

Micro-Epigenetic Markers in Viral Genome: SARS-CoV-2 Infection Impact on Host Cell MicroRNA Landscape

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Article received on the 2nd of October 2024 and accepted for publication on the 12th of November 2024

ABSTRACT

Introduction: MicroRNAs (miRs) are crucial micro-genetic markers that significantly manipulate gene expression in neoplastic/malignant and non-neoplastic diseases, as viral infections. Different expression patterns of miRs seem to partially influence the response rates to specific chemo-targeted therapeutic regimens and prognosis in cancer patients. Concerning their nature, miRs are short non-coding RNAs including 20-25 nucleotides hosted in intra- or intergenic regions. Their most important function is the positive regulation of post-transcriptional gene silencing levels. Based on this activity, they enhance normal cell functions, including proliferation, apoptosis and tissue differentiation. Their deregulation in cancerous cells due to epigenetic and transcriptional imbalances is correlated with an excessive production of target mRNA.

Objective: In the current paper, our aim was to generally describe the role of MiRs in cancer genome and we mainly focused on specific host target-cell miRs that are affected by SARS-CoV-2 in the COVID-19 pandemic.

Material and method: A systematic review of the literature was carried out based on the international database PubMed focused on miR nature, origin, structure and function in cancer genome and more recently on the influence of SARS-CoV-2 on affected cells. The following keywords were used: microRNA, SARS-CoV-2, COVID-19, infection, cancer, virus. A pool of 52 important articles were selected for the present review at the basis of exploring the SARS-CoV-2 efficacy in miRs.

Results: A broad set of miRs, including miR-122, miR-16-2-3p, miR-3605-3p, miR-15b-5p, miR-486-3p, miR-486-5p, miR-447b, miR-3672, miR-325, miR-447b and miR-222, has been identified to be deregulated by SARS-CoV-2 infection.

Conclusions: miRs represent significant micro-epigenetic markers frequently deregulated in SARS-CoV-2 mediated infection (COVID-19). Interactions between miRs and SARS-CoV-2 RNA genome are under investigation. miR overexpression/expression loss in SARS-CoV-2 affected epithelia is correlated with specific genetic and by epigenetic signatures in the corresponding patients.

Keywords: microRNA, SARS-CoV-2, COVID-19, infection, cancer virus.

INTRODUCTION

Coronavirus (CoV) Disease 2019 (COVID-19) demonstrates increased levels of infectivity that lead to significant mortality rates, especially in geographical areas with massive populations. Because of its rapid worldwide spread as pandemic infection, there is an increasing need and pressure for expanding the knowledge regarding the molecular substrate of the infection, and the target cell-virus attack reaction mechanisms for developing successive vaccines and anti-virus drugs (1). A broad spectrum of clinic-epidemiological studies analyzed the strong negative influence of the severe acute respiratory syndrome (SARS-CoV), Middle-East respiratory syndrome (MERS-CoV) and the current 2019/2020 severe acute respiratory syndrome-2 (SARS-CoV-2) on the national health systems worldwide. They acknowledged their inability to respond efficiently at least in the first phase, which has been also leading to personnel burn-out (2, 3). In order to respond to this emergency situation, a significant number of pharmaceutical companies invested in developing a variety of

anti-SARS-CoV-2 strategies, including monoclonal antibodies (mAbs) and vaccines, both of which being considered necessary for providing normalized conditions for restoring the globally disrupted social and economic activities (4, 5). In order to confront this situation, national health authorities worldwide – including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – proceeded to an initial approval and a conditional marketing authorisation after an early validation for a variety of vaccines. Concerning the commercially available vaccine types, some of them are based on inactivated pathogens using virus segments or protein/peptide chains, viral vectors. Furthermore, vaccines that use DNA plasmid as substrate and also nucleoside-modified viral messenger RNA that is encapsulated into novel, hi-tech nanoparticles, especially lipid nanoparticles (LPDs), have now authorization for massive population vaccination programs (6-8). Specific interactions between mRNA-based vaccines and target cells predominantly affecting the ribosome machinery lead to functional alterations in post-transcriptional/translational mechanisms (9, 10).

Besides the genetic mechanisms that modify the biological behavior of the virus (mutations: deletions, substitutions), the role and impact of epigenetic changes – such as DNA methylation, histone modifications and specific micro-genetic non-coding markers – on cell-targets remain under investigation. Interestingly, similar genetic and epigenetic mechanisms are involved in non- and virus-mediated carcinogenesis. Besides this, in viral infections there are unexplored roles of host cell microRNAs (miRs) that interact with the corresponding pathogens such as SARS-CoV-2.

In the current paper, we synthesize and describe a broad landscape of host human (h) miR markers that are deregulated as a result of SARS-CoV-2 mediated molecular pressure on the infected human cell substrate, as it also happens in emergence and progression of carcinogenesis.

SARS-CoV-2 genome – cell functional receptors

Since 2021, a broad variety of molecular studies reported evidence that the primitive strain of SARS-CoV-2 seemed to belong to the beta-coronavirus lineage B that shares a strong phylogenetic similarity with BatCoV RaTG13 type (11, 12). An approximately 30 kb non-segmented positive-sense RNA molecule correlated with the corresponding RNA-dependent RNA-polymerase (Rd-Rp) provides an aberrant intracellular virus replication inside the target epithelial cells. The SARS-CoV-2 virion has a spherical structure with a diameter of approximately 100 nm and consists of four prominent proteins. In fact, the spike surface glycoprotein (S), the main or matrix protein (M), the envelope protein (E) and finally the nucleocapsid protein (NC) are distinctly recognized under electronic microscopes. The whole viral domain is completed by the existence of 16 non-structural proteins (NSP1–NSP16). Those proteins are responsible for the production of crucial molecules, including the helicase and RNA-directed RNA polymerase that promotes viral replication and translation using the intracellular ribosome machinery of the target cells. Additionally, a group of seven assistant proteins that correspond to opening reading frames (ORF3a–ORF8) have been identified, with their functional role being still under investigation (13–15). Interestingly, on the external surface of the virus there are multiple S glycoprotein projections, which consist of two subunits, S1 and S2, that form a unique crown-like motif mimicking a corona. The S1 subunit pro-

vides the main viral receptor-binding domain (RBD), whereas the S2 subunit is involved in the development of a fusion mechanism due to the interaction of the cell membrane with the penetrative viral particles. More specifically, modified proteases, including furin, trypsin, cathepsin or serino-protease (transmembrane serine protease 2-TMPRSS2), induce the progression of the viral cell entry by enhancing and stabilizing the corresponding intracellular infection signal (16–18). Molecular, structural and crystallographic analyses focused on the virus-target cell interaction have already reported that human angiotensin-converting enzyme 2 (hACE2) was the main functional receptor for SARS-CoV-2 cell fastening. In fact, this region provides the perfect substrate for a strong viral attachment on the cell membrane, followed by the total entry and activation of the S1/S2 subunits complex (19). SARS-CoV-2 cell entry through the h ACE2 receptor triggers a cataract of intracellular reactions that induce signaling transduction also implicating crucial hypoxia regulatory molecules such as HIF-1a (20). In conjunction, the role of chromosome X that hosts not only the hACE2 gene (band Xp22.2) but also other critical molecules involved in immune response to SARS-CoV-2 viral infection is under investigation. Aggressive clinical and pathological phenotypes, that are characterized by poor response rates to anti-viral therapeutic regimens and poor survival, have been already detected and published in subsets of the corresponding infected patients, especially males (21).

MiRs: endogenous epigenetic markers in malignancy and infection

Regulated gene expression stabilizes genomic homeostasis in normal cells. MicroRNAs (miRs) are crucial micro-genetic markers that significantly manipulate gene expression in neoplastic and non-neoplastic diseases as viral infections (22). MicroRNAs are characterized structurally by chains of 20 to 25 nucleotides embedded in intra- or inter-gene regions. In fact, they are characterized as short and non-coding RNA micro-molecules (23). Their replication that leads to transcription is mediated by the RNA polymerase II enzyme. MiR maturation is a multi-step process in which pri-miRNAs are transformed into pre-miRs. In the nuclear microenvironment, the RNase III enzyme Drosha complex releases pre-miRs into the cytoplasm. Single-stranded ma-

ture miR is the final product of this procedure (24). Post-transcriptional gene silencing process is partially mediated by miR activity. Cancerous cells are characterized by different miR expression patterns. It is well scientifically established that genetic (e.g., mutations, translocations) and epigenetic (e.g., DNA hyper-methylation of tumor suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) alterations affect the functional roles of miRs. Furthermore, transcriptional modifications are responsible even for loss of miR-related repression of target mRNAs (25-27). Additionally, many miRs are functionally characterized by a biphasic expression pattern in solid malignant tumors with a different histogenetic origin. Mainly their up regulation induces their oncogenic activity, whereas their downregulation leads to a suppression of it (miRNA 29 in hepatocellular carcinoma and lung cancer, miRNA 26a in lung and breast cancer, respectively) (28, 29). Detecting specific mechanisms involved in the biogenesis, maturation and functional activity of miRNAs is a crucial step for understanding the different transcriptional-expression profiles that they create in genes. MicroRNA analyses provide unique genetic signatures in patients suffering by the same histopathological cancer type. They also should be used for prognostic tools for partly explaining the differences in response rates to specific inhibitor molecules (30).

Concerning interactions between viral cell entry and micro-genetic markers, a variety of hmiRs interact with the corresponding viral genomes. Specifically, miR-146 targets the enterovirus-71,

while miR-130a and MiR-122 target the hepatitis C virus (HCV); miR-221, miR-222, miR-103 and miR-34 target the human immunodeficiency virus type 1 (HIV-1). HBV-infected liver cells are characterized by increased miR-328-3p, miRNA miR-146a-5p, miR-345e5p. Let-7c-5p and miR-221 antagonize the respiratory syncytial virus (RSV) and miR-154-5p the human papilloma virus (HPV) 16/18 that is implicated in viral-mediated carcinogenesis (31-36).

The landscape of hmiRs in SARS-CoV-2

A significant number of molecular analyses have revealed a plethora of hmiRs that are affected by SARS-CoV-2 infection. Overactivation (overexpression) has been detected in miR-4485 (target genes: ACE2, toll-like receptor: TLR-4), miR-200c-3p, miR-1246, miR-125a-5p (target gene: ACE2), miR-98-5p (target gene: TMPRSS2), let-7e/ miR-125a (target genes: ACE2 and TMPRSS2) and miR-141/miR-200 (target genes: ACE2 and TMPRSS2). In contrast to the previous referred miRs, miR-183-5p, miR-146a-5p, miR-21-5p, miR-142-3p, miR-181a-2-3p, miR-31-5p and miR-99a-5p are deregulated (progressive loss of their expression (37-40). Some of them are considered important for aggressive phenotypes and severity of the infection (41). Concerning potential interactions between target cell genome and SARS-CoV-2 RNA, a broad spectrum of miRs has been identified including miR-122, miR-16-2-3p, miR-3605-3p, miR-15b-5p, miR-486-3p, miR-486-5p, miR-447b, miR-3672, miR-325, miR-447b and miR-222 (42-44). The

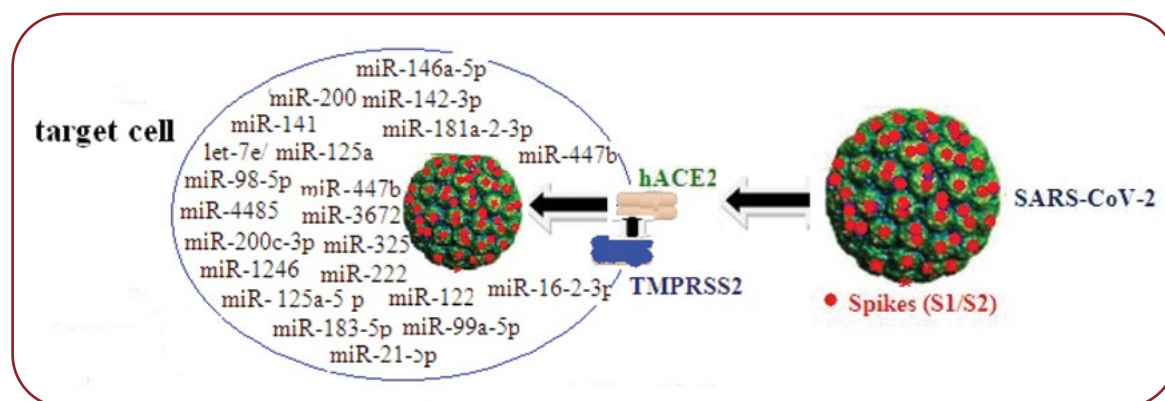


FIGURE 1. Schematic presentation of the intracellular host hmiR landscape that interacts with SARS-CoV-2, with a broad spectrum of miRs in critical genes that encode for functional receptors (hACE2, TMPRSS2) being implicated in SARS-CoV-2 cell entry. hmiRs=human microRNAs; hACE2=human angiotensin-converting enzyme 2; TMPRSS2=transmembrane serine protease 2

complete landscape of the previous referred host cell hmiRs is presented in Figure 1.

Understanding the role of epigenetic modifications in viral-mediated infections – as it happens in carcinogenesis – is a critical step for improving specific molecular knowledge and also for developing efficient anti-viral treatment strategies. Concerning anti-SARS-CoV-2 strategies there is a spectrum of monoclonal antibodies and vaccine platforms under validation for commercial use. In the field of miR molecular analyses, sophisticated and innovative techniques (e.g., comparative transcriptome analysis for gene co expression networks) have revealed differences in epigenetic response of the host cells under the pressure of SARS-CoV-2 infection (45, 46). Additionally, specific interactions between rapidly mutated virus and host genomic and epigenomic machinery create multi-form transcriptional and post-transcriptional micro-environment acting as eligible substrate for RNA-based anti-SARS-CoV-2 targeted drug development (miRNA-antisense – antago-miR) (47). Furthermore, identification of miRs binding sites on SARS-CoV-2 RNA sequences and also specific long non-coding RNAs (lncRNAs) – especially the lncRNA H19 that binds to the 5'UTR antagonizing the transcript of the viral gene spike – should be applied for targeting exclusive genomic motives of the virus (48). Additionally, miRs targeting h ACE2 (miR-4485) and also specific interactions between human circRNAs and miRNAs as well as human miRNAs and viral mRNAs represent interesting and very

promising molecular approaches (49, 50). Interestingly, a recent study explored the role of miRNAs hsa-miR-3132 and hsa-miR-4650 on the viral genome (51). They reported that specific mutations in the viral RNA genome caused the virus to evade the selective pressure mediated by miRNAs, with inducing its adaptive potential in the target human epithelial cells. ■

CONCLUSIONS

In conclusion, hmiRs represent significant micro-epigenetic markers which are frequently deregulated in SARS-CoV-2 mediated infection. Interactions between hmiRs and SARS-CoV-2 RNA genome are under hardworking investigation. Crystallizing the whole miR landscape and detecting overexpression/expression loss algorithms in them is a critical step for discriminating the corresponding patients by epigenetic signatures. This is an optimal approach for future efficient anti-viral RNA targeted treatment, as it has been already implemented in oncology by detecting specific micro-genetic signatures (51, 52). ■

Authors' contributions: article conception and design: AC, VP, DR and ET; article drafting: AN, ET, SM, SP, PP; critical revision of the manuscript for important intellectual content: DS, PF; approval of the final version of the manuscript: DP, NM, EK, VRVR, EK, PS.

Conflicts of interest: none declared.

Financial support: none declared.

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