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New insight into the basis for differences in cell size

May 27, 2003 – When a cell divides, the two new cells are often differently sized. This is seen in the cleavage of eggs in many species, as well as in the division of some stem cells, which results in a pair of cells, one or both of which has a different, more highly specified, character than its parent. A recent study has now shown one mechanism by which such cell size asymmetry is achieved.

The Laboratory for Cell Asymmetry, under group director Fumio Matsuzaki, has now identified a molecular determinant responsible for the generation of unequally sized daughter cells during the division of neuroblasts in the fruitfly, *Drosophila melanogaster*. This form of cell division generates a large neuroblast and a smaller ganglion mother cell, or GMC. The neuroblast retains similar properties and potential to that of its parent cell, while the GMC is more restricted in its developmental potency. Successive divisions of neuroblasts and their progeny cells ultimately give rise to the *Drosophila* nervous system, which provides a model for the fundamental processes at work in the development of more complex neural networks, including the human nervous system.

Asymmetric cell division is an essential aspect of differentiation, the process in which daughter cells acquire characteristics distinct from those of their parents. Previous studies have identified a number of molecular factors that move selectively to one side of a dividing cell, thereby determining the character, or fate, of both of the cells created in the division. The factors that are currently know to act in asymmetric division have been shown to regulate aspects such as the function and differentiative potential of the daughter cells, but the question of how difference in cell size is regulated at the molecular level has remained unanswered. The cellular mechanics of the process, however, have been studied, and it was known that different types of cells divide into different sized progeny either by the off-center positioning of the mitotic spindles (which dictate the point at which the cell cleaves), or their actual physical asymmetry. In *Drosophila* neuroblasts, spindle asymmetry is the main factor in generating unevenly sized cells.

In an article published in the May 27 issue of *Current Biology*, Naoyuki Fuse et al have shown for the first time how the spindles are instructed to form asymmetrically. The process is directed by one subunit of a G-protein (known as a heterotrimeric G protein) composed of three distinct parts. G proteins generally function to bind the energy-carrying molecules GDP and GTP, and activate or mediate a number of biological processes within the cell.

The Matsuzaki group found that in the absence of the Gβ subunit, neuroblasts form large, symmetrical spindles as they prepare to divide and generate cells of nearly equal size, instead of the normal large neuroblast/small GMC pair. Conversely, overexpression of Gβ resulted in small spindles, suggesting that the subunit works to suppress spindle development. Interestingly, this abnormal symmetry in size had no effect on the normal asymmetric distribution of other fate-determining molecules, demonstrating that the mechanisms underlying fate and size asymmetry are mutually independent. Flies with Gβ mutations also showed nervous system defects, which suggests that cell size is in itself important to the function of neuroblasts.

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