**Ecdysone-mediated Up-regulation of the Effector Caspase DRICE Is Required for Hormone-dependent Apoptosis in *Drosophila* Cells**

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The *Drosophila* steroid hormone ecdysone mediates cell death during metamorphosis by regulating the transcription of a number of cell death genes. The apical caspase DRONC is known to be transcriptionally regulated by ecdysone during development. Here we demonstrate that ecdysone also regulates the transcription of DRICE, a major effector caspase and a downstream target for DRONC in the fly. Using RNA interference in an ecdysone-responsive *Drosophila* cell line, we show that *drice* up-regulation is essential for apoptosis induced by ecdysone. We also show that *drice* expression is specifically controlled by the ecdysone-regulated transcription factor BR-C. Combined with previous observations, our results indicate that transcriptional regulation of the components of the core apoptotic machinery plays a key role in hormone-regulated programmed cell death during *Drosophila* development.

Programmed cell death is necessary to delete superfluous cells in metazoans and to maintain homeostasis (reviewed in Refs. 1 and 2). The core cell death machinery, consisting of the BH3-only proteins, BCL-2 family, caspase adaptors, and caspases, is highly conserved and is present in all metazoan cells (reviewed in Refs. 3–6). As most components of the cell death machinery are present constitutively within a cell, it is widely believed that execution of apoptosis is primarily regulated post-transcriptionally, that is apoptotic signals somehow feed into and activate preexisting caspase machinery. However, recent data suggest that many components of the core apoptosis machinery, including some caspases, are transcriptionally regulated during cell death and that the levels of the prosurvival and proapoptotic factors in the cell may be crucial to activate the apoptotic program (reviewed in Ref. 4). Consistent with this, there is evidence that various signals such as cytotoxic insults, hormones, and growth factors regulate the activation of the death program by controlling the balance between prosurvival and proapoptotic proteins of the core cell death machinery (4). To understand cell death regulation, it is thus essential to understand the transcriptional control of apoptosis execution.

Steroid hormones are known to regulate cell survival and cell death in many tissues. *Drosophila melanogaster* is an ideal model system to study steroid hormone-regulated apoptosis as a single steroid hormone, 20-hydroxyecdysone, regulates cell death during development (reviewed in Refs. 5 and 7–9). Ecdysone binds to its heterodimeric EcR/Usp receptor and transcriptionally regulates a number of primary response genes. Waves of ecdysone, produced at various times during fly development, regulate molting, cell proliferation, differentiation, and death in a highly controlled manner (5, 7–9). During the transition of larva into pupa, an ecdysone pulse toward the end of the third larval instar stage signals puparium formation, followed by a second pulse ~12 h later, which initiates head eversion. During this process obsolete larval tissues, such as salivary glands and midgut, are deleted and replaced by adult tissues (5, 7–9). Cell death in the larval midgut begins in response to the late larval pulse of ecdysone while the salivary glands undergo removal operation at 15 h later in response to the second hormone pulse (5, 7–9).

Recent data suggest that EcR/Usp and ecdysone-induced transcription factors including βTZZ-F1, BR-C, E74, E75, and E99 play a role in ecdysone-mediated cell death in the larval salivary gland and midgut (5, 8, 10–13). Studies, mostly with salivary glands, indicate that ecdysone controls the up-regulation of a number of proapoptotic genes such as *rpr*, *hid*, *dark* and *drone*, and down-regulates the expression of death inhibitors such as *diap1* and *diap2* (14–16). Among the seven *Drosophila* caspases (17), ecdysone is well known to regulate *drone* expression (18, 19). DRONC is a CED3/caspase-9-like apical caspase that is essential for several programmed cell death pathways in the fly (17, 18, 20). Our previous data with DRONC suggest that ecdysone-mediated up-regulation of *drone* is an important regulator of hormone-dependent cell death in *Drosophila* cells (19). One of the downstream targets of DRONC is the effector caspase DRICE (17). As DRICE is the major caspase-3-like effector enzyme in *Drosophila*, we tested whether it is also regulated by ecdysone. We report here that *drice* up-regulation by ecdysone plays an important role in hormone-dependent cell death.

**MATERIALS AND METHODS**

**Ecdysone Treatment of Salivary Glands**—Animals (W1118) were grown on bromphenol blue-supplemented food and stage by the gut clearance technique as previously described (13, 21). Late third instar larvae with empty guts were collected, dissected in Schneider’s cell medium (Invitrogen), and incubated with or without 1 mM ecdysone (Sigma) for 1 h at 25 °C.

**Cell Culture—*Drosophila* 1(2)/mba cells**, a kind gift from Dr. A. Dorn (Johannes Gutenberg University, Mainz, Germany) (22) were maintained as described previously (19). Cells, at 1 × 10⁵/well, were seeded in six-well plates in triplicate or quadruplicate and allowed to recover for 3 days. Where necessary, ecdysone (10 μM) (Sigma) was added for the desired time. For RNA interference (RNAi) experiments, cells were

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1 The abbreviations used are: RNAi, RNA interference; dsRNA, double-stranded RNA; DAPI, 4’-6-diamidino-2-phenylindole; amc, amino-methylcoumarin; RT-PCR, reverse transcription PCR.
treated with ecdysone until ~50% of control cells were apoptotic as the rate of l(2)mbn apoptosis varies between batches.

**Apoptosis Detection**—To assess apoptosis, cells were stained with 4′,6-diamidino-2-phenylindole (DAPI) fluorescent dye. Briefly, cells were fixed and stained with 1 μg/ml DAPI, 20% formaldehyde, and mounted 1:1 with 80% glycerol. Changes in nuclear morphology were observed by fluorescent microscopy and apoptosis (%) was calculated as the proportion of cells with condensed chromatin in a total count of at least 300 cells. Data were derived from three or four experiments.

**Caspase Assays**—Cell lysates were prepared by freeze thawing and clarified by centrifugation at 13,000 rpm for 5 min at 4 °C. Equal amounts of lysate were assayed for caspase activity using 100 μM VDVAD-amc and DEVD-amc substrates as described previously (23), and the release of amc was measured using a fluorometric plate reader (PerkinElmer Life Sciences) (excitation 385 nm, emission 460 nm).

**RT-PCR Analysis**—Total RNA was extracted from l(2)mbn cells using TRIzol reagent (Invitrogen) as per manufacturer’s protocol. 1–5 μg of total RNA was used as a template for cDNA synthesis, in a 20-μl reaction with 500 ng of oligo(dT)18, using a Superscript II RNase H-Reverse Transcriptase kit (Invitrogen), according to manufacturer’s protocol. Using 1.5 μl of 1:3 diluted cDNA template, PCR amplification was performed using appropriate primers in a 50-μl reaction employing 27–33 cycles. Drosophila rp49 was used as a control. Aliquots of PCR products (20 μl) were electrophoresed on 1.5–2% agarose gel for analysis.

**Immunoblotting**—Cell lysates were separated by 10% SDS-PAGE, transferred onto polyvinylidene difluoride membrane (Schleicher & Schuell) and blocked for 1 h in 5% skim milk (pH 7.5). Affinity-purified anti-DRONC (24) was used at a 1:300 dilution, and DRICE antibody (24) was used at a 1:500 dilution. Secondary alkaline phosphatase-conjugated anti-rabbit antibody (Amersham Biosciences) was used at 1:2000 dilution. Signals were detected using ECF system (Amersham Biosciences). Cytochrome c antibody was purchased from Pharmingen and used at a 1:2000 dilution as described (23, 24).

**RESULTS**

drice Is Up-regulated in Salivary Glands Treated with Ecdysone—It has previously been shown that edcsyne treatment of late second instar larvae salivary glands results in the up-regulation of drice mRNA (18). Because the effector caspases are necessary for salivary gland death to occur (5, 8) we investigated whether the major downstream effector caspase DRICE was also regulated by edcsyne. To determine whether drice mRNA expression is induced by edcsyne, dissected salivary glands from staged late third instar larvae were treated with edcsyne. After a 1-h edcsyne treatment a dramatic increase in drice mRNA levels was observed, demonstrating that edcsyne can induce drice expression in larval salivary glands (Fig. 1A). Caspase assays performed with lysates from edcsyne-treated salivary glands showed elevated caspase activity (Fig. 1B). In particular we observed a 4.5-fold increase in activity on DEVD-amc, which is a substrate for DRICE. Consistent with this observation, DRICE protein levels were elevated in extracts from edcsyne-treated salivary glands (Fig. 1C). These findings suggest the involvement of DRICE in edcsyne-regulated salivary gland death and more importantly demonstrate that drice mRNA is up-regulated by edcsyne.

**drcie Is Induced by Ecdysone in l(2)mbn Cells**—To further investigate the edcsyne-induction of drice transcription and dissect out its transcriptional regulation by various transcrip-
DRICE Is Necessary for Maximal Ecdysone-induced Caspase Activity—Because DRICE function is essential for the efficient execution of apoptosis in ecdysone-treated l(2)mbn cells we wanted to establish its contribution to caspase activity. Caspase assays were performed with lysates using DEVD-amc and VDVAD-amc substrates (Fig. 4, A and B, respectively). In the absence of DRICE, lysates displayed basal levels of DEVDase activity. Ablation of dcp-1 resulted in ~25% activity of controls. When both drc and dcp-1 were silenced DEVDase activity was virtually abolished (Fig. 4A). Previous studies have established that DCP-1 is a substrate for DRICE (26) and that DEVD-amc is a substrate for both DRICE and DCP-1. Because drc knockdown completely abolished DEVDase activity, whereas dcp-1 RNAi lysates still display DEVDase activity, these findings imply a necessity for DRICE in DCP-1 activation. Ablating drc results in DEVDase activity that is ~60% of controls (Fig. 4A). This is consistent with DRONC being an upstream activator of the effector caspases. When caspase assays were performed using a VDVAD-amc substrate, caspase activity following ecdysone treatment of drc or dcp-1 knockdown cells was only ~20% of controls (Fig. 4B). Silencing both drc and dcp-1 resulted in basal VDVADase activity (Fig. 4B). In the absence of drc expression ~60% of control VDVADase activity was observed (Fig. 4B). Because VDVADase activity in part represents DRONC activity, these data suggest that DRICE and DCP-1 may affect DRONC activity. In addition, because activity on both DEVD-amc and VDVAD-amc substrates is still present in drc knockdown cells, these data present evidence that DRICE activation may occur by means other than DRONC-mediated activation in l(2)mbn cells.

Evidence for a Caspase Activation Loop in l(2)mbn Cells—To further characterize the effect of ablating drc gene function we analyzed protein expression and processing of DRICE and DRONC. In ecdysone-treated control cells we observe up-regulation of DRICE precursor and accumulation of its processed form (Fig. 4C, DRICE proc.). The ablition of either drc or dcp-1 did not affect DRICE precursor levels; however, we see a reduced processing of DRICE. drc RNAi had a more profound effect on DRICE processing than dcp-1 RNAi, thus both DRONC and DCP-1 may be capable of activating DRICE. As discussed previously, ecdysone treatment of l(2)mbn cells leads to an accumulation of processed DRONC (Fig. 4C, control lanes). We observe substantially reduced processed DRONC in the absence of DRICE (Fig. 4C). dcp-1 RNAi did not have any significant effect on processed DRONC levels. Because processed DRONC levels are significantly lower in drc-ablated ecdysone-treated cells, we propose that DRICE is required for amplification of DRONC processing following the initial activation of the upstream caspase.

Ecdysone-induced Factors E74A, E74B, E75A, E75B, E93, or βFTZ-F1 Are Not Required for drc Up-regulation—Because we established drc up-regulation and the importance of DRICE in ecdysone-mediated apoptosis in l(2)mbn cells, we could now use this system to investigate the role of known ecdysone-induced transcription factors in drc transcription. We therefore carried out the RNAi ablation of several ecdysone-responsive transcription factors in l(2)mbn cells. The transcription factors E74A, E74B, E75A, E75B, E93, βFTZ-F1, and BR-C have been identified as important regulators of ecdysone-mediated salivary gland death (14, 15, 27, 28). In Fig. 5A we show the effect of ablating E74A, E74B, E75A, or E75B on ecdysone-induced l(2)mbn apoptosis. Compared with controls, induction of apoptosis by ecdysone treatment was not significantly affected by silencing any of these transcription factors.

**FIG. 2.** drc is regulated by ecdysone in l(2)mbn cells. Drosophila l(2)mbn cells were treated with 10 μM ecdysone for the indicated times. To determine apoptosis, chromatin condensation was analyzed by fluorescence microscopy and DAPI staining. A, at 0 h the cells are healthy and cycling. A cell division event is shown (*). Following 48 h of ecdysone treatment the characteristic nuclear fragmentation is evident. Arrowheads mark apoptotic cells. B, at least 300 cells were scored for each treatment time to calculate percent apoptosis. Error bars represent S.D. from three experiments. Graph is split to indicate data accumulated from two independent experiments.

**FIG. 3.** drc is required for ecdysone-induced l(2)mbn cell death. l(2)mbn cells were exposed to 40 nM dsRNA for drc, dcp-1, both drc and dcp-1, dronc, or a negative control for 3 days. Cells were then harvested or treated with 10 μM ecdysone. A, using gene-specific oligos, RT-PCR was used to confirm knockdown of drc, dcp-1, and dronc in ecdysone-treated samples. rp49 was used as loading control. B, percent apoptosis was assessed by chromatin condensation analysis of DAPI-stained cells. At least 300 cells were scored for each treatment. Error bars represent S.D. from three experiments. Graph is split to indicate data accumulated from two independent experiments.
When we silence E93, edcsyne-induced apoptosis was reduced by 35% compared with controls (Fig. 5B). βFTZ-F1 RNAi did not affect apoptosis induction (Fig. 5B). Thus, of the transcription factors studied, only E93 was identified as being important for regulation of ecdysone mediated apoptosis in l(2)mbn cells. We then analyzed drice transcription by RT-PCR. The ability of edcsyne to induce drice up-regulation was not affected by silencing E74A, E74B, E75A, E75B, E93, or βFTZ-F1 (Fig. 5, C and D). Because E93 RNAi did not affect drice transcription, the rate of apoptosis in E93 knockdown cells is likely to be reduced as a result of reduced dronc expression, which has been previously reported (15).

**DEVDAse Activity Is Not Directly Affected by the Ecdysone-responsive Transcription Factors E74A, E74B, E75A, E75B, E93, or βFTZ-F1**—Although drice transcription was not regulated by the ecdysone-responsive transcription factors E74A, E74B, E75A, E75B, E93, or βFTZ-F1, it was of interest to establish whether there was any effect on caspase activity. Analysis of DEVDAse activity shows that E74A, E74B, E75A, or E75B RNAi-treated cells achieve similar levels of DEVDAse activity as controls (Fig. 6A). E93 RNAi resulted in DEVDAse activity that was ~50% of control activity (Fig. 6B). Silencing βFTZ-F1 had no significant effect on DEVDAse activity (Fig. 6B). E74A, E74B, E75A, E75B, or βFTZ-F1 ablation had no significant effect on VDVAse activity in l(2)mbn cells, whereas E93 RNAi showed significantly reduced levels of activity (Fig. 6, C and D). Thus ablation of E93, but not E74A, E74B, E75A, E75B, or βFTZ-F1, leads to reduced caspase activity in ecdysone-treated l(2)mbn cells consistent with the effects we see on apoptosis induction. In the absence of E74A, E74B, E75A, E75B, or βFTZ-F1, DRICE processing following ecdysone-induction of DRICE was relatively unchanged compared with controls (Fig. 6E). Although we see less processed DRICE in E93 RNAi lysates, induction of DRICE precursor is not significantly affected (Fig. 6E). Thus none of the transcription factors E74A, E74B, E75A, E75B, or βFTZ-F1 regulates edcsyne-induced drice transcription or expression of this effector caspase.

**BR-C Regulates Ecdysone-induced drice Transcription**—The edcsyne-induced transcription factor BR-C plays a key role in salivary gland death and is a regulator of dronc transcription (14, 19). There are four isoforms of BR-C protein, Z1–Z4 (29). The Z2 isoform is constitutively present in l(2)mbn cells, and following edcsyne treatment the Z1, Z3, and Z4 isoforms are expressed (19). To test whether BR-C regulates edcsyne-induced drice transcription we carried out RNAi ablation of BR-C in l(2)mbn cells. BR-C RNAi significantly inhibited the rate of edcsyne-mediated apoptosis indicating that BR-C is an important regulator of edcsyne-induced apoptosis in l(2)mbn cells (Fig. 7A). Analysis of transcription by RT-PCR using total RNA shows that BR-C RNAi reduces edcsyne-induced transcription.
FIG. 6. E93 knockdown reduced caspase activity but did not affect DRICE levels in ecdysone-treated l(2)mbn cells. We further analyzed the RNAi experiments carried out in Fig. 5. A and B, DEVD-amc was used as a substrate to analyze DRICE-like caspase activity. Error bars represent S.D.; RFU, relative fluorescence units. C and D, caspase activity was assessed using VDAD-amc substrate. Error bars represent S.D.

FIG. 7. BR-C regulates drice expression in ecdysone-treated l(2)mbn cells. Drosophila l(2)mbn cells were treated with 40 nm dsRNA for BR-C or a negative control. Cells were harvested on day 3 or treated with 10 μM ecdysone. A, apoptosis was calculated as the percent of cells with condensed nuclei. At least 300 cells were scored for each treatment. Error bars represent S.D. from four experiments. B, RT-PCR was used to analyze drice expression and knockdown of BR-C. rp49 acts as loading control. DEVD-amc (C) and VDAD-amc (D) substrates were used to assess caspase activity in equal amounts of lysate. E, immunoblot analysis of DRICE and DRONC expression and the accumulation of their processed bands (proc). Cytochrome c (Cyt c) levels were used as loading control.

of drice (Fig. 7B). Activity on both DEVD-amc and VDAD-amc substrates was reduced to ~30% of control activity in l(2)mbn cells treated with BR-C dsRNA (Fig. 7, C and D) correlating with the effects seen on apoptosis induction. Immunoblot analysis indicated that processing of both DRICE and DRONC was markedly reduced upon knockdown of BR-C (Fig. 7E). Additionally, ecdysone-induction of full-length DRICE and DRONC was significantly reduced (Fig. 7E). Our results therefore demonstrate that BR-C is required for ecdysone-mediated regulation of drice transcription.

DISCUSSION

The data presented here demonstrate that drice expression is up-regulated in response to ecdysone in both larval salivary glands and Drosophila l(2)mbn cells. The observations are consistent with a large scale gene expression analysis during salivary gland cell death, which shows that drice, among many other genes, is up-regulated in dying salivary glands (30). When drice expression was ablated by RNAi, we observed low levels of caspase activity and a dramatic reduction in the rate of apoptosis following ecdysone treatment. In addition, our data suggest that DRICE is required for DRONC processing in ecdysone-treated l(2)mbn cells. Recent studies have shown that effector caspase activation in some tissues may occur in the absence of DRONC (13, 18). Data in this paper complement these findings and supports the observation that some DRICE activation may occur in the absence of DRONC.

Expression of the cell death genes rpr, hid, crq, dark, and dronc in salivary glands and midgut has been shown to be regulated by ecdysone-responsive transcription factors BR-C and E93 (14–16). The knockdown of BR-C in l(2)mbn cells reduced ecdysone-induced drice transcription and resulted in reduced DRICE expression, thus demonstrating that BR-C regulates drice transcription in l(2)mbn cells. E93 knockdown did not affect drice regulation following ecdysone treatment of l(2)mbn cells. As E93 regulates dronc expression (15, 21, 31), the decrease in apoptosis levels that we observed is likely to be a result of reduced dronc transcription and protein expression. Although BR-C and E93 are required in both salivary gland and midgut apoptosis, their functions differ between the tissues. For example, dronc expression is regulated in salivary glands by both BR-C and E93 but only by E93 in the midgut (15, 33). It would be interesting to test whether like dronc, BR-C regulation of drice is tissuespecific. The competence factor βFTZ-F1 is needed for the precise developmental re-expression of transcription factors including BR-C and E93 (32). We investigated its involvement in ecdysone-induced l(2)mbn apoptosis. Our findings demonstrate no clear role for βFTZ-F1 in regulating the apoptosis of l(2)mbn cells. We speculate that in l(2)mbn cells,
one dronc feedback (shown by broken lines) and DRICE processes DRONC. The processing of DRONC by DRICE further potentiates activation of the effector caspases, enabling efficient execution of apoptosis. The caspase cascade is further amplified by a positive feedback loop between DRICE and DCP-1.

Studies in this paper suggest that ecdysone-regulated DRICE is an essential effector of apoptosis execution in l(2)mbn cells. Based on the data presented here, we propose a model for DRICE-mediated amplification of the caspase cascade in ecdysone-treated cells (Fig. 8). Given that drice mutants are currently unavailable, specific ablation of this caspase in salivary glands and midgut may be required to further investigate the role of DRICE in ecdysone-induced programmed cell death in vivo.

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