



ARTICLE OF THE MONTH

MicroRNA-200c Contributes to Injury from Transient Focal Cerebral Ischemia by Targeting Reelin

Stary CM, Xu L, Sun X, Ouyang YB, White RE, Leong J, Li J, Xiong X, Giffard RG.
Stroke. 2015 Feb;46(2):551-6. doi: 10.1161/STROKEAHA.114.007041. Epub 2015 Jan 20.
PMID: 25604249

Happy New Year from the SNACC Education Committee! In this January 2016 installment of the SNACC Article of the Month, we look into a very interesting paper from *Stroke* that deals with novel potential targets for mitigating the injury that occurs after stroke. Stary *et al.* very elegantly determined that poststroke increase in microRNA-200c contributes to brain cell death by inhibiting a marker called reelin in mice, and that this may be a future target for stroke therapy. To delve further into some of the methodology and implications of the paper, we have recruited two excellent fellows at the University of Pennsylvania. Guy Kositratna, MD, has contributed before, and he is joined by David Wyler, MD, in elucidating for us what this paper truly means. We hope you'll find their commentary quite interesting, as we did, and will let your thoughts be known by logging in to the [SNACC LinkedIn feed](#) the [Twitter feed](#), or the [Facebook page](#). Happy 2016!

~John F. Bebawy, MD

Commentary

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In this study, Stary and colleagues conducted a set of experiments using adult male mice to look for the underlying mechanism of microRNA-200c in modulating the brain pathology following a transient focal cerebral ischemia. They found that the increase in poststroke microRNA-200c contributes to brain cell death by directly targeting reelin, an extracellular matrix protein that exerts an antiapoptotic effect on neural cells.

With some current evidence supporting the reelin-mediated neuronal protection by means of preserving mitochondrial homeostasis and several glia-mediated mechanisms, the authors suggested that inhibiting brain levels of microRNA-200c and upregulating reelin expression may offer clinical benefits in attenuating injury and enhancing recovery after the acute ischemic stroke.

MicroRNA is a small non-coding RNA molecule responsible for RNA silencing and post-transcriptional regulation of gene expression. During the past decade, it has been most extensively studied in terms of its role in regulating the brain pathogenesis associated with focal cerebral ischemia. Many microRNA families have been found highly expressed in animal stroke models and could be detected in blood samples. Temporal alterations of many microRNA profiles attributable to the transient focal ischemia have been demonstrated in an animal study in which those alterations occurred at different time points following cerebral reperfusion.

Expression of the microRNAs has also been investigated in humans. Kay and colleagues conducted a study looking at the microRNA profile in adult ischemic stroke patients with different functional statuses. Those were classified further according to the etiology of stroke -namely, large-vessel atherosclerosis, small-vessel disease, cardioembolism, and undetermined cause. The possibility to predict stroke type was observed on the basis of microRNA dysregulation profiles which were still detectable in peripheral circulation several months after the injury. Large-vessel disease and cardioembolic stroke together with the up-regulations of microRNA-103 and microRNA-29 appeared to correlate well with poor functional status (defined by mRS > 2). This gives us hope of using the microRNAs as markers for the diagnosis and prognostication of human stroke.

Stary and colleagues are the first group of people who discovered that poststroke rising of the microRNA-200c contributes to the brain cell death by directly inhibiting reelin expression. This evidence has led to a potential that the microRNA-200c -or perhaps the reelin too- might also be used as the clinical biomarkers to diagnose or prognosticate the ischemic stroke as many other families of them were proven so. Nevertheless, results from other recent studies may appear against this possibility.

One important consideration should include the matter of age and gender of the victims. Sexually dimorphic responses regarding the specific types of microRNA and the degrees of microRNA change in response to the cerebral ischemia have been revealed. It is suggested that age is the primary influence on the initial severity of stroke, while sex is the primary influence on stroke recovery. Therefore, in order to further conduct a study to validate the diagnostic and prognostic roles of microRNA-200c, both genders and a variety of age group of the subjects are necessary as Stary and colleagues included only adult male mice.

The authors emphasized the potential therapeutic benefits of inhibiting microRNA-200c and increasing reelin expression in the acute ischemic stroke. However, many neuroprotective agents to date have exhibited promising effects only in rodent experiments but most of them have failed to show benefit in humans. It would thus be helpful to see some data on primates before entering phase 2 and phase 3 clinical trials. This will be a prime challenge but at the same time a noteworthy endeavor for many neuroscientists in the future.

Further reading:

Saugstad JA. Non-Coding RNAs in Stroke and Neuroprotection. *Front Neurol*. 2015 Mar 13;6:50.