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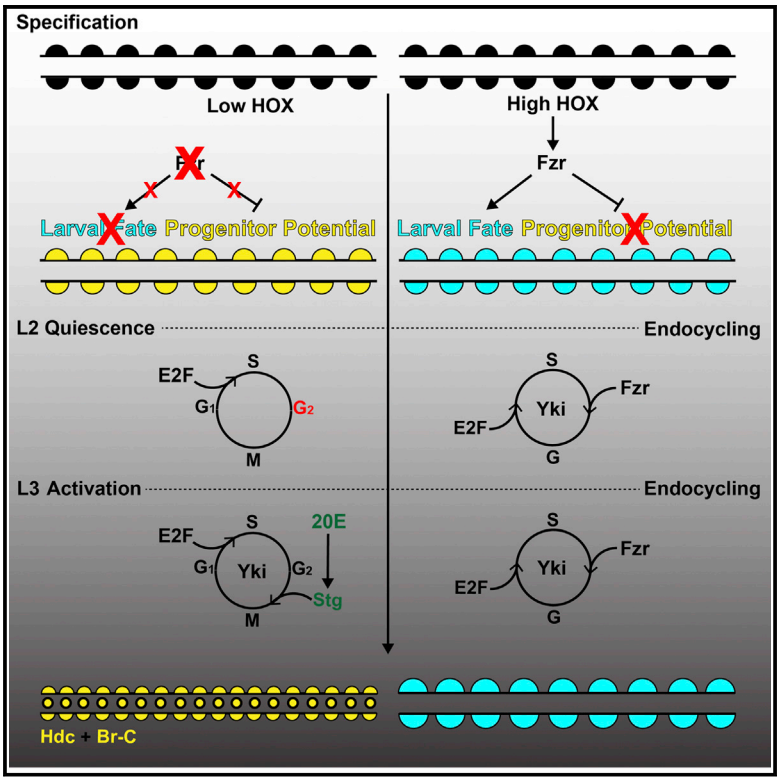
Cell Reports

# Specification of Differentiated Adult Progenitors via Inhibition of Endocycle Entry in the *Drosophila* Trachea

## Graphical Abstract




## Highlights

Fzr regulates cell-cycle mode and progenitor potential in the *Drosophila* trachea

Homeotic genes specify a set of differentiated tracheal cells as adult progenitors

Hormonal signaling through Ecdysone activates differentiated tracheal progenitors

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## In Brief

In this paper, Djabrayan et al. describe the genetic mechanisms mediating the specification, quiescence, and activation of a subset of differentiated tracheal cells as adult progenitors in *Drosophila*. They also show that a single factor is necessary and sufficient to couple cell-cycle mode with expression of adult progenitor markers.

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# Specification of Differentiated Adult Progenitors via Inhibition of Endocycle Entry in the *Drosophila* Trachea

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## SUMMARY

**A population of *Drosophila* adult tracheal progenitor cells arises from differentiated cells of the larval main trachea that retain the ability to reenter the cell cycle and give rise to the multiple adult tracheal cell types. These progenitors are unique to the second tracheal metamere as homologous cells from other segments, express *fizzy-related (fzr)*, the *Drosophila* homolog of CDH1 protein of the APC complex, and enter endocycle and do not contribute to adult trachea. Here, we examine the mechanisms for their quiescence and show that they reenter the cell cycle by expression of string/cdc25 through ecdysone. Furthermore, we show that preventing endocycle entry is both necessary and sufficient for these tracheal cells to exhibit markers of adult progenitors, thus modifying their genetic program. Finally, we show that Hox-mediated regulation of *fzr* expression is responsible for progenitor identity and thus specifies a group of differentiated cells with facultative stem cell features.**

## INTRODUCTION

The ability of differentiated progenitor cells or facultative stem cells to re-enter the cell cycle and replace lost tissue is a major feature in development, tissue homeostasis, wound healing, and regeneration. However, it is not clear how a population of multipotent differentiated cells that forms a functional tissue is singled out and is capable of reactivation. Here, we analyze this issue by examining the transition from the larval to adult body in *Drosophila*.

At the end of *Drosophila* embryogenesis just before the onset of the larval stages, most cells switch to the endocycle, a modified cell cycle that lacks an M phase, resulting in polyploid cells (Smith and Orr-Weaver, 1991; Ullah et al., 2009). Likewise, most embryonic tracheal cells switch to the endocycle, contribute to the larval trachea, and die at metamorphosis without contributing to the adult trachea (Whitten, 1957). During the third larval instar, adult tracheal progenitor cells begin to proliferate and eventually replace the larval trachea with adult structures (Guha et al., 2008; Sato et al., 2008; Weaver and Krasnow, 2008). Two classes of adult tracheal progenitor cells exist. On the one hand, the cells of the spiracular branch (SB) are specified during embryogenesis, remain quiescent and undifferentiated during larval growth as evidenced by their continuous expression of the transcription factor *escargot*, and do not form a functional organ until metamorphosis occurs (Pitsouli and Perrimon, 2010). On the other hand, a different class of adult tracheal progenitor cells comprise a population of differentiated tracheal cells in the dorsal branches (DBs) and in the dorsal trunk (DT) that during embryonic and larval life form a functioning part of the tracheal network (Guha et al., 2008; Sato et al., 2008; Weaver and Krasnow, 2008); these cells do not enter the endocycle and remain diploid according to their nuclear size, DNA content, and cell-cycle markers (Sato et al., 2008) until the third larval instar (L3) when they re-enter the mitotic cycle (Figures 1A and 1B) (Guha and Kornberg, 2005; Sato et al., 2008). Previous work has shown that the differentiated adult tracheal progenitor cells in the DT are specific to the second tracheal metamere (Tr2) and that the difference between the DT cells in Tr2 and those of the DT in other metameres is established by homeotic genes (Sato et al., 2008). However, nothing is known about how these cells remain quiescent, how they are triggered to proliferate to give rise to the adult trachea, or how they are set apart from the other tracheal cells not contributing to adult structures.

Here, we reveal how the DT tracheal adult progenitors are specified and the mechanisms that maintain their quiescence and later reactivate them. Moreover, we show that prevention of endocycle entry is both necessary and sufficient for the DT tracheal cells to exhibit markers of adult progenitors; thus, entering one or another mode of cell cycle (mitosis versus endocycle) is coupled to a switch in the cellular genetic program. These results indicate that restricting polyploidy is a means to keep a group of differentiated cells with facultative stem cell features.

## RESULTS

The cells identified as adult tracheal progenitors from the DT in the Tr2 metamere (hereafter referred as Differentiated Adult