This Week in The Journal

Role for Cep55 in Neural Stem Cell Division

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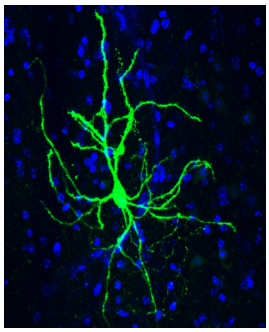
(see pages 3344–3365)

Early in nervous system development, neural stem cells (NSCs) proliferate through symmetric divisions that produce two daughter stem cells. Later, asymmetric divisions produce one postmitotic neuron and one neural precursor, which eventually divides symmetrically to produce two neurons. The number and timing of each of these types of division is calibrated to ensure that appropriate numbers of various types of neurons are produced before the progenitor pool is depleted. One stage at which such regulation occurs is cytokinesis, when mother cells' lipid, protein, and cytoplasmic components are partitioned between daughter cells.

After mitosis, cell division is initiated by a contractile ring that ingresses until daughter cells are connected by only a thin intercellular bridge. During this process, mitotic-spindle microtubules are incorporated into a midbody structure within the bridge. Components of the endosomal sorting complex required for transport (ESCRT) assemble on the midbody and mediate abscission, the final separation of cells. Work in cell lines suggested that the scaffolding protein Cep55 recruits ESCRT proteins to the midbody and is thus essential for abscission. But Little, McNeely et al. found that truncation of Cep55, which prevented it from associating with the midbody, had little effect on most tissues in mice. Moreover, most mutant fibroblasts and NSCs eventually underwent cell division in cultures. Nevertheless, mutant mice exhibited severe microcephaly and died in infancy.

Further investigation showed that Cep55 promoted, but was not mandatory for, ESCRT recruitment in both NSCs and fibroblasts. Possibly as a consequence of impaired ESCRT recruitment, abscission occurred more slowly than normal in mutant cells, and the number of binucleate cells was increased both in the developing brain and in other tissues. Notably, however, these defects increased apoptosis only in NSCs and neurons. In addition, mutant NSCs underwent symmetric neuron-producing divisions more often than normal.

These results suggest that Cep55 facilitates abscission in both neural and non-neural cells, and consequently, Cep55 mutation increases the production of binucleate cells throughout the body. Importantly, however, this abnormality triggers apoptosis primarily in neural cells. Cep55 mutation also promotes neurogenic division of NSCs, which likely depletes the NSC pool prematurely. These two effects explain why Cep55 mutation leads to microcephaly with minimal effects on the development of other organs.



A neuron in the medial intercalated cell cluster of the amygdala. These cells receive PACAPergic input from the basomedial nucleus. See Rajbhandari et al. for details.

PACAPergic Basomedial Amygdala Input to Intercalated Cells

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(see pages 3446–3461)

Being wary of danger is beneficial for survival, but excessive fearfulness when no threat is present is maladaptive and can manifest as anxiety or post-traumatic stress disorder (PTSD). Learning that stimuli formerly associated with threat no longer predict harm is called extinction; it involves suppression of fear responses generated by the central nucleus of the amygdala. This suppression is mediated partly by intercalated cell clusters in the amygdala, which receive input from the dorsomedial prefrontal cortex. Projections from the ventromedial prefrontal cortex to the basomedial amygdala also contribute to extinction (Izquierdo et al., 2016, Physiol Rev 96:695). Rajbhandari et al. now link these two pathways by showing that basomedial amygdala cells release pituitary adenylate-cyclase-activating polypeptide (PACAP)—a peptide linked to PTSD and threat responses—onto intercalated cells.

The authors found that PACAP-expressing cells were enriched in the lateral and basomedial amygdala, and their axons densely innervated medial intercalated cell clusters. Importantly, many PACAP-expressing cells also expressed vesicular glutamate transporter 2, suggesting they release glutamate as well as PACAP. Using a combination of Cre- and Flp-dependent recombinases, the authors expressed channelrhodopsin selectively in basomedial neurons that expressed PACAP and projected to intercalated cell clusters. Photoactivation of these neurons evoked glutamate-receptor-dependent EPSCs, sometimes followed by IPSCs, in intercalated cells. Notably, EPSC amplitudes decreased with each pulse during repetitive stimulation and were enhanced by an antagonist of the PACAP receptor PAC1.

Activation of PACAPergic projections to intercalated cell masses had no effect on the acquisition of contextual fear responses, but it reduced freezing during subsequent recall testing and extinction training. These effects were similar in males and females. In contrast, knocking out PAC1 in intercalated cells had sex-dependent effects. PAC1 knockout blunted acquisition of fear responses selectively in females, and it enhanced fear generalization and impaired fear extinction selectively in males. PAC1 knockout had no effect on recall in either sex.

These data suggest that the basomedial nucleus of the amygdala dampens fear responses partly through PACAPergic stimulation of medial intercalated cells. The sex-specific effects of PAC1 knockout suggest that this pathway may be more active in males than in females under normal conditions. This may explain why women are more susceptible to PTSD than men.

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