Response to Letter Regarding Article, “Circulating MicroRNA-208b and MicroRNA-499 Reflect Myocardial Damage in Cardiovascular Disease”

The stability and detectability of circulating microRNAs in human plasma provides exciting opportunities for the use of microRNAs as biomarkers for human disease. In an exploratory study, we have investigated the behavior of selected microRNAs, including the cardiac-enriched microRNAs -208b and -499 in a panel of cardiovascular diseases and found a striking elevation of the latter 2 microRNAs in plasmas of patients with acute myocardial infarction.1

Multiple groups have published concordant findings about the diagnostic accuracy of both microRNAs in the setting of acute myocardial infarction.2,3 However, differences in isolation efficiency have led reports on microRNA-208b levels—which are typically around the detection limit—to be more variable than levels of the more abundant microRNA-499. We therefore share the correspondents’ enthusiasm for microRNA-499 as a potential biomarker for acute myocardial infarction. Importantly, clinical relevance of such biomarkers will depend on the development of rapid and sensitive detection methods for plasma microRNA, as the Achilles’ heel of troponin testing (clinical chemistry’s gold standard for myocardial infarction) lies in its limited sensitivity during the first hours after onset of pain.

In addition, we agree that standardized normalization methods are a prerequisite for universal applicability of plasma microRNAs as biomarkers. Normalization using spiked-in synthetic oligonucleotides accurately corrects for confounders in RNA isolation, reverse transcription, and real-time polymerase chain reaction measurements. Alternatively, normalization using endogenous “stable” microRNAs should theoretically also correct for RNA stability during sample generation and storage (although no effect of prolonged storage at −80°C could be observed in our study). Unfortunately, there is no consensus regarding stable microRNAs for correction. The initially popular reference miR-164 was reported not to be reproducible by others.4 In practice, many studies use microRNAs that appear stable in their own arrays, and those are typically different per study. Thus, in our opinion, spike normalization represents the method of choice until genuinely stable plasma microRNAs are identified.

Data from us and other investigators open the exciting path to the clinical application of microRNA diagnostics. It seems a matter of time before a reliable diagnostic kit remedies the currently limiting issues of variable sensitivity, normalization, and detection pace.

Disclosures

None.

References

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