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Interplay between neural stem cell state transitions and the cell cycle

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Brain development goes through phases of organ growth followed by cell differentiation. In the *Drosophila* visual system neuroepithelial cells proliferate through symmetric divisions to expand the neural stem cell pool. At later stages neuroepithelial cells transform into asymmetrically dividing medulla neuroblasts. The neuroepithelial to neuroblast transition is induced by the transient expression of the transcription factor Lethal of scute (L'sc), which sweeps across the neuroepithelium as proneural wave. In this study we investigated the relationship between the neuroepithelial cell to neuroblast transition and the progression in the cell cycle.

By carrying out EdU incorporation and Fly-FUCCI live cell experiments we found that L'sc positive cells in the transition zone are arrested in G2 phase. After release of the G2 arrest cells enter mitosis and undergo a first asymmetric self-renewing division, which is characteristic for neuroblasts. Clonal misexpression analysis suggests that L'sc is upstream of cell cycle progression. We manipulated the function of cell cycle factors Cell cycle dependant kinase 1 (Cdk1) and its inhibitory kinases Wee1 and Myt1. Using mutations that render Cdk1 non-inhibitable we show that phosphorylation of Cdk1 at Tyrosine 15 is important for the timely neuroepithelial cell to neuroblast transition. Premature release of the cell cycle arrest might lead to cell apoptosis and ectopic delamination of cells in the transition zone. Preliminary results also indicate that Myt1 loss of function leads to failures in the timely downregulation of L'sc expression. In conclusion our study shows the intricate interplay between neural stem cell state regulators and the progression of the cell cycle.

Jury:
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