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Notch activity in neural progenitors coordinates cytokinesis and asymmetric differentiation
Filipe Pinto-Teixeira¹ and Claude Desplan¹,²*

Asymmetric division of neural progenitor cells is a crucial event in the generation of neuronal diversity and involves the segregation of distinct proteins into daughter cells, thereby promoting unique differentiation programs. Although it was known that Notch signaling acts postmitotically to orchestrate differentiation of daughter cells from asymmetrically dividing precursor cells, Bhat reported a previously uncharacterized role for Notch that occurs before cell division to promote the asymmetric localization of the protein Numb and the positioning of the cleavage furrow. Numb is an inhibitor of Notch activity; thus, this mechanism forms a regulatory feedback loop to control asymmetric cytokinesis and differentiation.

A fundamental event that enabled the development of multicellular organisms was the evolutionary acquisition of the capacity of a cell to divide asymmetrically: Mother cells divide to generate two distinct progeny, or stem cells self-renew and generate a progeny with a distinct fate. Cell division and cellular differentiation are tightly coupled, although we know little about how they are linked molecularly (1). The development of the central nervous system in Drosophila melanogaster embryos is a powerful model for studying the molecular basis of asymmetric cell division (2–6). In Drosophila embryos, neuronal precursors called neuroblasts (NBs) divide asymmetrically, self-renewing and producing a smaller ganglion mother cell (GMC). GMCs undergo terminal asymmetric division, producing two distinct neurons (7). NB asymmetric division invariably shows asymmetric cytokinesis, with the largest daughter cell maintaining the NB identity. Some GMCs seem to have maintained this characteristic, also exhibiting asymmetric cytokinesis. Notch, Numb, and InsCuteable (InsC) play a central role in the generation of asymmetric cytokinesis of GMCs and asymmetric differentiation of daughter neurons (2–5). A study by Bhat (8) addressed how these cellular and molecular events interact and reported that Notch, previously believed to act postmitotically in one of the neuronal progeny, also acts in the GMC to coordinate cytokinesis and asymmetric differentiation by regulating Numb localization.

The NB4-2 lineage is a well-studied example in the fly embryo where the first GMC (GMC-1) shows asymmetric cytokinesis, producing a larger-sized motor neuron (RP2) and a smaller sibling (sib) cell of unknown fate (2–5). This difference in cell fate is due to different Notch activity in the two daughter cells. As occurs in several other cell lineages, InsC and Numb initially show a uniform distribution in GMC-1. However, just before cytokinesis, the localization of InsC and Numb polarizes in an axis perpendicular to the plane of cytokinesis: InsC localizes to the apical pole and Numb to the basal pole. The asymmetric division of GMC-1 and specification of the daughter cells is tightly linked to the asymmetric segregation of InsC and Numb. The smaller apical daughter cell, where InsC accumulates, is specified as the sib cell by Notch activity, whereas the basal daughter cell inherits Numb, which specifies the RP2 fate by inhibiting Notch activity (2–5). This suggests a possible link between Notch and InsC, leaving open the question of how InsC and Numb asymmetric distributions are established in the GMC-1 before division.

Bhat analyzed the problem by looking at the GMC-1 lineage in flies homozygous for a mutant Notch allele that encodes a temperature-sensitive protein (NotchTS). Shifting NotchTS embryos to a higher-than-normal temperature temporarily inhibits Notch signaling, enabling Bhat to investigate exactly when Notch is required for asymmetric cell division. When the temperature shift occurred just after GMC-1 formation (early loss of Notch function), the daughter cells showed symmetric cytokinesis, producing two daughter cells of identical size. However, when Notch was inhibited later, just before the division of GMC-1 (late loss of Notch function), the basal daughter cell was larger than the apical daughter cell (Fig. 1). Both early and late loss of Notch function caused both daughter cells to be specified as RP2, indicating that the sib identity is defined by Notch before cytokinesis of the GMC.

In a newly formed GMC-1, Numb is initially distributed uniformly and later accumulates near the basal cortex, where it forms a crescent just before division. Bhat found that after temperature shift of NotchTS embryos soon after GMC-1 formation, no crescent formed and Numb remained distributed with both progeny inheriting Numb, hence leading to two identical-sized cells with RP2 fate (Fig. 1). Similar results were observed in embryos with mutations in mastermind (mam), which encodes an essential component of Notch signaling (9). These observations indicated that Notch signaling mediates Numb localization in GMC-1s through Mam before division. In NotchTS embryos temperature-shifted late during GMC-1 division, Numb formed a crescent that was still basally localized (although larger), thus explaining the production of cells of different sizes. However, the lack of Notch activity in the smaller cell prevented its development as the sib cell. This shows that asymmetric cytokinesis and cell fate are tightly linked through Notch activity in the premitotic GMC, forming an autoregulatory loop: Notch controls Numb localization and Numb controls Notch activity (2, 5, 6, 10) (Fig. 1).

In both NBs and GMCs, loss of InsC affects the orientation of the axis of cell division (3, 11). Additionally, InsC controls asymmetric Numb distribution (3). Bhat showed that early Notch signaling was required for the apical localization of InsC. Furthermore, when Notch function was inhibited at different times, asymmetric localization of Numb correlated with the asymmetric size of the daughter cells, implying that the larger the Numb crescent (less localized), the more symmetric the cytokinesis.

Taken together, these results suggest that apical-basal polarity inherited from the NBs is maintained in the GMCs under regulation by Notch signaling. In the absence of either InsC or Numb, both daughter cells adopt the sib cell fate through active Notch signaling.

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Fig. 1. Schematic representation of the asymmetric division of GMC-1. The localization patterns of Numb and Insc are shown. The size of the progeny reflects the asymmetric- or symmetric-sized division patterns induced by the Numb crescent. The dashed line on the GMCs represents the axis and position of cell division. The early distribution of Numb is punctate throughout the cortex of GMC-1, perhaps enabling restricted Notch signaling. In wild-type embryos, before cytokinesis, Notch activity localizes Insc and Numb to opposite locations in an axis perpendicular to the plane of cytokinesis. As a consequence, the smaller apical daughter cell accumulates Insc and is specified as a sib cell by Notch activity. The basal daughter cell inherits Numb, which specifies the RP2 fate by inhibiting Notch activity. In Notch mutant embryos, early or late loss of Notch function causes both daughter cells to adopt the RP2 cell fate. However, earlier inactivation of Notch leads to symmetric cell division, whereas late inactivation of Notch leads to asymmetric cytokinesis due to earlier Notch activity in the GMC-1 that enables partial localization of Insc and Numb.

How does Notch signaling become asymmetrically active in GMC-1? Bhat showed that the earlier distribution of symmetric Numb is not uniform but is punctate throughout the cell cortex. The author suggested that this enables Numb to only partially reduce Notch signaling, allowing enough Notch activity to promote the asymmetric localization of Insc and Numb but not enough to induce a premature sib cell identity to the GMC itself. How the apical-basal axis is defined in GMCs or inherited from the NB remains unanswered, and the molecular mechanism allowing asymmetric Notch activity to localise Insc and Numb is still a mystery. Nevertheless, the study by Bhat brings new insight into the timing of the requirement for Notch signaling in asymmetric cell division and challenges the established belief that Numb is the primary determinant of asymmetry in precursor cells, leading to asymmetric Notch activity in the daughter cells. Although there are cell lineages where Insc is not involved in asymmetric division, Bhat found that in precursor cells of many of these lineages, Notch regulated the localization of Numb. This finding suggests that such a premitotic feedback circuit may be a more universal strategy used to coordinate asymmetric cytokinesis and differentiation.

References

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