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Steroid Regulation of Midgut Cell Death during *Drosophila* Development

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Abstract

Steroid hormones trigger dynamic tissue changes during animal development by activating cell proliferation, cell differentiation, and cell death. Here we characterize steroid regulation of changes in midgut structure during the onset of *Drosophila* metamorphosis. Following an increase in the steroid 20-hydroxyecdysone (ecdysone) at the end of larval development, future adult midgut epithelium is formed, and the larval midgut is rapidly destroyed. Mutations in the steroid-regulated genes *BR-C* and *E93* differentially impact larval midgut cell death but do not affect the formation of adult midgut epithelia. In contrast, mutations in the ecdysone-regulated *E74A* and *E74B* genes do not appear to perturb midgut development during metamorphosis. Larval midgut cells possess vacuoles that contain cellular organelles, indicating that these cells die by autophagy. While mutations in the *BR-C*, *E74*, and *E93* genes do not impact DNA degradation during this cell death, mutations in *BR-C* inhibit destruction of larval midgut structures, including the proventriculus and gastric caeca, and *E93* mutants exhibit decreased formation of autophagic vacuoles. Dying midguts express the *rpr*, *hid*, *ark*, *dronc*, and *crq* cell death genes, suggesting that the core cell death machinery is involved in larval midgut cell death. The transcription of *rpr*, *hid*, and *crq* are altered in *BR-C* mutants, and *E93* mutants possess altered transcription of the caspase *dronc*, providing a mechanism for the disruption of midgut cell death in these mutant animals. These studies indicate that ecdysone triggers a two-step hierarchy composed of steroid-induced regulatory genes and apoptosis genes that, in turn, regulate the autophagic death of midgut cells during development.

Keywords

steroid; ecdysone; programmed cell death; apoptosis; autophagy; development; metamorphosis; *Drosophila*

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