

Circulating microRNAs: novel biomarkers for cardiovascular diseases?

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This editorial refers to ‘Circulating microRNAs are new and sensitive biomarkers of myocardial infarction?†, by Y. D’Alessandra *et al.*, on page 2765

MicroRNAs (miRNAs) comprise short, non-coding RNAs, which are important for many aspects of homeostasis and disease.^{1,2} MiRNAs are generally considered to act as intracellular endogenous RNAs to control gene expression on a post-translational level. However, recent studies demonstrated that miRNA can be detected in circulating blood and that these circulating miRNAs might be useful disease biomarkers, e.g. for certain forms of cancer.^{3,4}

D’Alessandra and colleagues have now demonstrated that circulating muscle-derived miRNAs might be useful as biomarkers of acute myocardial infarction (AMI)⁵ (Figure 1A). Specifically, the authors showed that muscle-enriched miRNAs, such as miR-1, miR-133a, miR-133b, and miR-499-5p, are elevated in plasma obtained from mice after coronary artery ligation as well as in humans with AMI.⁵ In line with these findings, other groups recently reported similar results.^{6,7} In experimental AMI models and in patients, Wang *et al.* showed that the muscle-enriched miR-1, miR-133a and miR-499 as well as the cardiac-specific miR-208 are elevated in plasma.⁶ Likewise, miR-499,⁷ miR-1,^{8,9} miR-133a/b, and miR-208⁹ were shown to be increased in small cohorts of humans after AMI. All of these studies suggest that circulating myocardial-derived miRNAs might be useful as potential biomarkers for infarction.

miRNAs as biomarkers for AMI: specificity, sensitivity, and practicability?

Although these recent findings are highly interesting, establishing circulating miRNAs as biomarkers for AMI is challenging and requires that several criteria are fulfilled. First of all, the detected

miRNA should rather specifically identify myocardial injury. It is well known that some miRNAs are expressed in a cell type- and tissue-specific manner, and, indeed, one of the miRNAs, namely miR-208a, is encoded by the α -myosin heavy chain gene and therefore is exclusively expressed in cardiac myocytes.¹⁰ Consistently, the level of miR-208 in blood from healthy volunteers or patients without an acute ischaemic event is very low, whereas circulating levels of miR-208 were significantly elevated after induction of AMI.⁶ However, D’Alessandra and co-workers were unable to detect elevated levels of circulating miR-208 in AMI patients, probably because the levels are below the detection limit of the protocol used to detect circulating miRNAs in this study. The other miRNAs, miR-1, miR-133a/b, and miR-499, that were proposed as potential biomarker for AMI are not exclusively expressed in cardiac myocytes, but are also detected in skeletal muscle cells.¹ Therefore, one may expect that injury to the skeletal muscle can lead to an increase in the levels of these miRNAs as well. However, in a model of hind limb ischaemia, that induces significant muscle injury, D’Alessandra *et al.* did not see any increase of miR-1, miR-133a/b, and miR-499. It is unclear how these results can be interpreted, since other studies indeed detected elevated circulating levels of miR-1 and miR-133a/b, but not miR-208, in sham-operated mice, indicating that tissue injury itself can lead to increased levels of muscle-enriched miRNAs. Consistently, in a side-by-side comparison of different miRNAs, the cardiac-specific miRNA miR-208 showed a superior receiver operating characteristic curve, similar to the well-established marker cardiac troponin I, indicating a high sensitivity and specificity.⁶ These data need to be confirmed in a larger scale prospective study.

In addition to a very high specificity and sensitivity, a clinically useful biomarker for AMI should be measurable early after onset of myocardial injury, and the measurements should be rapid and robust. Two of the studies addressed the kinetics of circulating miRNAs compared with established markers of AMI such as troponin. Muscle-derived miRNAs were shown to be elevated within 1 h after induction of coronary artery ligation in the mouse model. In humans, miR-1 and

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results) and an active uptake mechanism needs to be considered allowing these low concentrations to produce a biological response. Therefore, it remains to be determined whether a modulation of circulating miRNA translates into alteration of systemic gene expression.

In conclusion, the discovery of miRNAs circulating with the blood opens up intriguing possibilities for the use of the circulating miRNA patterns as a biomarker for cardiovascular diseases. This is not only of potential relevance for the identification of patients with AMI, where these markers need to compete with established and highly sensitive markers such as high sensitivity troponins, but might also be very useful for risk stratification, e.g. of patients with heart failure. In such a patient cohort, miR-423 was recently identified as a potentially promising marker.¹⁵

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