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# BIG1 is required for the survival of deep layer neurons, neuronal polarity, and the formation of axonal tracts between the thalamus and neocortex in developing brain

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## Abstract

BIG1, an activator protein of the small GTPase, Arf, and encoded by the *Arfgef1* gene, is one of candidate genes for epileptic encephalopathy. To know the involvement of BIG1 in epileptic encephalopathy, we analyzed BIG1-deficient mice and found that BIG1 regulates neurite outgrowth and brain development *in vitro* and *in vivo*. The loss of BIG1 decreased the size of the neocortex and hippocampus. In BIG1-deficient mice, the neuronal progenitor cells (NPCs) and the interneurons were unaffected. However, $Tbr1^+$ and $Ctip2^+$ deep layer (DL) neurons showed spatial-temporal dependent apoptosis. This apoptosis gradually progressed from the piriform cortex (PIR), peaked in the neocortex, and then progressed into the hippocampus from embryonic day 13.5 (E13.5) to E17.5. The upper layer (UL) and DL order in the neocortex was maintained in BIG1-deficient mice, but the excitatory neurons tended to accumulate before their destination layers. Further pulse-chase migration assay showed that the migration defect was non-cell autonomous and secondary to the progression of apoptosis into the BIG1-deficient neocortex after E15.5. In BIG1-deficient mice, we observed an ectopic projection of corticothalamic axons from the primary somatosensory cortex (S1) into the dorsal lateral geniculate nucleus (dLGN). The thalamocortical axons were unable to cross the diencephalon–telencephalon boundary (DTB). *In vitro*, BIG1-deficient neurons showed a delay in neuronal polarization. BIG1-deficient neurons were also hypersensitive to low dose glutamate (5 μM), and died via apoptosis. This study showed the role of BIG1 in the survival of DL neurons in developing embryonic brain and in the generation of neuronal polarity.