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SPOTLIGHT

Driven to cannibalism: A hormonal trigger for phagocytosis

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In this issue, Ghosh et al. (https://doi.org/10.1083/jcb.202411073) reveal that a hormonal cue induces ovarian stretch follicle cells to cannibalize adjacent nurse cells—a process necessary to remodel egg chambers into viable eggs.

Tissue development relies on the balance of two opposing yet complementary cell processes: proliferation and elimination. Like a sculptor, proliferation builds a broad foundation while cell elimination contours details by chiseling away pieces of tissue. Although the regulation of cell elimination is crucial to the form and function of tissues, the molecular mechanisms remain incompletely described. In a new study published in the *Journal of Cell Biology*, Ghosh and colleagues reveal that in the *Drosophila* ovary, a small population of cells is transformed into cellular cannibals by the steroid hormone ecdysone (1). This new role for a well-known temporal cue provides mechanistic insight into how specific cell fates can be harnessed to sculpt tissues.

Cell elimination through cannibalism

Cells and cellular debris are removed from a tissue through phagocytosis, a process wherein one cell consumes another. Since the initial characterization of immune cells engulfing bacteria, phagocytosis is regarded as a mechanism employed by a diverse population of cells ("phagocytes") specialized for cell elimination (2). Professional phagocytes, like macrophages in mammals and hemocytes in insects, are tailored for the detection and clearance of pathogens and apoptotic cells (3).

In the absence of professional phagocytes, epithelial cells can assume nonprofessional phagocytic activity. In *Drosophila* and zebrafish, epidermal cells act as amateur phagocytes to prune developing neurites and clear sites of neuronal injury (4, 5). In some organisms, this flexibility is not just advantageous but essential. Nematodes lack professional phagocytes, relying solely on nonprofessionals to clear unwanted material (6). This raises intriguing questions regarding how cells are recruited to become nonprofessional phagocytes and what limits their activity, with implications for cancer therapeutics and regenerative medicine (3).

Harnessing *Drosophila* to visualize developmental phagocytosis

Ghosh and colleagues use egg production in *Drosophila* to understand the regulation of phagocytosis in the context of normal development. The egg, a colloquial term for an oocyte surrounded by epithelial cells, is a great example of a tissue shaped by both cell proliferation and elimination. *Drosophila* are particularly advantageous due to their wealth of genetic tools and because egg development can be visualized from beginning to end in one ovariole, or string of increasingly developed egg chambers (Fig. 1 A) (7, 8). During early oogenesis, one oocyte differentiates within a cyst of 16 interconnected germ cells. Because the oocyte is largely transcriptionally quiescent, production of maternal factors is accomplished by the other 15 cells, called nurse cells (Fig. 1, B–B″). At stage 13, nurse cells "dump" their cytoplasmic contents into the oocyte and self-destruct (Fig. 1 B′). Nurse cell death and clearance are nonautonomous, controlled by neighboring somatic cells called stretch follicle cells. Phagocytic activity of stretch follicle cells is controlled by molecular mechanisms shared with professional phagocytes, including the transcription factor Serpent (GATA factor) and the transmembrane proteins Croquemort (CD36) and Draper (Fig. 1 C) (1, 7, 9).

A steroid hormone controls nonprofessional phagocyte recruitment

Using elegant live imaging, Ghosh and colleagues began by observing stretch follicle cells as they migrate anteriorly in small groups, extend protrusive arms, and wrap a nurse cell (Fig. 1 B′). Acidification and F-actin destabilization in the nurse cell following engulfment then initiated cell death (Fig. 1 B″). Live imaging confirmed previous studies noting that nurse cell death is activated nonautonomously (7). The process is reminiscent of *Caenorhabditis elegans* endodermal cells, which "nibble" at primordial germ cells to alter their shape (10).

Ghosh and colleagues noticed that a well-characterized reporter of ecdysone signaling was expressed in stretch follicle cells (1). Ecdysone is a steroid hormone, functionally equivalent to the mammalian hormone estrogen, that signals through a conserved nuclear receptor (EcR) (8). The authors elucidate the transcriptional network connecting EcR to the induction of an epithelial-to-mesenchymal transition in stretch follicle cells and the apoptotic breakdown of nurse cells (Fig. 1 C). They confirm that EcR is necessary for

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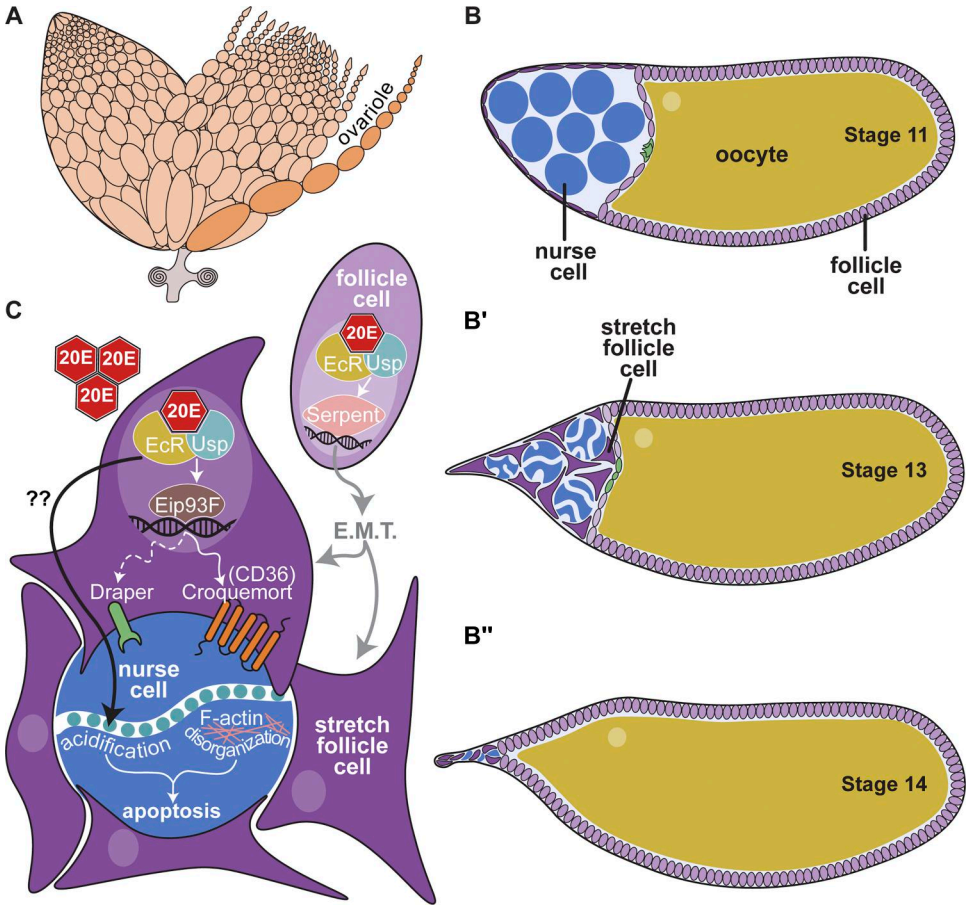

Figure 1. ***Drosophila* ovarioles offer a sequential view of nurse cell phagocytosis. (A)** The *Drosophila* ovary is composed of ovarioles, which are strings of progressively developed egg chambers. **(B)** Schematic view of nurse cell engulfment by stretch cells during Stages 11 (B), 13 (B′), and 14 (B") of egg chamber development. **(C)** Summary of molecular mechanisms regulating nurse cell phagocytosis by stretch follicle cells.

the accumulation of Serpent, Draper, and Croquemort, at least in part via Eip93F, an ecdysone-inducible transcription factor. Overall, the study reveals ecdysone as the temporal cue connecting nonprofessional phagocyte recruitment with nurse cell apoptosis.

A role for ecdysone in ovarian tissue remodeling is not entirely surprising. Larval growth and metamorphosis are driven through tightly regulated pulses of ecdysone production that coincide with tissue remodeling through both cell proliferation and cell elimination. For example, midgut breakdown, salivary gland reorganization, neuronal pruning, and hemocyte migration are initiated by high ecdysone titer and are linked with cell-autonomous activation of the apoptotic cascade (5–7). Further, in the wing disc and the ovarian epithelium, ecdysone signaling is essential for cell proliferation, also in a cell-autonomous manner (7, 8).

What is surprising is that ecdysone promotes phagocytosis in a specific subset of follicle cells, resulting in the death of their neighbors rather than themselves. EcR is ubiquitously expressed in the ovarian epithelium and promotes a variety of follicle cell behaviors (8). Late-stage egg chambers are the major site of ecdysone production in adults, suggesting all follicle cells are exposed to equivalent ecdysone titer. Yet, EcR only promotes Eip93F in stretch follicle cells (1). Why does this promote cannibalism rather than suicide? Further, how is this precise response controlled? One possibility is that a specific cellular response is activated depending on which additional transcriptional regulator(s) are also active in those cells. Precedent for this mechanism comes from neuronal remodeling, where EcR cooperates with JNK signaling to provide temporal control over phagocytosis (11). Future experiments investigating the cooperation of EcR and JNK signaling in the ovary may elucidate the temporal regulation of nurse cell clearance, with implications for a broader mechanism of action for EcR in nonautonomous cell elimination during tissue remodeling in other contexts, including metamorphosis and injury-induced regeneration.

Implications for phagocytosis beyond *Drosophila*

Ghosh and colleagues establish a mechanistic connection between nuclear receptor signaling and the induction of amateur phagocytosis, expanding our understanding of how endocrine factors promote local cell fate changes to ensure proper tissue remodeling. Of note, EcR is functionally conserved with other nuclear receptors, including retinoic acid receptor, recently implicated in dead cell clearance in the hair follicle stem cell

niche (12). Together, these findings underscore the need to view phagocytosis as a highly adaptable and developmentally integrated process responsive to physiological cues.

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