SNAP to attention: A SNARE complex regulates neuronal progenitor polarity

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SNARE vesicle targeting complex controls the polarity of neuronal progenitors. Kunii et al. (2020. J. Cell Biol. https://doi.org/10.1083/jcb.201910080) show that the SNAP23–VAMP8–Syntaxin1B complex is required for membrane targeting of N-cadherin and formation of adherence junction complexes in radial glia neuronal progenitors, the major prerequisite of cell polarity establishment.

Proliferation and maintenance of neural stem cells is crucial for proper establishment of the brain cytoarchitecture during development and correct functioning of the mature brain. In the vertebrate developing central nervous system (CNS), neural stem cells form a monolayer that enfolds the neural tube. The rostral, brain-forming part of the neural tube develops into a chain of ventricles, the brain ventricular system, connected with the central canal of the spinal cord (1). The ventricular system and central canal are filled with cerebrospinal fluid that immerses the layer of neural stem cells in the primary proliferative zone of the developing CNS, an area called the ventricular zone (VZ). Neural stem cells divide there and produce young neurons that, after exiting mitotic cycle, migrate out of the VZ to settle in their final location in the developing brain and differentiate into mature neurons that assemble neuronal circuits.

The cells of the VZ, also called neuroepithelium, are polarized like all epithelial cells. They have a basal side with which they are attached to the pial surface, while with their apical side they face the ventricular lumen. Radial glia cells (RGCs) that appear later in development are a class of polarized cells that are present in many places in the CNS but especially distinct in the forebrain. The degree of polarization of the RGC is even more pronounced than that of neuroepithelial cells, as their basal process is very long. RGC apical processes span the entire thickness of the developing neocortex and can extend as far as several millimeters in length in primates (2).

The polarity of RGCs is important for both their proliferation and for the postmitotic migration of young neurons. Detachment of their basal and/or apical processes results in abnormal proliferation and apoptosis, leading to abnormal cytoarchitecture of the postnatal brain (3). If only the basal process is detached from the pia, radial glia proliferation is undisturbed but neuronal migration is disrupted, also leading to defects in the proper construction of the brain (4).

It is not only the morphology of basal and apical processes that makes RGC a highly polarized cell. Presence of adherence junctions (adherence junctions complex; AJC) on the apical side of the cell membrane is another sign and determinant of asymmetry. Disruption of adherence junctions can cause disorders such as hydrocephalus and hemorrhage in humans (5).

Key proteins involved in the establishment and maintenance of AJC and polarity in RGCs are transmembrane N-cadherin and its cytoplasmic partner β-catenin (6). Disruption of the N-cadherin–β-catenin complex in the brain causes complete loss of both AJC and apico-basal polarity (6). Similarly, disruption of proteins that control N-cadherin trafficking, such as LIGL1, Dlg5, Numb and Numblike, can also cause failure of adherence junction formation (7).

In the current issue, Kunii et al. identified new players in this process, SNARE complex protein Snap23 and its binding partners (8). SNAP23 complex proteins NSF, soluble NSF attachment protein (SNAP), and syntaxin and its binding partner SNAP-25 were shown to be the main controllers of the synaptic vesicles’ fusion with presynaptic neuronal membrane (10).

Although it could be suspected that SNAP23 complex has a role in the polarity of the neuronal progenitors, knockout mice lacking components of the classical VAMP-syntaxin–SNAP25 complex did not show any abnormalities in the morphology of RGC. Kunii et al. hypothesized that other homologous SNARE complexes might control polarity of neuronal progenitors. To test this hypothesis, the authors inactivated a close homologue of Snap25, SNAP23, in the mouse CNS by conditional knockout. These
The study also raises a number of questions. For example, how is protein cargo specificity achieved? Which member of the SNARE complex can be replaced by a homologue without affecting specificity? Can SNAP25 fully replace SNAP23 in N-cadherin transport, or are other syntaxin homologues able to recapitulate Stx1B function? Another question to be addressed is whether localization of the SNAP23-containing complex is tightly regulated and, if so, how? It has been suggested that nonphosphorylated N-cadherin is removed from the basolateral side by Lgl1 via internalization (11). Conversely, atypical PKC phosphorylates N-cadherin on the apical side, preventing its interaction with Lgl1 and allowing N-cadherin retention on the apical membrane (Fig. 1 A; 11). Whether this is a mechanism that competes with SNAP23-mediated targeting remains to be clarified. It is also not clear whether the SNAP23-containing complex is required for targeting proteins located basolaterally such as Scribble-Lgl-Dgl.

In summary, this study uses a beautiful combination of mouse genetics and in vitro trafficking visualization and biochemistry to demonstrate an important role for the VAMP8–Stx1B–SNAP23 SNARE complex in the regulation of N-cadherin recruitment and neural progenitor polarity setting. Future work will undoubtedly provide further understanding of the role of the SNARE complex in radial glia and neuronal progenitor polarity setting.
insight into the mechanisms that regulate the function of this SNARE complex as well as the role of other SNARE proteins in this process.

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