

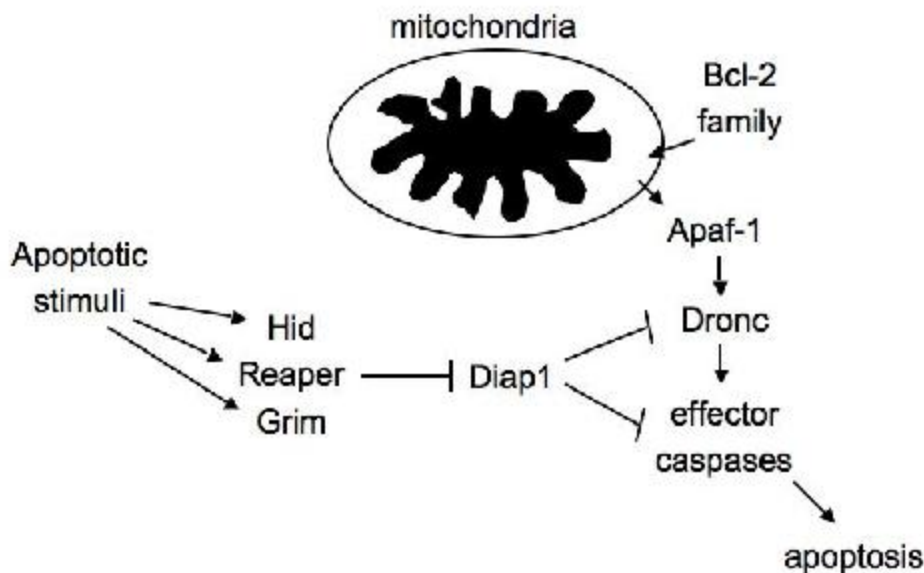
The Ryoo Laboratory Research Interest

Apoptosis and stress response in *Drosophila*: a model for studying growth control and neuronal degeneration.

Our laboratory is interested in understanding the basic mechanisms of apoptosis during animal development and in diseases. Our strategy is to use the genetic and cell biological tools of *Drosophila* as a model system.

Apoptosis is a morphologically distinct form of cell death that is programmed to sculpt body structures, maintain proper numbers of cells during development and eliminate damaged and potentially dangerous cells. Apoptosis is found defective in most cancers, and excess apoptosis underlies many neurodegenerative disorders. A critical event in apoptosis is the activation caspases, a family member of the Cysteine proteases that reside in living cells as inactive zymogens and activated in cells that undergo apoptosis. For proper apoptosis regulation, caspases are extensively regulated, both through its activators such as Apaf-1/cytochrome c and through its inhibitors such as IAPs (Inhibitor of Apoptosis Proteins). In *Drosophila*, various cell death stimuli converge on the transcriptional and post-transcriptional regulation of IAP inhibitors Reaper, Hid and Grim (Figure 1).

Figure 1: Caspase regulation in *Drosophila*



Our research program can be subdivided into two major areas. Our first area of interest is to understand the mechanism of caspase regulation. We have previously demonstrated that *Drosophila* IAP1 (DIAP1) acts as a ubiquitin-ligase that targets apical caspase Dronc in living cells, and undergoes auto-ubiquitylation during apoptosis (Ryoo et. al., 2002; Ryoo et. al., 2004). Furthermore, we showed that DIAP1 inhibition, which occurs in cells doomed to die, leads to the induction of secretory factors DPP and WG. In turn, these secreted factors promote the proliferation and growth of neighboring cells. We have proposed that this regulatory mechanism contributes to apoptosis-induced compensatory cell proliferation (Ryoo

et. al., 2004). We plan to further investigate the mechanistic basis of coordination between apoptosis and cell proliferation with a special focus on Diap1. In particular, we plan to identify Diap1 substrates that are targeted for ubiquitin-mediated degradation *in vivo* and examine whether they account for the apoptotic, or non-apoptotic roles of Diap1. Progress in this area may enhance our understanding of how tissue size is regulated during animal development and in cancer (Ryoo et. al., 2003).

Our second research program is aimed at understanding how endoplasmic stress (ER-stress) activates apoptosis. ER-stress is frequently caused by unfolded proteins in the ER, and is thought to be the cause of a wide variety of disorders, including alzheimer's disease, parkinson's disease, retinitis pigmentosa, multiple myeloma and diabetes. Although apoptosis is a pathologically relevant outcome of ER-stress, how caspases become activated under these conditions remains poorly characterized. We have begun investigating the *Drosophila* genes that make up the cellular response machinery to ER-stress, also known as the Unfolded Protein Response (UPR). Through this effort, we found that the *Drosophila xbp1* mRNA undergoes unconventional splicing in response to ER-stress, similar to those found in other organisms. This property was used to generate an ER-stress sensor where GFP is expressed in frame only after *xbp1* mRNA splicing. Significantly, *xbp1* splicing and ER-chaperone induction occurs in the *Drosophila* model for the Autosomal Dominant Retinitis Pigmentosa (ADRP), where the expression of mutant rhodopsin-1 molecules leads to late onset retinal degeneration. These developments provide a basis to investigate how ER-stress activates apoptosis in *Drosophila* disease models (Ryoo et. al., manuscript in preparation). Ongoing efforts aim to examine existing hypotheses and to identify new components linking ER-stress and caspase activation.

Selected References

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