



MicroRNAs and their role in atherosclerotic disease

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MicroRNAs (miRNAs) play important role regulating gene expression, interfering in mRNA stability or inhibiting protein translation. They are involved in the control of many signaling/regulatory networks in physiological and pathological context. miR-100 is part of the miR-99 family, located on chromosome 11q24.1, comprehending has-miR100 (AACCCGUAGAUCCGAACUUGUG), miR-99a (AACCCGUAGAUCCGAUCUUGUG) and miR-99b (CACCCGUAGAACCGACCUUGCG) having as target numerous genes, being one of the most important those related to mammalian target of rapamycin (mTOR) pathway.

miR-100 has a complex mechanism of action, not completely deciphered, what can be exemplified by two recently published articles describing opposite results regarding its behavior in relation to the mesenchymal stem cell fate. Frith *et al.* (1) reported that miR-100-5p, together with miR-143-3p is expressed in stiff substrates promoting osteogenesis, acting over the mTOR signaling, while Zeng *et al.* (2) showed that miR-100 inhibits osteogenic differentiation, targeting bone morphogenetic protein receptor type II (BMPRII).

Its role in tumors is also not fully understood but a recent meta-analysis comprehending a total of 16 articles with 1,501 patients demonstrated that a lower expression of miR-100 plays a negative role in the overall survival (OS) of patients with solid tumor, especially non-small-cell lung cancer, epithelial ovarian cancer, and bladder cancer (3).

Atherosclerosis is related to remodeling of the vascular wall driven by the inflammatory response to the sub endothelial accumulation of lipoproteins orchestrated by endothelial cells (ECs) and smooth muscle cells (SMCs),

involving inflammatory response, recruitment of monocytes and macrophages. miRNAs are involved in the cellular response during vascular remodeling promoting or limiting structural changes (4).

A recently published paper from Pankratz *et al.* (5) describes an important role of miR-100 in atherosclerotic disease, mainly affecting the inflammatory process through the regulation of mTOR and NF- κ B. Based on the principle that miR-100 is an antiangiogenic miRNA inhibiting mTOR pathway, most specifically through mTORC1-complex signaling partner raptor, they explored the transcriptome of human umbilical vein endothelial cells (HUVECs) after inducing miR100 overexpression. Their main result was the demonstration of a downregulation of adhesion molecules like E-selectin and vascular cell adhesion molecule-1 (VCAM-1). Since these genes do not contain binding sites for miR-100, they strengthened the knowledge that activity of miR-100 occurs through mTOR pathway.

They found that miR-100 interferes in the inflammatory properties of ECs attenuating the rolling and adhesion of leukocytes *in vitro* and *in vivo* models and inducing endothelial autophagy through stimulation of transcription factor EB (TFEB). The decrease in mTORC1 activity by miR-100 initiated autophagy, characterized by the use of degradation of cellular components in lysosomes what allows the maintenance of homeostasis under stress conditions.

Another important finding of this group was the negative control of NF- κ B by miR-100. Moreover, for the first-time authors showed that TNF- α downregulates miR-100 being this mechanism dependent on the integrity of the NF- κ B pathway.

Knowing that miR-100 is involved with leukocyte-endothelial interaction and autophagy, authors explored the involvement of this miRNA in the atherogenesis. They showed that miR-100 inhibition resulted in a significant increase in atherosclerotic plaque, decrease in the content of muscle actin in smooth muscle and an increase in macrophage accumulation in the plaque. An interesting additional finding was the increase in triglyceride, total cholesterol, and low-density lipoprotein cholesterol and reduction of high-density lipoprotein cholesterol levels.

Most importantly, was the documentation of the ability of simvastatin in increase and stabilize miR-100 levels in ECs, supporting the publication of Pruefer *et al.* (6) and Wei *et al.* (7) who found that simvastatin inhibits leukocyte-endothelial interaction and enhances autophagy via inhibition of mTOR signaling.

Since miR-100 is highly conserved between species, authors search for miR-100 status in atherosclerotic plaques in humans founding a correlation between miR-100 levels with signals related to vulnerability of the plaque. Their hypothesis is that miR-100 increases as a compensatory mechanism to stabilize the plaque, suppressing mTOR, opening the possibility to use miR-100 as a biomarker of vascular events.

Other miRNAs have been related with atherosclerotic disease (8). Downregulation of miR-145 promotes lesion formation, miRNA-126 signs for endothelial repair, elevated miR-155 levels are characteristic of proinflammatory macrophages and atherosclerotic lesions (9), and miR-21 promotes cellular response that leads to neointima formation (4).

In summary, miRNAs seem to have a fundamental role in cardiovascular diseases and future studies will undoubtedly help to elucidate their key roles in this highly prevalent disease with great impact in quality of life and longevity.

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