MicroRNAs: Panacea or Pandora's box?

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Paraplegia is a devastating complication of aortic surgery. Depending on the specific anatomic parameters and techniques of operation, incidence has been reported to vary from 0% to 32%, with most recent averages still exceeding 5%.¹ The fundamental problem is one of imbalance between oxygen supply and demand as a result of aortic clamping. Numerous strategies have been used to ameliorate this injury, including distal aortic perfusion, maintenance of mean systolic arterial pressure, cerebrospinal fluid drainage, hypothermia, epidural cooling, selective spinal cord perfusion, sequential aortic crossclamping, reimplantation of intercostal arteries, identification and preservation of the artery of Adamkiewicz, and adjunctive pharmacologic therapies (steroids, mannitol, barbiturates, etc), as recently outlined by Takayama and Borger² in a recent edition of the *Journal*. The fact that thoracic endovascular aneurysm repair carries the same risk of paraplegia as open procedures supports the observation that spinal cord ischemia is primarily a matter of collateral blood flow and ischemic tolerance, rather than assisted circulation and selective intercostal reattachment, supporting the relative importance of cerebrospinal fluid drainage and maintenance of perfusion pressure relative to other techniques.³ Strategies that might improve spinal cord tolerance for ischemia or interfere with the mechanisms of ischemia-reperfusion injury therefore provide a promising and important area for further investigation.

First discovered more than 2 decades ago, microRNAs (miRNAs) are small, noncoding RNA molecules containing approximately 22 nucleotides that function in the posttranscriptional regulation of gene expression through base pairing with complementary sequences within mRNA molecules and silencing gene expression by cleavage, destabilization, or interference with messenger RNA (mRNA) translation.^{4,5} Animal miRNAs recognize their target mRNA with as few as 6 to 8 nucleotides (the seed region), and this relative lack of specificity enables a

given miRNA to have multiple discrete mRNA targets, fostering regulation of entire physiologic processes rather than specific proteins. A given miRNA may have hundreds of different mRNA targets, and a given target might be regulated by multiple miRNAs.⁶ Manipulation of miRNA expression therefore has the theoretic potential to control entire physiologic processes while simultaneously risking triggering multiple unanticipated pleiotropic effects. Much of the progress in miRNA research has been made with the use of antisense oligonucleotides (antagomirs) that target specific miRNAs and that can be chemically modified and bound to carrier molecules to improve hybridization affinity, resist degradation, and promote tissue uptake.⁷

It is just this approach that is reported by He and colleagues⁸ in this issue of the *Journal*. In a rat model of aortic clamping-induced spinal cord ischemia, they have convincingly demonstrated that the previous introduction of a lentivirus vector containing an oligonucleotide that specifically targets miRNA 320 improved hind limb motor function and increased motor neuron survival. They further demonstrated that introduction of this antagomir to miRNA 320 specifically reduced miRNA 320 expression and upregulated the expression of phosphorylated heat shock protein 20 (pHSP20). MicroRNA 320 was selected because of previous evidence implicating inhibition of this nucleotide in cerebral ischemic neuroprotection,⁹ whereas pHSP20 has been shown to be the target of the miRNA 320 regulation of cardiac ischemia-reperfusion injury.¹⁰

Should we now start performing preoperative intrathecal injection of lentivirus-laden oligonucleotides for all our thoracoabdominal aortic reconstructions? Not just yet. Even assuming that one were to construct an effective and specific antagomir to miRNA 320 that did not require the clinically unacceptable lentivirus vector and was biochemically active after intravenous injection (which has been accomplished for numerous other miRNA-inhibiting oligonucleotides), the aggregate physiologic impact at this time is unpredictable. By mapping miRNA path to gauge the impact of miRNA 320a modulation, Sepramaniam revealed approximately 145 pathways being affected, with as many as 1500 target genes (Figure 1).⁹ Whether pHSP20 is the critical mediator of spinal neuroprotection in the study of He and colleagues,⁸ a helpful participant, or merely a physiologic bystander is not addressed by this report. What might have proved helpful would have been investigation of the impact of pHSP20 inhibition (either through a specific chemical inhibitor or conversion to a mouse model with specific genetic knockout of pHSP20

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Possible pathways/genes affected by miR-320a modulation.

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FIGURE 1. Possible pathways and genes affected by microRNA 320a modulation. Compilation of possible genes affected by microRNA 320a modulation was adapted from the KEGG Pathway Database. Green ovals represent targets of microRNA 320a; green rectangles represent other genes in the pathway; pink ovals represent secondary messengers; blue right arrows represent direct interaction; dashed blue right arrows represent indirect interaction; and broken red right arrows represent aquaporin interaction. For a complete description of all terms used in the figure, see Figure 5 in Sepramaniam and colleagues.⁹ Reprinted with permission.⁹ © 2010 The American Society for Biochemistry and Molecular Biology.

expression) on the results of miRNA 320 inhibition. Such information would be useful not only for a clearer elucidation of the molecular mechanism of neuroprotection in this model but also for direction in the development of more targeted therapies. As is so often the case in molecular genetic investigation, He and colleagues⁸ may well have uncovered more questions than answers; however, they have clearly helped to focus our attention on a potentially productive path toward resolution of an unresolved and clinically compelling challenge.

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