Author has nothing to disclose with regard to commercial support.

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REPLY: MICRORNA-BASED SPINAL CORD PROTECTION: THE POSSIBLE SIDE EFFECT CANNOT BE NEGLECTED

Reply to the Editor:

MicroRNAs (miRNAs) are short, single-stranded, noncoding RNAs that modulate the expression of target proteins by annealing to complementary sequences in their target messenger RNAs (mRNAs). Because individual miRNAs often target numerous related mRNAs, the modulation of a single miRNA can have multiple biologic functions through regulation of different target proteins in different tissues or cells in different physiologic or pathophysiologic processes. Although miRNA-targeted modifications are becoming an attractive tool in preclinical study, they still have not entered the clinic.

In my group's recent report,¹ the miRNA *miR-25* was found to be upregulated in spinal cords by exosomes derived from mesenchymal stem cells genetically modified to overexpress *miR-25* and induced neuroprotective effects against transient ischemia, possibly by inhibition of reduced

nicotinamide adenine dinucleotide phosphate oxidase 4. Although the neuroprotection of *miR-25* was highlighted in our report, the side effects of *miR-25* in the central nervous system as well as other tissues were not fully investigated. Some effects are known; *miR-25* functions as an oncogenic miRNA, playing crucial roles in the development of many tumor types, including brain tumors.² The potential tumorigenic effects on the nervous system may be a side effect not to be ignored when upregulation of *miR-25* is used to induce neuroprotection. Furthermore, the function of *miR-25* in other organs or tissues besides the nervous system should also be considered. I thank Katz and colleagues for their insightful comments on the important role of *miR-25* in the myocardium. Inhibition of *miR-25* has been indicated to be a clinical candidate for therapy of heart failure through myocyte calcium ion handling.³ In this light, upregulation of *miR-25* in myocardium would result in cardiac risks. However, *miR-25* has also been reported to protect cardiomyocytes against oxidative damage by targeting the mitochondrial calcium uniporter.⁴ Expressional change of *miR-25* seems to act as a double-edged sword specific to different target mRNAs under different pathophysiologic processes, even in the same tissue. In fact, the application of miRNA-targeted therapy may be very complex because of the multiple functions of a single miRNA achieved by targeting different mRNAs. When one role of any given miRNA by targeting a special protein is underlined, the other functions of the miRNA by targeting other proteins would turn into side effects, which should be avoided. In our recent study,¹ the exosomes containing elevated *miR-25* were administered by intrathecal injection, not intravenous injection, which may concentrate the *miR-25* within spinal cords and to a certain extent avoid the distribution with the blood flow of *miR-25* to other organs, such as the heart. Because the exosome can penetrate the blood brain barrier, however, the *miR-25* expression in organs beyond the spinal cord cannot be avoided completely by the intrathecal injection, and this expression should be evaluated accurately in further investigations. Before moving forward with *miR-25* as a clinical candidate for spinal cord protection, it will be important to learn about the expression levels and functions of *miR-25* outside the spinal cord and its effects not related to alleviation of oxidative stress. Our recent study¹ is just a preliminary animal experiment, and there is still a long way to go before the possible clinical application of *miR-25* for spinal cord protection.

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