

Pros and Cons of miRNAs as Non-Invasive Circulatory Biomarkers

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Editorial

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INTRODUCTION

Non-invasive circulatory biomarkers are highly preferable for diagnosing chronic and other debilitating diseases. It is relatively simple, economic and feasible for repeated monitoring to track the disease progressions. In most of the cancers, surgical interventions are necessary to diagnose. Similarly, in Alzheimer disease (AD) invasive lumbar punctures have to be performed for CSF withdrawal in order to diagnose various stages of AD by quantitative estimation of tau and A β levels. These diagnosing procedure are not always risk-free and it causes uncomfortable pain to the patients. Therefore, non-invasive biomarkers are attractive options for earlier diagnosis of diseases. In addition to existing non-invasive biomarkers such as proteins and lipid, recently miRNAs are in the focus as circulatory biomarkers. miRNAs are short non-coding RNA (~22 nts), mostly that base pair specifically to the 3' untranslated region (UTR) of the transcripts and therefore regulate gene expression by either mRNA degradation or translational inhibition. miRNA biogenesis starts in nucleus, where RNA polymerase II or III produces long pri-miRNA transcript (1000 nts) that yields hairpin pre-miRNA (70 nts). Upon exportation to cytoplasm, RNase Dicer and double-stranded RNA-binding protein (TRBP) cleaves the hairpin pre-miRNA to mature miRNA (22 nts). Resulting in two strands, namely functional and passenger. While the passenger strand gets degraded, functional strand gets incorporated into RNA-induced silencing complex (RISC) along with Argonaute (Ago2) proteins to direct RISC to silence partially based paired transcript which underlies the principle of miRNA-mediated gene regulation ^[1].

miRNAs being secreted to the blood stream and its high stability against nuclease digestion and also carried by vehicles such as high density lipoprotein, exosomes, argonaute protein complex, micro vesicles and apoptotic bodies makes it as one of the most preferred choices among the alternatives for stable biomarker. These miRNAs are secreted from the cells to communicate with other cells to mediate intercellular communications ^[2]. It is hypothesized that when the cell is under stress it passes the underlying information through these secreted miRNAs. So, these are potential candidate for intercellular signaling (miRNAs in circulation mostly that are encapsulated in vesicles) or indicators of cellular state (miRNAs in circulation due to apoptosis).

PROS OF CIRCULATORY miRNAs

Main advantages of circulatory miRNAs as biomarkers includes, its occurrence in the bio fluids that are easily accessible. Mostly serum, plasma, PBMCs, whole blood (also saliva, tears and urine) have been used as source for detecting circulating miRNAs that could reflect diseased conditions. Secondly, improvement in the tools such as RT-qPCR, next-generation RNA sequencing, nano string technique, micro-array platforms and highly efficient biosensors are able to detect miRNAs in these complex bio fluids. Thirdly, miRNAs are very unique and the total number of identified human miRNAs is almost 1/10th of number of genes. This small count of miRNA signatures are unique to the pathways that altered in the diseased states. Not only has a potential of diagnostic marker but also as a prognosis and therapy monitoring marker for diseases is an added benefits of circulatory miRNAs. Potential of circulatory miRNAs in cancer and in Alzheimer's disease have been reviewed briefly ^[3-5].

CONS OF CIRCULATORY miRNAs

Diagnostic biomarker should be always detected consistently with independent experiments. Unfortunately there is vast discordant reports which speculates doubt in the specificity of miRNAs for particular diseases. Source of the miRNAs in the circulation is unclear and also analytical variables (pre and post) in the miRNA detection causes lack of reproducibility among studies. Further, occurrence of similar miRNAs in various diseases and also influence of other uncontrollable factors (such as smoking, diet, circadian cycles, etc.,) makes difficult to understand circulatory miRNAs specificity to particular disease. Various anomalies and challenges in miRNA as circulatory biomarker have been discussed ^[6-8].

CONCLUDING REMARKS

In summary, it is obvious that non-invasive circulatory miRNAs are highly potential biomarkers, however further investigations have to be done to answer lack of reproducibility, unraveling possible erroneous attribution to disease contributed by confounding factors (such as miRNAs solely from blood cells which could be a contaminating source) and variation among detection techniques. Harmonization in the techniques and arriving at consensus data, could unleash its ability for translating into clinical utility as a reliable biomarker.

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