

What lies beneath APP

Huntingtin, α -synuclein and the amyloid precursor protein (APP) are molecules familiar to most neuroscientists because of their involvement in several neurodegenerative disorders. But, surprisingly, we know little about their roles in healthy neurons. Two recent papers provide some clues as to the function of APP by showing that it might participate in the control of cell motility and gene expression.

Both studies initially focused on the well-characterized interaction between APP and another protein of unknown function — FE65. In addition to its interaction with APP, FE65 binds to Mena, a protein that is thought to participate in the regulation of actin dynamics. Sabo *et al.* co-expressed APP and FE65, and found that both proteins colocalized with Mena and integrins at cell-adhesion sites known as ‘focal complexes’ — dynamic membrane sites commonly located at the leading edge of migrating cells. Furthermore, by using a motility assay in which a scratch is made to a confluent cell layer, they found that cells expressing APP and FE65 migrated faster to ‘heal the wound’ compared with cells that only expressed APP.

But not all the action is at the membrane; the interaction between the cytoplasmic tail of APP and FE65 might also regulate nuclear gene expression. When the presenilins cleave APP, they produce β -amyloid and an intracellular segment. As the intracellular segment of other presenilin substrates can regulate transcription, Cao and Südhof explored whether the cytoplasmic tail of APP had a similar role. They found that a fusion protein between APP and the nuclear binding domain of Gal4 could activate gene expression only if FE65 was also present. Moreover, they discovered that the two proteins formed a complex with Tip60, a histone acetyltransferase that participates in DNA repair and transcription.

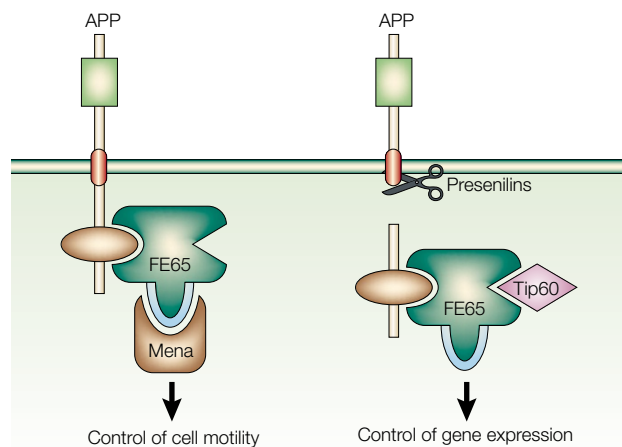
Although it remains to be seen whether native APP has similar functions in neurons, the results from both studies provide an intriguing insight into this enigmatic protein.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Sabo, S. L. *et al.* The Alzheimer amyloid precursor protein (APP) and FE65, an APP-binding protein, regulate cell movement. *J. Cell Biol.* **153**, 1403–1414 (2001) | Cao, X. & Südhof, T. C. A transcriptionally active complex of APP with FE65 and histone acetyltransferase Tip60. *Science* **293**, 115–120 (2001)

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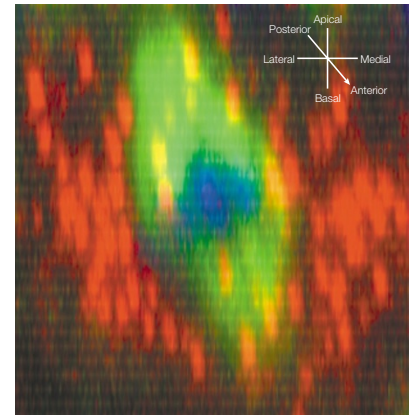


Glide to divide

The developing *Drosophila* central nervous system (CNS) contains at least two types of neural precursor cell — neuroblasts, which generate neurons only, and neuroglioblasts, which give rise to both neurons and glia. The generation of glia depends on the transcription factor *Glide/gcm* (Glial cell deficient/glial cell missing). Like many neuroblasts, neuroglioblasts divide asymmetricaly and their progeny become specified by cell fate determinants that segregate into one or other of the daughter cells. As reported in *Developmental Biology*, Ragone *et al.* have examined the segregation of *glide/gcm* RNA during neuroglioblast division and, in the process, have uncovered some distinctive features of the mode of asymmetric division in these cells.

The authors focused on the 6-4T neuroglioblast (NGB6-4T). This cell initially divides to give a neuroblast (which subsequently divides symmetrically to give two neurons), and a glioblast (which generates three glial cells). They showed that the mode of NGB6-4T division has several distinguishing features. First, the two cells produced by NGB6-4T division are quite similar in size, unlike those produced by the asymmetric division of neuroblasts. Also, whereas neuroblasts divide along the apico-basal axis of the neuroepithelium, the NGB6-4T cells divide obliquely, such that the glioblast daughter cell acquires a basal, anterior and medial position with respect to the neuroblast daughter cell. *glide/gcm* RNA accumulates in particles at the medio-basal anterior side of the cell during metaphase and it segregates into the glioblast daughter cell on division. The particulate distribution of the RNA is unusual in itself, as determinants that segregate during asymmetric cell division generally accumulate in a homogeneous crescent in the cell cortex.

Localization of *glide/gcm* depends on the Stauf and Miranda proteins, which also localize the Prospero (Pros) transcription factor. Pros co-



6-4T neuroglioblast in anaphase showing accumulation of *glide/gcm* RNA (red) at the medio-basal anterior side. α -Tubulin (green), chromatin (blue). Image courtesy of Angela Giangrande, Institut de Génétique et Biologie Moléculaire et Cellulaire, Strasbourg, France. See movie online.

segregates with *glide/gcm*, and *pros* mutant flies are deficient in all the glial progeny of the NGB6-4T. However, gain-of-function experiments showed that Pros is not sufficient to activate *glide/gcm* gene expression, and Ragone *et al.* propose that its role is to maintain *glide/gcm* expression in the daughter cell. The *pros* mutant CNS shows an increase in the number of cells expressing *eagle*, which is a characteristic of the neurons that arise from NGB6-4T. This indicates that daughter cells that fail to maintain *glide/gcm* expression revert to a neuronal cell fate.

So, NGB6-4T cells have a distinctive oblique mode of asymmetric cell division, during which *glide/gcm* becomes segregated into the daughter cell that will give rise to glia. After division, *glide/gcm* expression must be maintained in the daughter cell in order for gliogenesis to occur, and this maintenance requires the function of Prospero. This research hints at possible common mechanisms of asymmetric division in *Drosophila* cells that generate glia; for example, the PIIb cell, which produces a glial precursor in the peripheral nervous system, also divides obliquely. However, PIIb does not express *glide/gcm* before division, ruling out a causal relationship between expression of this determinant and the orientation of the mitotic spindle. It will be very interesting to find out what other characteristics are shared by gliogenic precursors in *Drosophila*.

Heather Wood

References and links

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