Does the Effect of MicroRNAs in Vascular Neointimal Formation Depend on Cell Cycle Phase?

To the Editor:

In the June 8, 2007 issue of *Circulation Research*, Ji et al presented the results of their study in which they described the micro (miRNA) expression signature in the vessel wall. In addition, they studied the role of miRNA in vascular neointimal lesion formation. Among the miRNA dysregulated after balloon angioplasty of the rat carotid artery, the authors focused on miR-21, showing that antisense oligonucleotide mediated inhibition of miR-21 reduces neointimal formation after balloon angioplasty in vivo and exerts an antiproliferative and proapoptotic effect in vitro on vascular smooth muscle cells (VSMCs). The study raises hopes for therapeutic targeting of miRNA in the treatment of diseases characterized by neointima formation, such as atherosclerosis, postangioplasty restenosis, and graft vasculopathy.

When the authors reported the results of miR-21 blockade with an antisense oligonucleotide in cultures of VSMCs, they observed that miR-21 knockdown and serum deprivation induced a disproportionate apoptosis, indicating a synergistic effect with a mechanism that was not clear. Another unexplained result was the small effect of miR-21 knockdown on the expression level of a candidate target: PTEN.

In their recent report, Vasudevan et al showed that serum deprivation with consequent arrest of the cell cycle may have profound effects on the mechanism of action of miRNA. In conditions of cell cycle arrest, miRNA can enhance mRNA translation. This effect is mediated by the recruitment to mRNA of FXR1, a protein that stimulates translation, whereas, in presence of normal cell growth, the RNA-interfering silencing complex recruits to mRNA GW 182, a translational inhibitor. Therefore, the effect of miRNA knockdown may be reverted, depending on different culture conditions. In the accompanying editorial to the article by Vasudevan et al, Buchan et al suggest that differential effects of miRNA at various cell cycle stages or during cellular stress may explain some confusion in the field, including differences in the extent of repression by a given miRNA.

This raises the opportunity to pose some questions about the results obtained by Ji with VSMCs cultures. What was the percentage of VSMCs arrested in G1/G0 phase of the cell cycle by serum deprivation? If significant, then we could hypothesize that some miRNA in the cultured cell (including miR-21) was stimulating rather than inhibiting translation of their mRNA targets. Probably, the population of cultured VSMCs was heterogeneous, with the possibility of divergent actions exerted on them by miRNA. This may explain the different results on apoptosis observed by the authors in serum-deprived VSMCs as compared with cells cultured with 10% serum. The heterogeneity of the cultured cells may also be the explanation for the unpredicted small effect on PTEN express changes after miR-21 knockdown.

Studies like that of Ji et al are of great importance because they shed light on the mechanisms of miRNA regulation of key physiological and physiopathological processes. miRNA-based therapeutics is a growing field with the potential of an enormous expansion of therapeutic targets. However, it is also a newborn field, and the development of new drugs based on miRNA requires great effort to understand and use their complex mechanism of action.

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