MicroRNA-223 Made Its Way Into Vascular Research

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Our blood vessels, from small capillaries to large arteries, build the basis for life, and their regulation and homeostasis need to be tightly controlled. Regulatory RNAs, including microRNAs (miRNAs/miRs) and long noncoding RNAs, play a crucial role in the maintenance of the cardiovascular system and on deregulation can lead to the onset and progression of many diseases. MiRNAs also emerged as therapeutic targets and diagnostic molecules in cardiovascular diseases.1,2

To date, miR-223 never showed up prominently in vascular research or in previous endothelial miRNA-profiling studies. In this issue of Circulation Research, Shi et al.4 identified the reason why only recently miR-223 made its way into vascular research. The authors identified that freshly isolated endothelial cells display high levels of miR-223 that was lost quickly under culture conditions. The origin of such high miR-223 content in endothelial cells is currently unclear. Most studies have shown high miR-223 contents in platelets, immune cells, and fibroblasts, whereas miR-223 expression in endothelial cells was described to be rather low.5,6 Although there seems to be only a modest role of miR-223 in platelet production and even fewer effects on platelet function,7 the current study shows important effects in endothelial cells. Because in most studies usually a culture period is needed before cells are studied, it is likely that early during culture endothelial cells lose miR-223 expression. The authors experimentally excluded the possibility that myeloid cell contamination contributed to the high miR-223 signals seen in freshly isolated human umbilical vein endothelial cells. However, recently platelets and macrophages were shown to transfer miR-223 to endothelial cells.8,9 In vivo, it is possible that the high content of miR-223 is not derived from the own endothelial transcriptional machinery but is rather the result of miRNA uptake from other cells, although the authors presented some evidence against this miRNA transfer theory. However, if the in vivo situation the authors found in freshly isolated endothelial cells is much more relevant when miR-based therapies are to be developed. The current study also suggests paying more attention when using endothelial cell lines, or primary cells are cultured for some time because this largely alters the cellular transcriptome, proteome, and functionality of the cells. Other highly endothelially expressed miRNAs as found by the authors include miR-126 and miR-24, the latter being shown to be an attractive target to enhance angiogenesis and improve outcome after myocardial infarction.10

The authors presented solid genetic and pharmacological evidence that loss of miR-223 reprograms endothelial cells to a more angiogenic status, whereas high miR-223 levels prevent growth factor–mediated increase in endothelial proliferation and migration (Figure). As the authors have only used polymerase chain reaction–based approaches to detect miR-223 in freshly isolated endothelial cells, a future effort should be to use techniques such as in situ hybridization or in situ hybridization/polymerase chain reaction to monitor endothelial miR-223 in real in vivo scenarios in intact organs under health and disease/stress conditions. Because miR-223 may be required for the maintenance of endothelial cell quiescence, it still needs to be shown whether vascular stress diminishes miR-223 levels in vivo.

The reason why certain miRNAs including miR-223 were dramatically (>100-fold) silenced during culturing remains partly unanswered, and the authors suggest epigenetic phenomena to be involved. MiR-223 is rapidly silenced in hematopoietic cells during leukemia through dysregulation of chromatin modifiers.11 Epigenetic phenomena, such as DNA methylation, often require the presence of CpG islands.12 The miR-223 promoter harbors such an island that becomes hypermethylated in cancer, leading to rapid miR-223 silencing.13 In addition, methylated CpG sites act as binding sites for the epigenetic modifier methyl-CpG-binding protein 2, which recently has been described to be involved in angiogenic responses.11 Thus, it will be exciting to study the role of epigenetic modifications contributing to the endothelial regulation of miR-223 and overall endothelial homeostasis, in general, under health and acute/chronic cardiovascular disease conditions.

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Figure. MicroRNA (miR)-223 as a regulator of endothelial angiogenic activity. In vivo, high miR-223 levels maintain a nonproliferative status partly by tight control of β1-integrin expression levels, whereas cell culture conditions and addition of growth factors lead to epigenetic/transcription factor–mediated silencing of miR-223 expression and thus stimulation of angiogenesis. bFGF indicates basic fibroblast growth factor; and VEGF, vascular endothelial growth factor.
Some other issues that may be additionally studied in the future include the role of miR-223 in tip/stalk cell development and regulation, the role of miR-223 in other vascular cell types such as pericytes or smooth muscle cells, and the use of other epitopes for the purification of endothelial cells such as CD31 to exclude the possibility that only a subfraction of endothelial cells was isolated.

Next to its diagnostic value, miR-223 inhibition may be of great therapeutic use. Because this miRNA seems to be ubiquitously expressed with many functions in other cell types, especially local therapeutic approaches using miR inhibitors could be of interest. This may include therapeutic developments in the fields of peripheral artery disease or coating of vessel stents with miR-223 inhibitors to enhance re-endothelialization.

In conclusion, Shi et al. made an important observation that should be taken into account in future research; caution is needed when extrapolating miRNA expression findings ex vivo/in vitro into an in vivo scenario. In addition, the authors identified a novel finding with potential clinical importance of miR-223 to be of great diagnostic and therapeutic use in the combat of cardiovascular diseases.

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**Disclosures**

None.

**References**


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