Přehledový článek | Review article

Is the microRNA-221/222 Cluster Ushering in a New Age of Cardiovascular Diseases?

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SOUHRN

Kromě regulace genové exprese regulují krátké nekódující molekuly RNA (microR, miR) rychlost degradace a translace informační RNA (messenger RNA). Krátké nekódující molekuly miR vykazují vysokou expresi v kardiovaskulárním (KV) systému, což ukazuje na jejich významnou úlohu ve vaskulárním zdraví. Proces vzniku a rozvoje aterosklerózy je dáván do souvislosti s miR-221 a -222. Krátké nekódující molekuly miR-221/222 působí proti vzniku stenóz a mohou potenciálně sloužit jako marker remodelace myokardu. Přesto ještě potrvá dlouho, než bude možno považovat molekuly miR-221/222 jako možný cíl léčby. Identifikace, ověření a poznání funkcí genových cílů, všechny tyto procesy jsou nesmírně důležité.

ABSTRACT

In addition to regulating gene expression, microRNAs (MiRs) regulate messenger RNA degradation and translation rates. MiRs have a high expression in the cardiovascular (CV) system, indicating an important role in vascular health. The atherosclerotic process has been related to miRs-221 and -222. MiRs-221/222 possess anti-stenotic activity. MiR-221/222 may potentially serve as a marker for myocardial remodeling. There is still a long way yet before miRs-221/222 can be recognized as a potential therapeutic target. Identification, validation, and understanding of the function of gene targets are all critical.

Introduction

MicroRNAs (miRs) are endogenous non-coding RNAs that influence gene expression via regulating messenger RNA degradation and translation.[1] So far, over 1,000 miRs have been identified and described.[2] Some miRs impact the production of other miRs, leading in the establishment of complex regulatory networks. MiRs encode most mammalian proteins, and more genes may be regulated indirectly. As a result, it's unsurprising that miRs may play a critical role in a variety of biological activities at the molecular level.[3] This review aims to investigate the link between miR-221/222 and cardiovascular diseases (CVDs).

Vascular system and miR-221/222

The high level of miRs directly affects the vascular system.[3–6] Ordinary conditions, the endothelium is responsible for maintaining vascular homeostasis. Endothelial dysfunction is a critical threshold for atherosclerosis.[7]

Almost all of the coagulation cascades are associated with miRs. MiRs have been linked to pro-atherogenic pathways.[8,9] Blood vessel homeostasis requires angiogenesis, which is involved in atherosclerosis. Several miRs appear to be angiogenetic or anti-angiogenetic.[10]

MiRs-221/222 play a vital role in maintaining vascular homeostasis.[11] For the miRs-221/222, Celic et al. summarized the known evidence on their characteristics and possible clinical applications.[12] Clinically, it is critical to evaluate the possibility that miR 221/222 may be therapeutic in cardiovascular disease and cancer.

Obesity and diabetes result in decreased miR 221 levels,[13] while severely obese patients had higher levels of both miRs.[14] MiR-221 was shown to be overexpressed in the serum of diabetics with microvascular problems.[15] Those with metabolic syndrome had higher circulating miR-221 levels.[16] Low miR-221 levels are caused by strokes and atherosclerosis.[17] In diabetics with coronary artery bypass grafts, serum miR-221 was elevated and corrected by metformin.[18] Carotid atherosclerosis patients also showed higher miR-221 levels.[19] In contrast, atherosclero-

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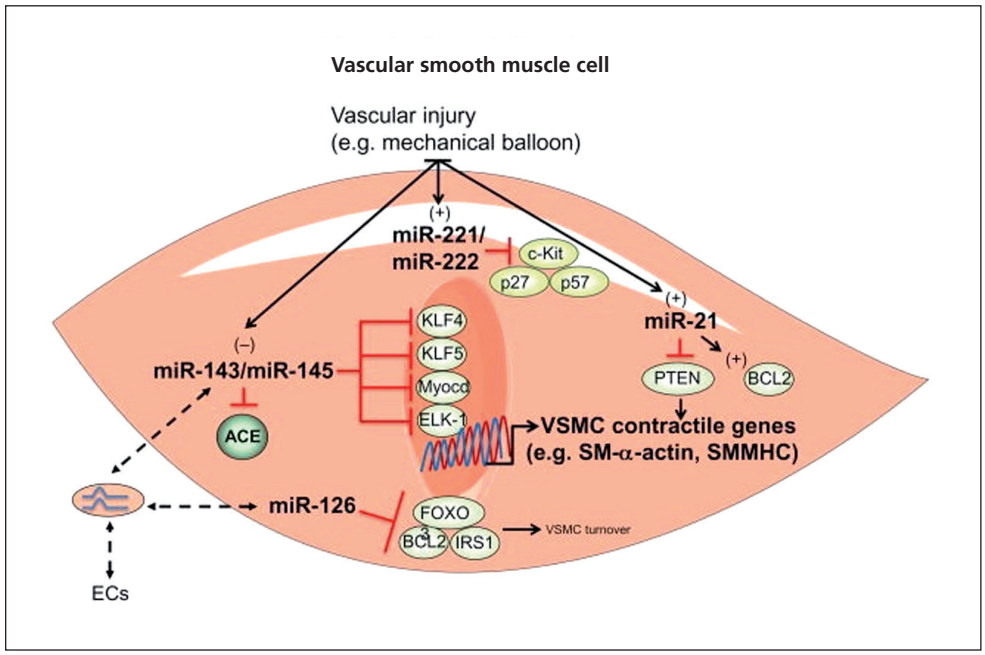

Fig. 1 – MiRs-221 and -222 and their role in atherosclerosis.

sis obliterans patients had lower serum miR-221.[20] Thus, miR-221/222 may be utilized to assess CV risk. But more research is needed to validate this.

MiRs-221 and -222 have been linked to the atherosclerotic processes (Fig. 1).[21,22] Atherosclerotic lesions increase vascular calcification risk.[23,24] As a result, alteration of miRs-221/222 activity may be helpful in illness follow-up.[25]

Studies to halt the growth and migration of endothelial cells are continuing. The conflicting effects of this may be clinically relevant in patients with CAD.[26] Cardiomyocytes transduced with lentivirus precursors of miR-21, -24, and -221 lived substantially longer after transplantation in mice.[27] They control cardiac remodeling and the migration of progenitor cells.[28]

Inhibitors or mimics of miRs may improve or raise miR activity in non-target tissues. The suppression of P27's antiproliferative action promotes cancer. For cell-specific interactions, adeno-associated viruses are preferred due to their inherent serotype diversity and organ-specific cell receptor tropism.[29]

MicroRNA-221/222 in heart failure (HF)

MiR-221-3p and miR-222-3p (miR-221/222) are differently regulated in human and mouse cardiomyopathies.[30] The miR-221/222 family has not been implicated in the pathophysiology of pressure overload–induced heart dysfunction. Studies on miR-221/222 in the heart have relied on cardiomyocyte-specific transgenic mice, which ignore endogenous miRNA levels and cell source(s).[31] Other than the cardiac effect, miR-221 and miR-222 have been related to renal and liver fibrosis.[32]

Recently, miR-221 and miR-222 were found upregulated in cardiac cells. HF is self-induced with increased fibrosis, reduced autophagy, and cardiomyocyte dysfunction in mice.[33] Mice with inducible cardiomyocyte miR-222 production were safeguarded against ischemia/reperfusion damage. Upregulation of miR-221 or miR-222 in cardiomyocytes causes cardiac remodeling, probably due to their impact on cardiomyocyte function and survival.[34]

MiRNA-221/222 family is downregulated by TGF-β and pressure overload to enable fibroblast activation and fibrosis formation. In vivo administration of miRNA-221/222 mimics may restore TGF-β signaling in cardiac fibroblasts. Excessive miR-221/222 expression induces aberrant distribution in cardiac cells. MiR-221/222 may also be as an indicator of myocardial remodeling. A recent study indicates that decreased miR-222 plasma levels may be a risk of atrial fibrillation. Given that miR-221 is associated with myocardial collagen volume fraction in aortic valve stenosis patients, miR-221 and miR-222 may be used as biomarkers for myocardial fibrosis.[35]

Other situations

Inflammatory reactions are controlled by the miR-221/222. As a result of its suppression, viral myocarditis is more likely to result in increased inflammation and cardiac damage.[36] In human umbilical vein endothelial cells (HUVECs), miR-221/222 inhibited Ets-1 and p21 expression. MiR-221/222 overexpression may protect HUVECs against ox-LDL-induced apoptosis. Qin et al.[37] thought that if miRNAs' functions in endothelial apoptosis and atherosclerosis are understood, they will be viable therapeutic targets.

Conclusion

MiRs-221/222 have diverse roles in many tissues. The evidence on their involvement in CVD origin and development is mounting. The current results support their

potential application as cardiac biomarkers. They may be useful for interfering with miRNA-regulated circuits. These may need cell-targeting. It will take time to establish miRs-221/222 as therapeutically relevant targets. Their gene targets need to be characterized and validated, and their roles understood.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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