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Commentary

Not all myocardial infarctions are created equal: The potential of circulating microRNAs to discern coronary artery dissection

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Acute myocardial infarction (AMI) is a dramatic manifestation of ischemic heart disease and represents a major cause of mortality worldwide, responsible for over 1 million hospitalizations annually in the United States [1]. Notwithstanding, AMI encompasses different etiopathogenic mechanisms and, although atherothrombosis is the most common one [1], epidemiological evidence accumulates on the relevance of other causes, including spontaneous coronary artery dissection (SCAD). Described for the first time in the early 30 s, SCAD is obviously not a rare disease and may account for up to 4% of all AMIs and for 35% of those in young women (< 50 years old) [2]. It is characterized by the development of a hematoma in the media of the coronary artery with delamination of vessel wall and compression of the lumen, thus reducing coronary blood flow to prompt myocardial ischemia. In the light of the different pathogenesis, it is not unexpected that clinical management of acute SCAD and atherothrombotic AMI requires specific considerations as, for example, an invasive treatment strategy (i.e., percutaneous coronary intervention, PCI) results in higher complication rates and less predictable outcomes, whereas conservative management may be preferable in these patients [2,3]. However, the clinical presentation of SCAD is the similar to atherothrombotic AMI, and diagnosis requires experienced interventional cardiologists and invasive approaches such as coronary angiography and optical coherence tomography. Hence, the discovery of easy-to-assess biomarkers for diagnosis of SCAD in patients with symptoms of AMI in emergency settings (e.g., emergency and chest-pain units) would improve their early identification and enable benefits with regards to therapeutic management.

In this article of *EBioMedicine*, Lozano-Prieto and colleagues report on the diagnostic power of circulating microRNAs for this purpose [4]. MicroRNAs are endogenous short non-coding RNAs with a major influence in the pathogenesis of cardiovascular diseases [5,6]. They are remarkably stable in plasma and serum and have therefore been explored as potential diagnostic or prognostic biomarkers in various diseases including AMI [7]. The authors confirmed that AMI influence the expression of circulating microRNAs and, more importantly, identified and validated a specific microRNA signature able to discern between atherothrombosis or SCAD as the etiology of AMI. Indeed, the simultaneous detection of higher circulating let-7f-5p, miR-146a-5p, miR-151a-3p, and miR-223−5p showed a really good accuracy (*C*-statistic: 0.88, 95%CI: 0.72−1.00) with 68% positive and 83% negative predictive values for the diagnosis of SCAD across the two independent cohorts in England and Spain, which minimize the possibility of operator- and site-dependent biases.

Not only may circulating microRNAs serve as biomarkers but experimental and clinical studies also suggest that they may mediate a network of intercellular communication by affecting gene expression in recipient cells [6]. For this reason, the authors have explored the possibility that the identified microRNAs could take part in the pathogenesis of SCAD by targeting specific transcripts in cells relevant to the progression of vascular diseases. Indeed, most of the validated targets of the deregulated microRNAs were enriched in processes of blood vessel development, vascular smooth muscle cells proliferation, and TGF-β signaling pathway, which has been implicated in the pathogenesis of SCAD in a recent genetic association study [8]. Interestingly, the genes for the precursors of 2 out of the four regulated microRNAs (*MIRLET7F2* and *MIR223*) are hosted in the *X*-chromosome, thus potentially contributing to the large prevalence of SCAD in women (87−95% of reported SCAD cases) [2,3,9]. Nonetheless, an inference of a causal role derived from the current study is limited. Although the authors detected differences in circulating levels of some targets (e.g., CXCL8, TGFB1, MMP2), these results are not consistent with the paradigm of a microRNA-mediated regulation, with targets and microRNAs being concomitantly upregulated. Multiple reasons can explain this apparent paradox, including the

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observation that circulating and intracellular pools of microRNAs undergo different regulatory processes, as already reported for let-7f-5p in diabetes [6,10]. Hence, additional experimental studies are warranted to dissect the intimate mechanisms of microRNA regulation of SCAD.

Overall, the study by Lozano-Prieto et al. presents a promising non-invasive tool for diagnosis of SCAD and an attractive standpoint for future large prospective and multicentric clinical trials for a definitive validation of the discriminatory power of the identified microRNA signature. While the lack of standardization in methodology, data normalization and analytical workflows still hamper a rapid adoption of circulating microRNAs as biomarkers in the clinic, their remarkable discriminatory power revealed by studies such as the current one, once confirmed and replicated, will possibly provide the physicians with an important tool for diagnosis of SCAD with the ultimate goal to optimize the clinical management and reduce the complications of invasive therapeutic and diagnostic procedures in those patients.

Declaration of Competing Interest

None

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Contributors

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References

[1] Eisen A, Giugliano RP, Braunwald E. Updates on acute coronary syndrome: a review. JAMA Cardiol 2016;1:718–30.
[2] Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, Rose CH. Spontaneous coronary artery dissection: JACC state-of-the-art review. J Am Coll Cardiol 2020;76:961–84.
[3] Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, Brass N, Lavoie A, Bishop H, Lavi S, Pearce C, Renner S, Madan M, Welsh RC, Lutchmedial S, Vijayaraghavan R, Aymong E, Har B, Ibrahim R, Gornik HL, Ganesh S, Buller C, Matteau A, Martucci G, Ko D, Mancini GBJ. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. Eur Heart J 2019;40:1188–97.
[4] Lozano-Prieto M, Adlam D, García-Guimaraes M, Sanz-García A, Vera-Tomé P, Rivero F, Cuesta J, Bastante T, Baranowska-Clarke A, Vara A, Martin-Gayo E, Vicente-Manzanares M, Martín P, Samani NJ, Sánchez-Madrid F, Alfonso F, de la Fuente H. Differential miRNAs in acute spontaneous coronary artery dissection: pathophysiological insights from a potential biomarker. EBioMedicine 2021. doi: 10.1016/j.ebiom.2021.103338.
[5] Santovito D, Egea V, Bidzhekov K, Natarelli L, Mourao A, Blanchet X, Wichapong K, Aslani M, Brunssen C, Horckmans M, Hristov M, Geerlof A, Lutgens E, Daemen M, Hackeng T, Ries C, Chavakis T, Morawietz H, Naumann R, von Hundelshausen P, Steffens S, Duchene J, Megens RTA, Sattler M, Weber C. Noncanonical inhibition of caspase-3 by a nuclear microRNA confers endothelial protection by autophagy in atherosclerosis. Sci Transl Med 2020;12:eaaz2294.
[6] Peters LJF, Biessen EAL, Hohl M, Weber C, van der Vorst EPC, Santovito D. Small things matter: relevance of microRNAs in cardiovascular disease. Front Physiol 2020;11:793.
[7] Santovito D, Weber C. Zooming in on microRNAs for refining cardiovascular risk prediction in secondary prevention. Eur Heart J 2017;38:524–8.
[8] Verstraeten A, Perik M, Baranowska AA, Meester JAN, Van Den Heuvel L, Bastiaanen J, Kempers M, Krapels IPC, Maas A, Rideout A, Vandersteen A, Sobey G, Johnson D, Fransen E, Ghali N, Webb T, Al-Hussaini A, de Leeuw P, Delmotte P, Lopez-Sublet M, Pappaccogli M, Sprynger M, Toubiana L, European/International Fibromuscular Dysplasia Initiative R, Laer LV, Van Dijk FS, Vikkula M, Samani NJ, Persu A, Adlam D, Loeys B. Collaborators of the European/international fibromuscular dysplasia R and initiative. enrichment of rare variants in loeys-dietz syndrome genes in spontaneous coronary artery dissection but not in severe fibromuscular dysplasia. Circulation 2020;142:1021–4.
[9] Di Palo A, Siniscalchi C, Salerno M, Russo A, Gravholt CH, Potenza N. What microRNAs could tell us about the human *X* chromosome. Cell Mol Life Sci 2020;77:4069–80.
[10] Santovito D, De Nardis V, Marcantonio P, Mandolini C, Paganelli C, Vitale E, Buttitta F, Bucci M, Mezzetti A, Consoli A, Cipollone F. Plasma exosome microRNA profiling unravels a new potential modulator of adiponectin pathway in diabetes: effect of glycemic control. J Clin Endocrinol Metab 2014;99:E1681–5.