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Editorial

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Targeting New Players Offers us Novel Strategic Approaches but may also Lead us to Labyrinth in Highly Integrated Networks for Gene Regulation

Shinji Yokoyama

Institute of Biological Functions, Chubu University, Aichi, Japan.

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RNA is used not only as translation signal message of nucleotide sequence coded in DNA to amino acid sequence in protein, but also for various other functions, such as transfer RNAs for protein biosynthesis or regulatory RNAs involved in expression of other genes. Most recently, a small RNA of some 22-nucleotides length was identified in 2001 as microRNA (miRNA) that modifies activity of messenger RNA, seemingly as siRNAs to regulate post transcriptional regulation of various gene expression[1-4]. miRNA was found not only in cells but also in extracellular microvesicles such as those in blood plasma, and became to be believed to play a role in intercellular communication[5]. Many miRNAs were suggested to be involved in expression of the genes related to cholesterol metabolism or atherosclerosis, such as miRNA-15a, 16, 20b, 21, 21-3p, 25, 26, 26b, 27a, 27b, 28-3b, 30c, 33, 34, 34a, 92a, 96, 106, 122, 125a, 126, 128, 130b, 130a, 144, 148a, 155, 185, 210, 221, 222, 223, 423, 455, 758[6, 7]. Some of these are proposed as candidates for biomarkers and others are argued for as targets of therapeutic approaches to treat or prevent atherosclerotic vascular diseases. However, the findings are still mostly observational and descriptive and many of them are not highly specific. Hence, the more the miRNA and their target genes are identified and the reactions are understood, the more we encounter puzzling, enigmatizing and confusing of multifactorial networks for gene regulation. Can we find any specific switch to manipulate the network to reach desirable outcome? Gene regulation network is so much integrated and complicated that we end up with totally unexpected results on many occasions.

In this issue of the Journal of Atherosclerosis and Thrombosis, Lu and her colleagues report association of another miRNA with atherosclerosis, miRNA-320b[8] known for its link to cancer and inflammation. It was highly expressed in the peripheral blood monocytes of the patients with coronary artery disease. This miRNA suppressed "cholesterol efflux" in *in vitro* cell culture system by targeting ATP binding cassette transporter A1/G1 (ABCA1/G1) and also endonuclease-exonuclease-phosphatase family domain containing 1 (EEPD1), which had recently been reported to be associated with LXR/ABCA1 pathway[9]. It also reduced ABCA1/G1 and EEPD1 expression in apolipoprotein E-knockout mice and increased atherosclerotic vascular lesions as well as NF-κB and pro-inflammatory cytokines in macrophages.

These are certainly new discoveries for atherogenic development mechanism. It is of course very important to expand and accumulate our findings in this newly established and rapidly developing field. However, what do we do with these findings? We perhaps know only a part of the gene regulation network by miRNA 320b as anything else. Although, we accumulated huge amount of knowledge about regulation of the genes and thereby found many candidate targets to treat or prevent various disorders. We do have a few compounds that were designed to target regulation of gene expression and translated to clinical use, but not many attempts to develop such drugs have been successful, except for empirical success of fibrate drugs, activators for PPARα. We should work hard to find pharmacological/therapeutic approach toward gene transcription/translation steps. We need not to be too pessimistic but should not be too optimistic either.

Address for correspondence: Shinji Yokoyama, Institute of Biological Functions, Chubu University, Kasugai, Aichi 487-8501, Japan.
E-mail: syokoyam@isc.chubu.ac.jp
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Conflicts of Interest

None.

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