

miRNA-197 and miRNA-223 and cardiovascular death in coronary artery disease patients

Esteban Orenes-Piñero¹, Francisco Marín², Gregory Y. H. Lip³

¹Proteomic Unit, Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Universidad de Murcia, Murcia, Spain; ²Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca (IMIB-Arrixaca), Universidad de Murcia, Murcia, Spain;

³University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK

Correspondence to: Prof. Gregory Y. H. Lip, MD. University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, UK. Email: g.y.h.lip@bham.ac.uk.

Submitted Apr 03, 2016. Accepted for publication Apr 10, 2016.

doi: 10.21037/atm.2016.05.27

View this article at: <http://dx.doi.org/10.21037/atm.2016.05.27>

Coronary artery disease (CAD) is commonly associated with the presence of atheromatous plaques in the coronary arteries. The growth of these plaques may cause arterial stenosis and blockage of the blood flow, leading to cardiac ischemia and clinical symptoms, such as acute coronary syndrome (ACS) or stable angina pectoris (SAP). Due to the high morbidity and mortality rate, CAD has probably the most serious cardiovascular disorder threatening people's health in Western countries (1).

It is widely accepted that the erosion of vulnerable plaques results in the formation of luminal thrombi secondary to platelet activation and the release of thrombogenic elements within the atherosclerotic lesions. Indeed, coagulation components and platelet activation play a major role in the development and outcome of coronary atherosclerosis.

MicroRNAs (miRNAs) are endogenous, conserved, single stranded, small (approximately 22 nucleotides in length), non-coding RNAs that repress gene expression at the post-transcriptional level by targeting mRNA (2). According to the miRNA database (miRBase), the human genome encodes 2,588 mature miRNA sequences, which may target more than 60% of human protein-coding genes. miRNA anneals to complementary sequences in the 3'-untranslated regions (3'UTR) of target mRNAs of protein-coding genes, causing mRNA to be cleaved or to repress the translational machinery needed for protein synthesis. Thus, miRNA can either inhibit translation or induce degradation of its target mRNA or both, depending upon the overall degree of complementarity of the binding site, the number of

binding sites, and the accessibility of those binding sites (3). The stronger its complementarity with the prospective target RNA, the more likely that the miRNA will degrade the target mRNA, and those miRNAs that display imperfect sequence complementarities with target mRNAs primarily, result in translational inhibition (4,5).

Accumulating studies reveal the importance of miRNAs in regulating key signaling and lipid homeostasis pathways that alter the balance of atherosclerotic plaque progression and regression. Several miRNAs have been associated with cholesterol homeostasis by production and clearance of lipoproteins that deliver [low-density lipoprotein (LDL)] and remove [high-density lipoprotein (HDL)] cholesterol from cells and tissues. Thus, miR-148a, miR-128-1, miR-130b and miR-301b have been identified as negative regulators of LDL receptor expression and activity, promoting the clearance of circulating LDL particles (6,7). On the other hand, miRNAs have also been identified to act as critical regulators of HDL biogenesis. Many miRNAs have been identified that target ATP-binding cassette transporter-A1 (ABCA1) to reduce cholesterol efflux to apolipoprotein-A1 *in vitro*, including miR-33, miR-758, miR-26, miR-106, miR-144, as well as the above-mentioned miR-128-1 and miR-148a (8-10).

Importantly, miRNAs are not only associated with lipoprotein metabolism but they are also implied in the regulation of endothelial cell inflammation and plaque progression. For example, several studies highlight that miR-181b and miR-146a regulate distinct components of NF- κ B signaling being atheroprotective (11). Moreover,

miRNAs also regulate leukocyte recruitment and activation in atherosclerosis, one of the earliest pathogenic events in atherosclerosis. A growing list of miRNAs are implicated in regulating the activation of leukocytes, including miR-let7a, miR-19a, miR-21, miR-27a, miR-33, miR-124, miR-125a, miR-146a, miR-155, miR-214, and miR-223 (12).

All these observations point out the importance of miRNAs as potential biomarkers of atherosclerosis progression and consequently, with CAD. Indeed, a number of studies have analyzed the profiling of specific miRNAs as diagnostic markers and as predictors of future cardiovascular events in CAD patients. For example, Schulte *et al.* (13) reported the capacity of miRNA-197 and miRNA-223 in predicting cardiovascular death and burden of future cardiovascular events in a large cohort of CAD patients. In this study, 873 consecutive patients [38.9% (n=340) cases of ACS and 61.1% (n=533) cases of SAP] were included in the miRNA quantification analyses after RNA isolation, and cardiovascular death was observed in 2.1% (n=18) of the patients over a median follow-up time of 4 years (IQR, 2.78–5.04). Cox regression analysis adjusted for age and gender revealed relevant prognostic power of miR-197 and miR-223 with respect to the primary end point cardiovascular death in the overall group [miRNA-197: HR =1.77 per one SD increase (95% CI, 1.20–2.60), P=0.004, C-index =0.78; miRNA-223: HR =2.23 per one SD increase (95% CI, 1.20–4.14), P=0.011, C-index =0.80]. In addition, subgroup analysis for ACS patients revealed a stronger association between elevated levels of miR-197 and miR-223 and future cardiovascular death [miRNA-197: HR =2.24 per one SD increase (95% CI, 1.25–4.01), P=0.006, C-index =0.89; miRNA-223: HR =4.94 per one SD increase (95% CI, 1.42–17.20), P=0.012, C-index =0.89].

Nonetheless, the rather small number of cardiovascular death endpoints may limit the validation of the observed findings in this study. This may influence the statistical ability to detect small effects and contains a risk of statistically overfitting the results, especially with respect to the subgroups ACS and SAP. We also need to see more characteristics of the cardiovascular death patients, as this is the primary endpoint of the AtheroGene study. Such information, together with a multivariate analysis may help the readers to clarify the role of miR-197 and miR-223 for the prediction of cardiovascular deaths in this cohort. We should stress the importance of new statistical approaches for giving us the additional information of these biomarkers in clinical practice (14).

Finally, some biomarkers for predicting cardiovascular

events or deaths in community-based populations have not consistently added information to standard risk factors. Although the use of circulating biomarkers to aid risk prediction is attractive, prior studies have not consistently demonstrated the value of biomarkers for prognosis or diagnosis beyond standard risk factors in low to intermediate risk individuals in different cohorts.

Acknowledgements

Dr. Orenes-Piñero is supported by a postdoctoral contract from Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Murcia, Spain.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Zhijun Han, MD (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Piccolo R, Giustino G, Mehran R, et al. Stable coronary artery disease: revascularisation and invasive strategies. *Lancet* 2015;386:702-13.
2. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281-97.
3. Agarwal V, Bell GW, Nam JW, et al. Predicting effective microRNA target sites in mammalian mRNAs. *Elife* 2015;4.
4. Orenes-Piñero E, Montoro-García S, Patel JV, et al. Role of microRNAs in cardiac remodelling: new insights and future perspectives. *Int J Cardiol* 2013;167:1651-9.
5. Navas-Carrillo D, Ríos A, Rodríguez JM, et al. Familial nonmedullary thyroid cancer: screening, clinical, molecular and genetic findings. *Biochim Biophys Acta* 2014;1846:468-76.
6. Goedeke L, Rotllan N, Canfrán-Duque A, et al. MicroRNA-148a regulates LDL receptor and ABCA1 expression to control circulating lipoprotein levels. *Nat Med* 2015;21:1280-9.
7. Wagschal A, Najafi-Shoushtari SH, Wang L, et al. Genome-wide identification of microRNAs regulating cholesterol and triglyceride homeostasis. *Nat Med* 2015;21:1290-7.

8. Rayner KJ, Esau CC, Hussain FN, et al. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature* 2011;478:404-7.
9. Ramirez CM, Dávalos A, Goedeke L, et al. MicroRNA-758 regulates cholesterol efflux through posttranscriptional repression of ATP-binding cassette transporter A1. *Arterioscler Thromb Vasc Biol* 2011;31:2707-14.
10. Sun D, Zhang J, Xie J, et al. MiR-26 controls LXR-dependent cholesterol efflux by targeting ABCA1 and ARL7. *FEBS Lett* 2012;586:1472-9.
11. Sun X, Belkin N, Feinberg MW. Endothelial microRNAs and atherosclerosis. *Curr Atheroscler Rep* 2013;15:372.
12. Feinberg MW, Moore KJ. MicroRNA Regulation of Atherosclerosis. *Circ Res* 2016;118:703-20.
13. Schulte C, Molz S, Appelbaum S, et al. miRNA-197 and miRNA-223 predict cardiovascular death in a cohort of patients with symptomatic coronary artery disease. *PLoS One* 2015;10:e0145930.
14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157-72; discussion 207-12.

Cite this article as: Orenes-Piñero E, Marín F, Lip GY. miRNA-197 and miRNA-223 and cardiovascular death in coronary artery disease patients. *Ann Transl Med* 2016;4(10):200. doi: 10.21037/atm.2016.05.27