With the advent of next generation sequencing technologies it became evident that the majority of the human genome is transcribed, whereas only 1.5% to 2% of the genome encode proteins.1 The remaining transcripts are referred to as noncoding RNAs. With respect to microvascular dysfunction, functional roles of noncoding RNAs are in particular evident for microRNAs (miRNAs, miRs),2 which belong to the group of small noncoding RNAs (<200 nt). In contrast, the contribution of long noncoding RNAs (lncRNAs; >200 nt) is not conclusively defined. Even though the particular functions of lncRNAs seem to be diverse, their mechanisms of action can be grouped into 3 main themes.3 Hence, lncRNAs can (1) function as decoys for proteins or RNAs, (2) serve as scaffolds for higher order complexes, or (3) act as molecular guides to ensure the proper localization of their binding partners. Taking these central functions into account, which finally encompass the fields of transcriptional and post-transcriptional regulation, as well as subcellular dynamics, dysregulation of lncRNA expression is often associated with complex human diseases.4 In the field of vascular biology, the importance of lncRNAs in cellular homeostasis was recently uncovered by the finding that the lncRNA MALAT1 was identified to be crucial for the angiogenic response of endothelial cells as well as for vascularization in vivo.5

In this issue of Circulation Research, Yan et al6 revealed a regulatory role of the lncRNA myocardial infarction–associated transcript (MIAT) in diabetes mellitus–induced microvascular dysfunction. MIAT (which is also known as RNCR2, AK028326, or Gomafu) was first identified as susceptible locus for myocardial infarction7 and was reported to be highly expressed in retinal precursor cells.8 Manipulation of MIAT expression is often associated with complex human diseases.4 In the field of vascular biology, the importance of lncRNAs in cellular homeostasis was recently uncovered by the finding that the lncRNA MALAT1 was identified to be crucial for the angiogenic response of endothelial cells as well as for vascularization in vivo.5

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From the Institute of Cardiovascular Regeneration, Centre of Molecular Medicine, J.W. Goethe University Frankfurt, Frankfurt am Main, Germany; and German Center of Cardiovascular Research (DZHK), Frankfurt, Germany.

Correspondence to Stefanie Dimmeler, PhD, Institute of Cardiovascular Regeneration, Centre of Molecular Medicine, J.W. Goethe University Frankfurt am Main, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany. E-mail dimmeler@em.uni-frankfurt.de


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Long Noncoding RNAs in Diabetic Retinopathy
Nicolas Jaé, Stefanie Dimmeler
sponges for microRNAs. However, the competing endogenous RNA hypothesis has been discussed controversially because it is difficult to imagine how changes in the expression of an individual miRNA, which contributes only to a minor fraction of the overall miRNA targets, could influence enough miRNA molecules to affect gene expression. Denzler et al\(^5\) recently tested this hypothesis and showed that overexpression of miRNA can affect miRNA target derepression only if ≈150,000 competing miRNA-binding sequences were overexpressed. Whether the same stoichiometry is required, if noncoding RNAs (instead of mRNAs) are used to scavenge microRNAs needs to be determined. Several publications showed that noncoding RNAs such as circRNAs, which comprise >60 miRNA binding sites, or long noncoding RNAs in the cardiovascular system can act as sponges for miRNAs.\(^{15,16}\) Yan et al\(^6\) specifically addressed whether MIAT acts as a sponge for miR-150. Two prerequisites have to be fulfilled to ensure that a given lncRNA can act as microRNA sponge: (1) The lncRNA and the corresponding miRNAs have to be expressed in the same cellular compartment, and (2) a reasonable stoichiometric ratio of the lncRNA and the given miRNA. In this context, the lncRNA must have multiple miRNA binding sites or must be expressed at levels that are sufficient to bind a biologically meaningful number of miRNA molecules. The latter point is particularly important because most IncRNAs are expressed at lower levels compared with mRNAs. In this study, Yan et al\(^6\) carefully controlled the localization of MIAT and showed that MIAT and miR-150 are both nuclear localized and thus may bind each other. Although microRNA-mediated silencing occurs predominantly in the cytoplasm, Argonaute-2 has been previously reported in the nucleus.\(^17\) However, as mentioned above, the stoichiometry needs to be carefully considered: MIAT does not belong to the highly expressed miRNA targets. Moreover, the stoichiometry has been documented after overexpression of MIAT, which may result in artificially high levels of the lncRNA. Given the epigenetic functions of IncRNAs and the established role of MIAT in regulating miRNA splicing,\(^3\) alternative explanations for a MIAT-dependent regulation of vascular endothelial growth factor expression may have to be considered as well. An interesting experiment would have to be determined whether diabetes mellitus–induced MIAT upregulation is sufficient to derepress miR-150 target genes and whether MIAT-dependent regulation of vascular endothelial growth factor is causally mediated by miR-150.

In summary, the study by Yan et al\(^6\) provides important and novel insights into the regulation and function of IncRNAs in the vasculature. Given that the IncRNA field is still in its infancy, many questions are arising that need to be addressed in the future. The therapeutic benefits seen after shRNA-mediated silencing opens up novel therapeutic opportunities to target cardiovascular diseases. The eye is easily accessible, however, for other indications, antisense approaches, which do not require vector-based overexpression, might be advantageous. The development of safe and efficient tools to modulate IncRNA functions, as it has been done for microRNAs,\(^{18}\) may be helpful to develop therapies for other cardiovascular diseases.

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**References**


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