Cell Death Regulation: Lessons from *Drosophila*

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We are using Drosophila as a model system to understand cell death regulation. DRONC is a functional homologue of mammalian caspase-2/-9 and requires DARK (dApaf1), a CED-4/Apaf-1 like adaptor, for its activation. Similar to the Apaf-1/caspase-9 apoptosome and caspase-2 activation complex, DRONC appears to be recruited to a large DARK-dependent complex. *dronc* mutants are pupal lethal and our studies show that DRONC is required for many forms of developmental cell deaths and apoptosis induced by DNA damage. DRONC is also required for the autophagic removal of larval salivary glands during metamorphosis, but not for histolysis of larval midguts. Our results indicate that DRONC is involved in specific developmental cell death pathways and that in some tissues, effector caspase activation and cell death can occur independently of DRONC. Since activation of DRONC can result simply by the removal of DIAP1, it can be achieved either by sequestration of DIAP1, or an increase in the intracellular levels of DRONC and DARK proteins. Both of these mechanisms are evident during developmental PCD and are primarily controlled at the level of transcription. For example, during the histolysis of larval tissues insect hormone ecdysone upregulates *dronc*, *drice* and *dark* transcription, and downregulates *diap1* gene expression. Thus during developmental cell death, synchronous removal of large number of cells may be achieved by transcriptionally controlling the levels of the components of the caspase activation machinery. Similar mechanisms may also control developmental PCD in mammals.