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APOPTOSIS IN DROSOPHILA

Cell death: what can we learn from flies? Editorial for the special review issue on *Drosophila* apoptosis

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Fifteen years after the identification of a small deletion (H99) in the *Drosophila* genome, revealing *rpr*, *hid*, and *grim* genes (RHG genes)[1], the field of apoptosis in *Drosophila* has grown dramatically. Models to study developmental apoptosis have diversified due to the powerful genetic tools in *Drosophila* and the numerous roles played by apoptosis in its development. Compared with *C-elegans,* where the role of apoptosis is mainly to eliminate unwanted cells, apoptosis in *Drosophila* is more diverse and complex resembling that in mammals. Apoptosis in *Drosophila* not only controls cell proliferation, elimination of damaged or developmentally confused cells but also organ size and the architecture of the tissues.

This issue of the *Apoptosis* journal includes ten review papers by experts in the field of *Drosophila* apoptosis. They provide an overview of apoptosis studies and alternative death pathways in *Drosophila* [2–11]. As the field gets larger, data on regulation mechanisms of the core apoptotic pathway, new models and concepts pave the way for studying of apoptosis. In an attempt to see where the field is heading and to identify the remaining key questions, I provide an overview of some of the recent studies described in the special issue and highlight new concepts. Unfortunately, due to topic overlap and space constraints, several topics did not get a dedicated review in this issue, and I apologize to those whose work was not mentioned. Several of these topics got excellent coverage in recent reviews: cell death in compensatory proliferation [12], cell competition [13], the role of the Hippo/Salvador pathway in apoptosis [14], the regulation of apoptosis in the pupal retina [15] and the role of alternative death pathways such as autophagy [16].

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Apoptosis during embryogenesis

Zhou and Colleagues [2, this issue] focus on the historical model of apoptosis in *Drosophila* embryogenesis. The authors review the roles of apoptosis in development and its control mechanisms. During embryonic development, apoptosis eliminates supernumerary cells, controls cell proliferation and is also responsible for sculpting the tissue. The genes *rpr*, *hid* and *grim* are transcribed at about embryonic stage 11 and their products antagonize the *Drosophila* inhibitor of apoptosis, protein (DIAP1), removing the inhibition of caspases, and triggering apoptosis. It is still not fully understood how developmental pathways integrate both differentiation and apoptosis in tissues. The identification of developmental factors, such as Deformed, Abdominal B, which regulate RHG gene transcription [17], was a step towards the identification of *rpr* transcriptional regulators but a thorough analysis of findings is needed to fully understand the transcriptional regulation of RHG genes. Recently, Zhou and colleagues showed that epigenetic regulations play an active part in the coordinated expression of *rpr* and *hid* during apoptosis in embryos, suggesting that a complete understanding of RHG regulation may lie in alternative approaches [18].

In contrast to *rpr* and *grim* which are only expressed in cells destined to die, *hid* is also transcribed in some living cells. This suggests that in addition to transcriptional regulation, *hid* is also post-transcriptionally regulated. Bilak and Su cover in detail the mechanisms of Hid regulation [3, this issue] in developmental and DNA damage-induced

apoptosis models. Hence, Hid can be regulated at the transcriptional, post-transcriptional and post-translational levels depending on the tissue or cell type in which it is expressed. Regulators include the Ras/MAPK, Hippo and JNK pathways, p53, the micro RNAs bantam, miR-6 and miR-2/13 and also the cell cycle regulators RBF1 and E2F.

Inhibitor of apoptosis proteins

Drosophila Inhibitor of apoptosis protein 1 (Diap1) is a critical inhibitor of apoptosis during *Drosophila* development. All living cells are thought to express Diap1, which restricts caspase activation. In embryos lacking *Diap1*, all cells enter apoptosis synchronously [19]. Orme and Meier review past and current findings on the complex interplay between the mechanisms regulating Diap1 and caspase protein stability [4, this issue].

IAP-mediated inhibition of caspase is a complex mechanism. Diap1 binding through its Baculovirus IAP repeat (BIR) domains to caspase is necessary, but not sufficient, for caspase inhibition. Diap1 also contains a really interesting new gene (RING) domain conferring E3 ubiquitin ligase activity, which transfers a ubiquitin group to caspases and supposedly targets them to the proteasome for degradation.

The story could have ended here but additional levels of complexity have recently been demonstrated. Firstly, Diap-mediated caspase ubiquitylation causes inhibition by both degradative and non-degradative mechanisms. Diap1 mediates ubiquitylation of Dronc (caspase 9 homolog) but only targets it for degradation when it is associated with the Apaf-1-like protein, Dark, in the apoptosome [20]. However, Diap1-mediated ubiquitylation inhibits the effector caspase Drice (caspase 3 homolog) but does not induce its degradation. Instead the addition of ubiquitin groups to Drice sterically interferes with substrate binding and catalytic activity [21]. Secondly, these studies have shown that caspase-mediated cleavage of Diap1 [21] and Dark [20] is required to induce Diap1 inhibition. These auto-inhibitory feedback loops, may explain how caspase activation can be maintained at low levels in living cells and achieve a non-apoptotic function (see below "Roles of caspases in non-apoptotic cellular functions").

The role of mitochondria in apoptosis

The role of mitochondria in *Drosophila* is still the subject of numerous debates. In their review, Krieser and White present recent advances which have shed light on the role of members of the Bcl2 family and Cytochrome-C (Cyt-C). They also focus on the role of mitochondrial dynamics in apoptosis, a topic that has changed the debate [5, this issue].

Mitochondria have a central role in the intrinsic apoptotic pathway in vertebrates. Stimulation of apoptosis, causes members of the pro-apoptotic Bcl-2 family to trigger mitochondrial events, including the release of mitochondrial factors such as Cyt-C. Released Cyt-C interacts with Apaf-1 inducing the formation of the apoptosome, caspase activation and apoptosis (for review [22]).

It is believed that mitochondria only play a limited role in *Drosophila* apoptosis, in contrast to that in mammals [23]. This is because: (1) no developmental apoptosis defect was observed in mutants of the *Drosophila bcl-2* homologs, *debcl* and *buffy* [24], 2) apoptosis occurs normally in *Drosophila* cell lines depleted in Cyt-C [25, 26] and 3) structural data showed that the apoptosome can form in the absence of Cyt-c *in vitro* [27]. Thus, it was suggested that the apoptosome is constitutively active and that the rpr/IAP pathway is sufficient to explain apoptosis in *Drosophila*.

There is mounting evidence to challenge this view: (1) the *Drosophila* Bax/Bak ortholog *debcl* is required for some developmental apoptosis [28], (2) developmental apoptosis in the retina and non-apoptotic activation of caspase require Cyt-c [29–31] and (3) active apoptosome complexes are constantly subjected to feedback inhibition in living cells [20]. This suggests that activation of the apoptosome is not constitutive and that the apoptosome is activated by a signal (Cyt-c or another factor) in dying cells. Although the mechanisms by which Debcl and Cyt-c activate apoptosis remain unclear, these results suggest that mitochondria contribute to *Drosophila* apoptosis in several cellular contexts. The recent observation that mitochondrial fission is required for apoptosis, further implies that mitochondria have an important function in *Drosophila* apoptosis [32, 33].

Cell death in germ cells and in the ovary

K. McCall and colleagues [6, this issue] give a complete and comprehensive overview of cell death models during oogenesis. *Drosophila* germ cells and ovaries offer a wide range of models for the study of developmental cell death, in addition to cell death brought about by nutrient deprivation, DNA damage, or environment-related risks such as cellular phone radiation [34, 35]. Cell death is normally observed during embryogenesis in germ cells although it also occurs in the germarium, and at mid- and late oogenesis in the adult female fly. However, with the exception of programmed cell death (PCD) in ovarian polar cells, PCD during oogenesis is not by classical apoptosis

[36]. For example, none of the RHG genes is required for ovarian cell death. In addition, while the effector caspase *dcp-1* has little or no role in most developmental apoptosis, it is required for autophagy and starvation-induced cell death in the germarium and at mid-oogenesis [37]. Mutations in autophagy genes reduced DNA fragmentation but not nuclear condensation. These results suggest a close relationship between apoptotic and autophagic pathways for ovarian cell death. The conditions and the molecular pathways by which a cell triggers apoptosis and/or autophagy need to be defined.

Role of caspases in non-apoptotic cellular functions

The mechanisms leading to caspase activation have been extensively studied during apoptosis. However, caspases can also be involved in vital cell processes. Arama and col. review the role of caspases during development in mammals and *Drosophila* models [7, this issue]. Apoptotic-like mechanisms in which part of the cell content is digested in a process that requires caspase activation are involved. This is, for example, the role of caspases during sperm terminal differentiation in *Drosophila* where the formation of the flagella requires the elimination of intra-cellular content [29]. Caspases are also involved in cellular compartment clearance during the process of dendritic pruning of sensory neurons [38].

Activated caspases also specifically regulate developmental pathways. For example, macrochaete differentiation is controlled by caspases. Apoptotic gene mutant flies exhibit one or several extra macrochaetes on their notum. One proposed mechanism is that the lack of caspase activation in sensory organ precursor (SOP) cells leads to Wingless signaling activation and the formation of an extra sensory neuron [39].

One of the mysteries in the field of apoptosis is how caspase activation can be restricted to particular developmental tasks without leading to cell death. There are several non-exclusive explanations: (1) This could be simply a question of levels, where low levels of caspase activation bring about subtle developmental regulation while high levels trigger apoptosis. Recent studies showing that caspases are activated at low levels in living cells to ensure their own inhibition [4, this issue] support this hypothesis. (2) A compartmentalized activation of caspases may ensure that only targeted processes are affected. (3) The production of apoptotic inhibitors may limit caspase activation to restricted areas or tasks. The identification factors controlling the spread of caspase activation within cells will be a major step forward in the understanding of apoptosis regulation.

Endoplasmic reticulum stress and apoptosis

There has been increasing interest in the contribution of the endoplasmic reticulum (ER), to the regulation of apoptosis. In some diseases such as diabetes and neurodegenerative diseases, misfolded/unfolded proteins accumulate in the ER, inducing ER stress and the activation of the unfolded protein response (UPR). Although sustained ER stress triggers apoptosis in certain cellular models (for review [40]), the role of ER stress in the progression of diseases remains unclear. *Drosophila* has only recently emerged as a biological model system to study ER stress and the UPR. Rasheva and Domingos [8, this issue] review the rapidly growing field of ER stress and apoptosis covering both the mammalian/yeast systems and the more recent studies using the *Drosophila*.

Studies on yeast and mammals have identified the UPR effectors that enable the cell to cope with the accumulation of unfolded/misfolded proteins in the ER. The UPR has primarily a protective role through the activation of Ire1/Xpb1, Atf6 and Perk pathways. It results in the production of ER chaperones, activation of ER degradation proteins and translational attenuation, which lead to a reduction of misfolded protein load in the ER. However, in cells submitted to an intense or sustained ER stress, the UPR activates caspase-dependent cell death [40]. Caspases 9 and 3 are activated in ER stress-mediated apoptosis although their activation does not seem to require the mitochondrial Cyt-C/Apaf-1 pathway [41]. In mice, it has been proposed that calpains induce caspase 12 activation and subsequent activation of caspase 9 and 3 [42]. However, the role of caspase 12 in humans is not clear.

In a *Drosophila* autosomal dominant retinitis pigmentosa model, photoreceptor cells accumulate misfolded Rhodopsin 1 (Rh1) proteins that trigger ER stress. Here, the effectors of the Ire1/Xbp1 pathway limit the accumulation of misfolded Rh1 proteins and protect photoreceptor cells from death. In contrast, ectopic ER stress activation induced by expression of a spliced variant of *xbp1* leads to photoreceptor cell death that cannot be inhibited by the caspase inhibitor p35 [43]. This suggests that caspase-independent death pathways may also be activated.

We have shown that induction of moderate ER stress in adult *Drosophila* photoreceptor cells does not trigger cell death but instead activates a protective mechanism that stimulates an anti-oxidant response and inhibits caspase activation [44]. Cultured mammalian cells subjected to mild ER stress also show a protective response that may be due to the instability of mRNAs and proteins that promote apoptosis [45]. Thus, the UPR not only limits the accumulation of misfolded proteins, but also protects tissues from apoptosis. It still has to be demonstrated in vivo whether moderate ER stress plays an anti-apoptotic role in

normal and/or pathological conditions in mammals. Nevertheless, *Drosophila* promises to be a useful genetic model for the identification of apoptotic gene targets regulated by UPR effectors.

Drosophila model of neurodegenerative diseases

Human brain disorders, such as Alzheimer's, Parkinson's or Huntington's disease, are associated with neuronal cell loss but the pathways that lead to neurodegeneration are still under investigation. Apoptotic characteristics, such as caspase activation or TUNEL staining, are often detected in affected brain tissues but they play a limited role in neuron cell death. Neurodegenerative diseases commonly involve alternative death pathways induced by pathological proteins, which cause a disruption of mitochondrial dynamics and redox status. The situation is complex as many neuropathological models use distinct pathways to trigger cell death. B. W. Lu [9, this issue] exhaustively reviews the available *Drosophila* neurodegenerative models, ranging from Parkinson's and Alzheimer's to polyglutamine diseases. The number of *Drosophila* models has recently increased and they are now widely used for genetic and chemical compound screening.

The role of mitochondrial fission/fusion in neurological diseases is currently under deep scrutiny. Parkinson's disease models in *Drosophila* have shown that dynamin GTPases Drp1 and Opa1 regulate neurodegeneration [46–48]. Increased fusion or decreased fission may lead to neurodegeneration in *pink1* and *parkin* mutants. Hence, enhanced fission by over production of Drp1 or reduced fusion by mutation in *opa1* rescues dopaminergic neuron loss in *pink1* mutant. This contrasts with the observation that Drp1-mediated fission is required for apoptosis (see the review on Mitochondrial apoptosis (in this issue [5]). One possible interpretation is that the role of fission in cell death may be context dependent. The exact relationship between mitochondrial dynamics and cell death needs to be determined. It is also unclear whether mechanisms identified in a particular neurodegenerative condition are applicable to other neurodegenerative diseases.

JNK-dependent cell death

In addition to the core apoptotic pathway, the c-Jun N-terminal Kinase (JNK) pathway is also closely linked to cell death regulation. JNK is a pleiotropic pathway which regulates a broad range of biological processes, including proliferation, differentiation, morphogenesis, and apoptosis (for review see [49]). In *Drosophila*, JNK has been implicated in development in dorsal and thorax closure, imaginal disc eversion, planar cell polarity. It is also involved in the immune response, response to cellular damage, wound healing, longevity and apoptosis (for reviews covering these topics see [50–52]). T. Igaki gives an overview of the literature on JNK signaling and apoptosis in *Drosophila* [10, this issue].

Initial studies have shown that the activation of the Tumor Necrosis Factor/Tumor Necrosis Factor Receptor (TNF/TNFR) system in flies (Eiger/Wengen) induces JNK-dependent cell death in stress situations but is not required for developmental apoptosis [53–55]. However, a recent study showed that JNK signaling contributed to morphogenetic apoptosis during normal development. Morphogenetic apoptosis is induced when a morphogenetic gradient is interrupted [56]. This allows a continuous gradient to be regenerated after a discontinuity. Until recently, this process was thought to be activated only in mutants (*eg*: mutant clone in morphogen signaling), but it is required for the normal joint formation in leg development. Hence, a sharp discontinuous Dpp signaling occurs during normal segmentation of the distal legs of *Drosophila* [57].

Recent work has demonstrated that JNK-mediated cell death suppresses pre-malignant cells via endocytic activation [58]. In this model, the *Drosophila* TNF-JNK signaling pathway is seen as tumor suppressor pathway. This study and previous work on JNK regulation illustrate what a powerful tool *Drosophila* genetics is in deciphering the multiple functions of pleiotropic pathways.

Apoptotic corpse engulfment

The removal of apoptotic cells by phagocytes is essential to avoid release of cellular contents and potential inflammatory response. Engulfment requires the expression of an "eat me" signal at the surface of the apoptotic cell, recognition by the engulfing cell, followed by internalization and processing of the dead cells. In their review Baker and col. summarize the recent findings on these pathways. They cover recognition, internalization, and processing mechanisms in *Drosophila* phagocytosis [11, this issue].

Regarding apoptosis, the popular view is that dying cells are recognized and engulfed by phagocytes. However, *C-elegans* studies show that engulfment genes take an active part in the activation of the apoptotic machinery. Hence, mutations in engulfment genes may enhance the survival of many cells normally destined to die [59, 60]. A recent study in *Drosophila* went further by showing that during the cell competition process, engulfing genes such as *draper* (*drpr*), *myoblast city* (*mbc*) and *Wiskott-Aldrich Syndrome* (wasp) are required for the death of minutes cells (heterozygous mutants with a defective ribosomal protein) [61]. Baker and colleagues [11] discuss the evidence that

may explain the mechanisms by which engulfing genes activate apoptosis in neighbouring cells.

Conclusions

Drosophila has proved to be a powerful tool for deciphering conserved regulatory mechanisms controlling cell death in living organisms. The comparison of cell death mechanisms between *Drosophila* and mammals has also revealed some differences. The study of these differences has enabled current views to be challenged and unexpected regulatory pathways in normal or pathological situations to be detected.

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