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Progenitor properties of symmetrically dividing *Drosophila* neuroblasts during embryonic and larval development

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ABSTRACT

Asymmetric cell division generates two daughter cells of differential gene expression and/or cell shape. *Drosophila* neuroblasts undergo typical asymmetric divisions with regard to both features; this is achieved by asymmetric segregation of cell fate determinants (such as Prospero) and also by asymmetric spindle formation. The loss of genes involved in these individual asymmetric processes has revealed the roles of each asymmetric feature in neurogenesis, yet little is known about the fate of the neuroblast progeny when asymmetric processes are blocked and the cells divide symmetrically. We genetically created such neuroblasts, and found that in embryos, they were initially mitotic and then gradually differentiated into neurons, frequently forming a clone of cells homogeneous in temporal identity. By contrast, larval neuroblasts with the same genotype continued to proliferate without differentiation. Our results indicate that asymmetric divisions govern lineage length and progeny fate, consequently generating neural diversity, while the progeny fate of symmetrically dividing neuroblasts depends on developmental stages, presumably reflecting differential activities of Prospero in the nucleus.

Introduction

Asymmetric cell division is a fundamental mechanism in the establishment of cellular diversity. In general, the daughter cells of asymmetric divisions differ from each other with respect to gene expression and/or cell shape, features that play important roles in various contexts of development and tissue homeostasis. *Drosophila* neuroblasts provide an excellent model for studying asymmetric division because they undergo typical asymmetric divisions, with the daughter cells exhibiting differential gene expression and cell size. Neuroblasts repetitively divide into a larger neuroblast and a smaller ganglion mother cell (GMC), while the GMC divides once into a pair of neurons or glia (Wang and Chia, 2005). During these divisions, cell fate determinants such as Prospero (Pros) and Brain tumor (Brat) asymmetrically localize to the basal cortex (Hirata et al., 1995; Betschinger et al., 2006; Bello et al., 2006; Lee et al., 2006b). This is achieved by the binding of these 'basal determinants' to the adaptor protein Miranda, which itself localizes asymmetrically due to the function of the aPKC–PAR complex (the apical complex) (Ikeshima-Kataoka et al., 1997; Shen et al., 1997; Kraut et al., 1996; Matsuzaki et al., 1998; Schober et al., 1999; Wodarz et al., 2000; Schaefer et al., 2000; Parmentier et al., 2000; Petronczki and Knoblich, 2001). The basal determinants then segregate into the GMC by the alignment of their polarized distribution with that of the spindle, consequently switching gene expression in the GMC from the neuroblast mode into neuronal differentiation.

Asymmetric divisions of neuroblasts play critical roles in the generation of neuronal diversity in embryos, since decisions regarding neuronal fates are highly stereotyped and deterministic. Neuroblasts sequentially express a set of transcription factors, including Hunchback (Hb), Krüppel (Kr), Pdm1/Pdm2 (Pdm), and Castor (Cas), essentially in an invariant order, while sibling GMCs virtually maintain the expression of these genes inherited from the mother neuroblast (Isshiki et al., 2001; Pearson and Doe, 2003; Grosskortenhaus et al., 2005). As a result, each GMC gives rise to a neuroblast lineage that is different from the next in its expression of the temporal identity genes, although it is unclear how differential progression in gene expression between neuroblast and sibling progeny occurs.

Recent studies also revealed that elimination of the basal determinants results in tumor formation in larval neurogenesis. Transplantation of larval brain cells mutant for *prospero, numb* or *miranda* into wild-type adult fly causes malignant tumors (Caussinus and Gonzalez, 2005). Furthermore, mosaic clones of *prospero*, *numb* or *brat* mutants in the larval brain result in overproliferation of progenitor cells (Betschinger et al., 2006; Bello et al., 2006; Lee et al.,

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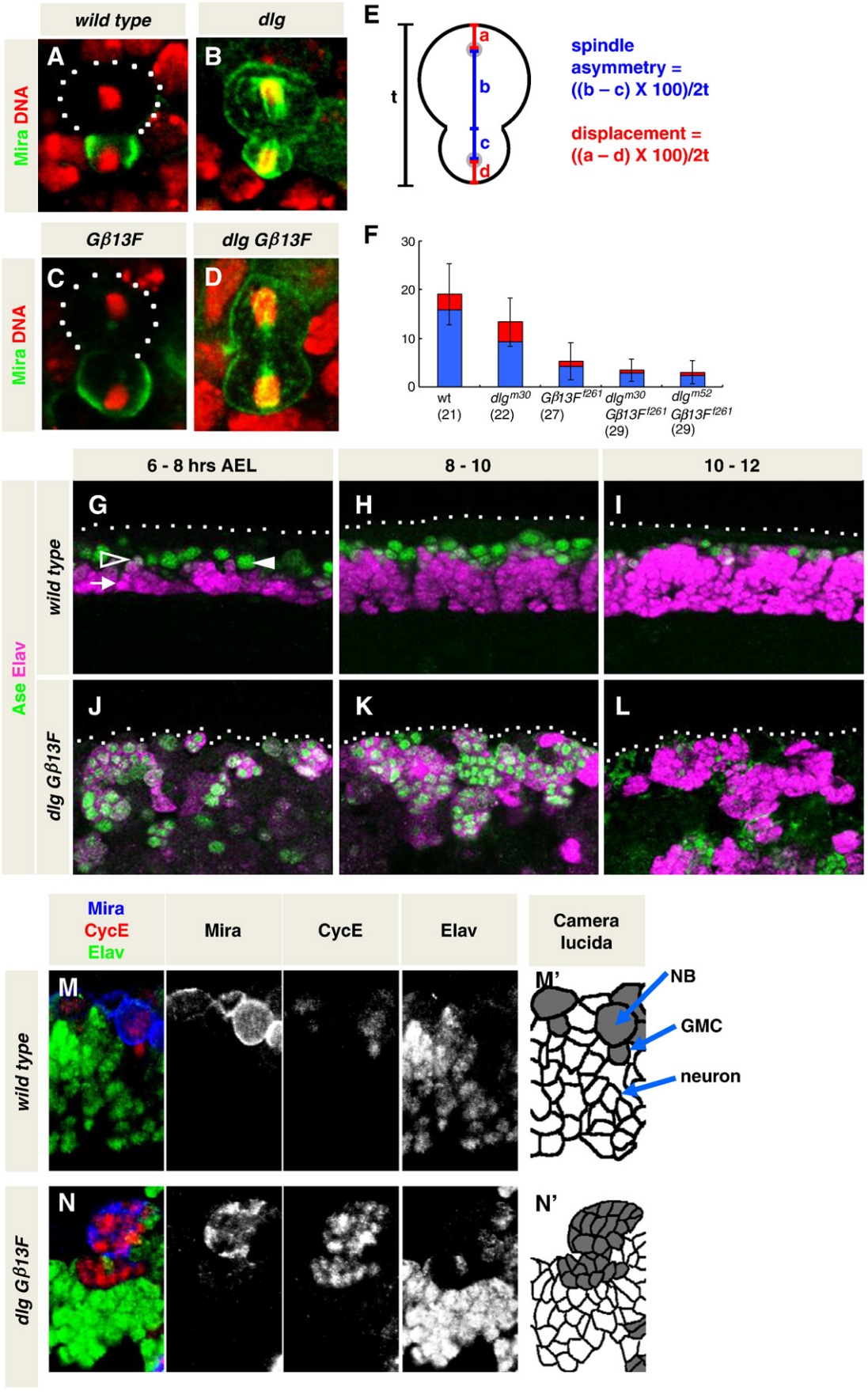
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E
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dlgm30 Gβ13Ff261 (29)
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