Caspase-9 is an initiator caspase that mediates apoptosis induced by cytotoxic agents. Cardone et al. (1) reported that Akt, a kinase that suppresses apoptosis, phosphorylates caspase-9, thereby preventing activation of this protease. This finding is of fundamental importance because it explains how growth factors can prevent cell death and because it demonstrates that caspases, a central part of the apoptotic machinery, can be regulated by phosphorylation.

Given that importance, we tried to establish a reason for our failure to detect phosphorylated caspase-9 in cell lines we have analyzed. In particular, we decided to test, using a functional assay, whether caspase-9 is regulated by Akt phosphorylation. We planned to reintroduce caspase-9 or its Akt phosphorylation site mutants into cells derived from mice deficient in caspase-9. We reasoned that the lack of endogenous caspase-9 would allow unambiguous detection of the mutations’ effect.

The experiment remained unfinished, however, because we found that mouse caspase-9 had no Akt phosphorylation sites, despite the close similarity between human and mouse proteins (Fig. 1). Subsequently, we found that Akt phosphorylation sites were also absent in caspase-9 obtained from MDCK cells, a dog kidney cell line used by Cardone et al. (1) to make the original observation. Hence, Akt can phosphorylate caspase-9 in neither mice nor dogs. Such a variability among species runs counter to the observation that the Akt phosphorylation site in Bad—a protein that is involved in apoptosis and is regulated by Akt—is conserved from zebrafish to humans. Either it must be assumed that Akt regulates apoptosis differently in mice and humans, or the notion that caspase-9 is regulated by Akt phosphorylation has to be reexamined.

**Fig. 1.** An alignment of the human caspase-9 sequence, which contains the consensus Akt phosphorylation sites, with the corresponding sequences from mouse and dog. Numbering is derived from human caspase-9. The arrow indicates serine 196, which was reported to be phosphorylated by Akt (1).
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Editor's Summary

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