Now BID can be added to this list of ATM/ATR targets. Although BID clearly induces apoptosis following activation of death receptors, its role in controlling apoptosis following DNA damage needs to be clarified. The dotted arrow shows a link that is suggested from Zinkel and colleagues' results, but has yet to be demonstrated.

Although there are some confusing results, the two papers convincingly establish that the apoptotic protein BID is a target of ATM and that it has an unanticipated role in controlling cell-cycle progression following DNA damage. The data demonstrate that BID and ATM come together in one arm of one pathway, but also underscore the notion that the two proteins have other distinctive biochemical and functional roles. Thus, it is not surprising that the effects of their loss are quite different: mice lacking BID develop a blood disorder resembling chronic myelomonocytic leukaemia[7], whereas mice and humans lacking ATM develop acute lymphoid leukaemias and lymphomas[8]. It makes sense that cells would have a multi-pronged, coordinated response to stresses such as DNA damage, because it would be advantageous to simultaneously control DNA repair, cell-cycle progression and programmed cell death. BID is unlikely to be the last example of a protein that stands at a crossroads to influence multiple parts of the stress response. ■

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1. Zinkel, S. S. *et al. Cell* **122**, 579–591 (2005).
2. Kamer, I. *et al. Cell* **122**, 593–603 (2005).
3. Zha, J. *et al. Science* **290**, 1761–1765 (2000).
4. Wang, X. *Genes Dev.* **15**, 2922–2933 (2001).
5. Kastan, M. B. & Bartek, J. *Nature* **432**, 316–323 (2004).
6. Danial, N. N. & Korsmeyer, S. J. *Cell* **116**, 205–219 (2004).
7. Zinkel, S. S. *et al. Genes Dev.* **17**, 229–239 (2003).
8. Shiloh, Y. *Nature Rev. Cancer* **3**, 155–168 (2003).