

## MicroRNAs as Molecular Biomarkers for Viral Infections

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### Editorial

MicroRNAs (miRNAs) are a class of small non-coding endogenous RNA molecules which act as critical regulators of a wide range of biological processes, such as cell cycle control, apoptosis, stem cell differentiation, hematopoiesis, neurogenesis, metabolism and secretion of biomolecules, aging, immune responses or viral infections [1]. The function of miRNAs is based on their partial complementarity to one or more messenger mRNAs, resulting in the downregulation of gene expression in a variety of modes, including translational repression, mRNA cleavage and deadenylation. The non-prerequisite requirement for an absolute nucleotide match between miRNAs and mRNA molecules has as a consequence, individual microRNAs targeting as many as 100 different mRNAs. Furthermore, individual mRNAs may contain multiple binding sites for different miRNAs, resulting in a complex regulatory network.

Apart from their significant roles in fundamental biological procedures, the differential expression of miRNAs has been associated to various human diseases [2]. Recently, the discovery of stable miRNAs in body fluids which may originate from intracellular processes in human organs has led to the suggestion of exploiting the circulating miRNAs as biomarkers with diagnostic or prognostic value. This concept was first explored in a variety of human cancers; however, growing evidence extends the impact of circulating miRNAs as potential biomarkers in infectious diseases [3].

As regards viral infections, emphasis has been given on miRNAs whose potential has been studied both in experimental systems and virally infected human samples. It is noteworthy that upon infection, viruses are able to regulate both the miRNAs encoded by the host and their own genome [4]. Depending on the mode of infection, lytic or latent, and the immune state of the patient, immunocompetent or immunosuppressed, orchestrated alterations in a series of miRNAs may occur, establishing a miRNA signature which could be associated to diagnosis, staging, progression, prognosis or response to treatment for a specific infectious disease. Most of the viruses of medical interest, such as HSV-1, HSV-2, CMV, EBV, KSHV, polyoma viruses, adenoviruses, HPV, HBV, HCV, HIV and others, encode their own miRNAs which are under investigation and validation for their diagnostic potential as biomarkers for infectious diseases caused by them [5]. Characteristic examples include the EBV encoded miR-BART2-5p, 13 along with 15 miRNAs in plasma which have been found to associate with high morbidity and mortality of chronic active EBV infection [6]. In addition, KSHV results in strong upregulation of host miR-132 in endothelial cells leading to inhibition of antiviral innate immunity an induction of abnormal endothelial cell proliferation in Kaposi's sarcoma [7]. Potential miRNAs biomarkers significantly contributing to current diagnostic approaches and

prognosis have been thoroughly studied in chronic infections and cancer associated hepatitis B and C viruses and miRNA panels have been suggested for preventive screening, as prognostic markers for risk stratification of recurrence and hepatocarcinogenesis, as well as timely therapy [8].

The great expectations for the utility of miRNAs as biomarkers in viral diseases should be assessed very carefully, considering several scientific and technical aspects. For example, the miRNA expression profiles must be specific to tissue and disease and therefore both the sample and the control should be carefully selected. Changes in the expression profile of particular miRNAs could originate from virally infected cells but also from different sources of circulating miRNAs. Obtaining biological fluid samples from the infected tissue should be preferable whenever possible. Moreover, particular care should be taken as regards the standardization of Real-Time PCR methods employed for the quantification of circulating miRNA as well as of the miRNAs used for the normalization.

The discovery of circulating miRNA in the blood/serum during different viral infections constitutes a diagnostic challenge and has the potential to become a powerful non-invasive biomarker in coming future. In this perspective, the clinical aspects of early diagnosis, identification of high risk patients for viral infection, recurrence or relapse, monitoring of disease progression, or prediction for antiviral drug response could be approached applying well-established miRNA platforms. Nevertheless, in the diagnostic context, the biomarker potential of each miRNA has to be very carefully assessed to establish clinical relevance.

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