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The impact of MicroRNAs (miRNAs) on the genotype of coronaviruses

Duran Canatan

Antalya Genetic Diseases Diagnosis Center, Antalya, Turkey

Summary. The beginning of 2020 has seen the emergence of COVID-19, an outbreak caused by a novel coronavirus, SARS-CoV-2, an important pathogen for humans. SARS-CoV-2 is an RNA virus containing 29891 nucleotides encoding 9889 amino acids. The genome is arranged as 5p-replicase (orf1/ab)-structural proteins [Spike (S) -Envelope (E) - Membrane (M) -Nucleocapsid (N)] –3. Viruses are obligate intracellular infectious agents that use the host cellular machinery to ensure their own fitness and survival. MicroRNAs (miRNA9) systems are potent post-transcriptional gene expression regulators that are important modulators of viral infections, and could play an important role in the treatment of viral infections. This review focuses to the genomic structure of coronaviruses, the functions of genomic proteins, the effects of micro RNA (miRNA) on virus replication and its pathogenesis. (www.actabiomedica.it)

Key words: MicroRNAs, Coronaviruses, genome, impacts

Introduction

Coronaviruses (CoVs) are enveloped, single chain RNA viruses belonging to the Coronavirinae subfamily of the Coronavirdiae family. There are four types of CoV, including Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV) and Gammacoronavirus (γCoV). A total of 6 CoVs are known to infect humans, consist of two alpha CoV (HCoV-229E and HKU-NL63) and four beta CoV (HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV (1).

Although human CoVs have been identified for decades, their clinical importance and epidemic possibility was not recognized until the outbreak of SARS-CoV and MERS-CoV. The first coronavirus outbreak is known as SARS-CoV occurred in China in 2002-2003 and the second outbreak, MERS-CoV, occurred in the Middle East countries in 2012.

Both SARS and MERS present with a spectrum of disease severity ranging from flu-like symptoms to acute respiratory distress syndrome (ARDS). Atypical symptoms such as diarrhoea and vomiting may developed in both SARS and MERS patients. Diagnosis of SARS and MERS is based on a comprehensive contact and travel history and precise laboratory tests (2).

New coronavirus (2019-nCoV) epidemic started in Wuhan, China in December 2019. The World Health Organization has officially declared the COVID-19 outbreak as a pandemic on January 30, 2020. The new coronavirus affects the respiratory system by using angiotensin converting enzyme 2 (ACE2), like SARS-CoV and MERS-CoV.

It has an incubation period of 1-14 days, usually ranging from 3-7 days. The most common symptoms in mild and moderate patients are fever, weakness, and dry cough followed by headache, nasal congestion, sore throat, muscle pain, and gastrointestinal symptoms. It causes lung damage and respiratory failure in severe affected patients (3).

This short review focuses on the genomic structure of coronaviruses, the functions of genomic proteins, the effects of micro RNA (miRNA) on virus replication and pathogenesis.

Structure of the genome

The entire genome sequence of 2019-nCoV HKUSZ-005b is available in GenBank (accession no. MN975262). The single stranded RNA genome of 2019-nCoV consists of 29891 nucleotides encoding 9889 amino acids. The virus genome is arranged as 5p-replicase (orf1 / ab) -structural proteins [Spike (S) -envelope (E) - Membrane (M) -Nucleocapsid (N)] - 3. It has 89% nucleotide similarity with bat CoV-ZXC21 and 82% with human SARS-CoV (4,5).

Functions of non-structural and structural proteins

The genome of coronaviruses contains a variable number of open reading frames (ORF), translates two polyproteins, such as pp1a and pp1ab, and these encode 16 non-structural proteins, the remaining ORFs encode structural proteins. It has four structural proteins that represent the virus and infection. The S proteins creates spikes on viral surface to bind to host receptors. The M protein has three transmembrane domains and binds to the nucleocapsid. The E protein plays a role in virus recognition and viral pathogenesis. The N protein contains two domains that can bind the virus RNA genome through different mechanisms (6,7).

Coronavirus replication and pathogenesis

Coronaviruses use the ACE2 receptor in the airways of humans. Spike (S) glycoprotein and ACE2 receptor interaction is a critical step for coronavirus entry. The S protein is an important determinant of virus entry into host cells. It consists of two subunits, S1 and S2; S1 determines virus-host range and cellular orientation, and S2 mediates virus-cell membrane fusion. After membrane fusion, viral genome RNA translates to two polyproteins, pp1a and pp1ab, which encode non-structural proteins and form a replication-transcription complex in the double membrane vesicle. The newly formed envelope glycoproteins are placed on the endoplasmic reticulum or Golgi membrane and form new nucleocapsids with the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate chamber. While the virus enters in the cells, it presents its antigen. Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG (8-11).

Micro RNAs

Micro RNAs (miRNA) are 18-24 nucleotide-length RNA molecules that transcribe from RNA genes in genome-encoding intron or exon regions and in protein-free regions, but do not encode protein.

Traditional gene regulation is in the form of DNA/messenger RNA (mRNA)/protein production. However, in all genome sequencing studies, approximately 1.5-2 % of the total RNA molecule is responsible for protein coding, most of the rest of it is called non-protein encoding RNAs (npcRNAs) (12).

These non-protein coding RNA molecules bind to the target mRNA that complement the nucleotide sequences and regulate gene expression by suppressing the protein conversion process or disrupting the mRNA. Using this pathway, MiRNAs play an important role in homeostatic processes such as cell proliferation, cell differentiation, or cell death.

MiRNAs have recently emerged as important modulators of viral infections. MiRNAs can function as suppressors of gene expression by targeting cellular or viral RNAs during infection (13).

Effect of host miRNAs on virus replication and pathogenesis

MiRNA-mediated viral infection regulation has been described in a wide variety of host and guest types, in both DNA and RNA viruses. Among the cellular miRNAs that directly target host or viral transcripts, various ways of interaction have been observed, such as: a) escape of cellular miRNAs, b) wide defect in the miRNA pathway, c) unable to regulate host or viral gene expression.

These interactions have been identified by two outcomes that viral replication directly alters: a) inhibition of translation of the viral genome, that prevents viral replication, and (b) stabilization of virus RNA. Both mechanisms regulate RNA virus replication within specific cells and/or tissues (14,15).

To investigate regulatory relationships between host miRNAs and related viruses is available a database, called ViTa, at: Http://vita.mbc.nctu.edu.tw/ to the database. It can be accessed free of charge (16).

A high sequence homology has been shown between SARS-associated coronavirus (SARS-CoV) and 2019-nCov. According to recent reports, converting enzyme 2 (ACE2) is essential for 2019-nCov to enter cells. Recent single-cell RNA studies have also shown that ACE2 is expressed in human lung cells (17).

At present, there is no single specific antiviral therapy for COVID-19 and the main treatments are supportive.

MiRNAs typically inhibit the translation and stability of messanger RNAs (mRNAs), controlling genes involved in cellular processes such as inflammation, cell cycle regulation, stress response, differentiation, apoptosis, and migration. A total 13 cellular miRNAs that affect the MERS-CoV genome have been identified. It has been hypothesized that they can be used as antiviral therapeutics against MERS-CoV infection (18). Novel anti-viral therapeutic approaches to prevent and treat respiratory viral infection are needed according to the WHO initiative Battle against Respiratory Viruses.

Out of 2565 miRNAs, miR-4778-3p, miR-6864-5p and miR-5197-3p were identified as the most effectively interacting with the gRNA of coronaviruses (19).

Overall, these results suggest that corona virüs respiratory infections were induced or inhibited by expression of certain miRNAs in airway cells that favor viral replication, pathogenesis, and also suppress anti-viral responses. Thus, cellular miRNAs could be the best candidates for development of miRNA-based therapies for corona virus diseases.

MiRNAs also function as oncogenes or tumor suppressors with different modular structures in carcinogenesis. Due to these features, we carried out miRNA studies on biomarker of cancer in our center between 2016-2019. As a result of our study, we found a total of 23 microRNAs unique and sensitive as biomarkers in eight different cancer types such as lung, breast, colon prostate, bladder, stomach, pancreatic and hepatocellular carcinoma (20).

We are preparing new projects to investigate the effect of MiRNAs on Covid 19 and to use them as biomarkers in healthy individuals, as well as for therapeutic patients' purposes.

In conclusion, microRNAs have recently emerged as important modulators of viral infections. We hope that they could play an important role in the treatment of viral infections, as anti-viral therapy and gene therapy in near future.

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Correspondence:
Prof. Dr. Duran Canatan MD
Antalya Genetic Diseases Diagnosis Center
Arapsuyu Mh. 600 Sk 39/A
07070 Konyaalti, Antalya,Turkey
E-mail: durancanatan@gmail.com