1. **No.**

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2. **Title**

   A Novel Therapeutic Strategy for Ischemic Stroke Based on Understanding Adult Neurogenesis via Signaling of Nicotinic Acetylcholine Receptors

3. **Period**

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4. **Summary**

Cerebral ischemic stroke causes frequently death and disability; yet, the therapeutic approaches have been so far limited. After stroke, most of neurons die in the ischemic core region, leading to induction of the severe brain dysfunction. Here we studied mechanisms that regulate neuronal survival around the infarct area, to develop a novel therapy for ischemic stroke. To investigate the profile of gene expression, which is induced immediately after middle cerebral artery occlusion (MCAO) in mice, RNA samples were prepared from the control and ischemic sides of neocortex at 2 h after stroke and subjected to RNA-Seq analysis. Among 37 candidate genes obtained from RNA-Seq, we found by in situ hybridization that 25 genes were expressed more abundantly in the ischemic side than the control side of cortex. Notably, the activity-dependent transcription factor gene, *Npas4*, was significantly induced in both excitatory and inhibitory neurons around the infarct cortex. We previously reported that *Npas4* usually facilitates the dendritic spine formation in the olfactory bulb interneurons (*Cell Rep* 8: 843-857, 2014), suggesting its role in restoring neurons from the infarct cortex. Then, we performed either loss- or gain-of -*Npas4* function experiment followed by MCAO. *Npas4* knockout mice following the MCAO surgery showed an increase of the infract size and the severe behavioral dysfunction. Interestingly, transient induction of *Npas4* expression prior to the MCAO surgery gave rise to a significant reduction of the infract size, compared with the control. Moreover, we performed a systematic search for *Npas4*-downstream genes to identify a member of the small GTPase superfamily that mediates neuroprotective effects of *Npas4*. Expression of this gene suppresses the membrane localization of voltage-gated Ca^{2+} channels to inhibit excess Ca^{2+} influx, thereby protecting neurons from excitotoxic death. This gene expression via *Npas4* is necessary and sufficient to promote neuroprotection and neuroplasticity in injured and healthy brains. This gene is also induced in human cerebral organoids under ischemic-culture conditions, nominating it as a new target for drug discovery.