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11:30 a.m.
101 Biochemistry

**Death by Degradation: Regulation of Apoptosis by Ubiquitin
Pathway Proteins**

Research in the Steller Laboratory

Inhibitor of Apoptosis Proteins (IAPs) are a conserved family of cell death regulators that can bind to and inhibit caspases. Many IAPs function as E3-ubiquitin ligases to stimulate degradation of important cell death proteins, including caspases. However, IAPs must be inactivated in cells that are doomed to die. Work in *Drosophila* first demonstrated that this is accomplished by Reaper-family proteins. Reaper induces apoptosis by both disrupting caspase-IAP interactions, and also by specifically stimulating the degradation of *Drosophila* IAP1 (Diap1). Diap1 is also a key regulator for compensatory proliferation. In many metazoans, stress-induced apoptotic cell death can be compensated for by extra-proliferation of neighboring cells. Inactivation of Diap1 stimulates activation of the JNK pathway, which in turn induces transcriptional activation of the mitogens Wingless and Dpp in doomed cells. These findings show that apoptotic cells can activate signaling cascades to stimulate tissue regeneration. We have also generated mice lacking the mammalian IAP-antagonist ARTS. Deletion of the *Sept4* gene, which encodes ARTS causes elevated XIAP protein levels in certain tissues and defects in the caspase-mediated elimination of bulk cytoplasm during spermiogenesis. *Sept4*-Null mice also have cell death defects and show increased spontaneous tumor formation. These observations provide *in vivo* evidence for a critical physiological role of IAP regulation in the control of cell death and tumor suppression in mammals.

References

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