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Downregulation of microRNA-146a in diabetes, obesity and hypertension may contribute to severe COVID-19

Jelena Roganović [*,1]

Department of Pharmacology in Dentistry, School of Dental Medicine, University of Belgrade, Belgrade, Serbia

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is able to produce an excessive host immune reaction and may leads to severe disease- a life-threatening condition occurring more often in patients suffering from comorbidities such as hypertension, diabetes and obesity. Infection by human corona viruses highly depends on host microRNA (miR) involved in regulation of host innate immune response and inflammation-modulatory miR-146a is among the first miRs induced by immune reaction to a virus. Moreover, recent analysis showed that miR-146 is predicted to target at the SARS-CoV-2 genome. As the dominant regulator of Toll-like receptors (TLRs) downstream signaling, miR-146a may limit excessive inflammatory response to virus. Downregulation of circulating miR-146a was found in diabetes, obesity and hypertension and it is reflected by enhanced inflammation and fibrosis, systemic effects accompanying severe COVID-19. Thus it could be hypothesized that miR-146a deficiency may contribute to severe COVID-19 state observed in diabetes, obesity and hypertension but further investigations are needed.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is able to produce an excessive host immune reaction and sometimes leads to severe disease- a life-threatening pneumonia and acute respiratory distress syndrome (ARDS). ARDS is characterized by elevated proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukins: IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP1), an increased incidence of shock and adverse clinical outcomes [1]. Risk for developing severe and critical state of COVID-19 was found to be more likely in patients suffering from comorbidities such as hypertension and diabetes/obesity [2] yet underlyng mechanisms still not elucidated. Infection by human corona viruses as well as other respiratory viruses highly depends on host microRNA (miR) involved in maintaining the epithelial cell barrier in the respiratory tract and regulation of virus entry and replication [3]. MicroRNAs (miRs) are small (20–22 nucleotides), non-coding RNAs involved in the post-transcriptional negative regulation (suppression) of target genes expression. Around two–thirds of human mRNAs are predicted to be regulated by miRs and while single miR can regulate different mRNAs, each mRNA could possibly be regulated by a huge number of miRs [4]. Mature miRs are deriving from primary transcripts which are processed in the nucleus by microprocessor complex (Drosha/DGCR8/RNASEN), exported to cytoplasm mainly through interaction with Exportin-5, where finally is processed via Dicer enzyme [5]. Circulating/extracellular miRs, found in diverse body fluids, are highly stable due to their encapsulation within exosomes, microvesicles and apoptotic bodies or complex with high-density lipoproteins and Argonaute2. In this way, they are able to reach distant tissues cells and alter gene expression [6]. Moreover, it has been proposed that circulating miRs as epigenetic regulators are able to disseminate pathophysiological epigenetic signature from one host cell to another, neighbor or distant cells, a phenomenon defined as epigenetic damage transmission [7]. miR-146a is abundantly expressed in mammals, is among the first miRs induced during immune activation and considered to be a dominant, negative regulator of the innate immune response [8]. The circulating-exosomal miR-146a is able to modulate the antiviral response in the recipient cell, acting as a critical factor for the development of viral infection [9].

Hypothesis

Downregulation of miR-146 observed in diabetes, obesity and

* Address: Dept. of Pharmacology in Dentistry, Faculty of Dental Medicine, University of Belgrade, Dr Subotica 1, 11000 Belgrade, Serbia.
E-mail address: jelena.roganovic@stomf.bg.ac.rs.
[1] ORCID: 0000-0002-2950-4056.

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hypertension may contribute to severe COVID-19 due to a promotion of excessive cytokine production and lack of feed-back mechanism to limit inflammatory damage of tissues.

Diabetes/obesity and cardiovascular disease are risk factors for severe COVID-19 and are associated with circulatory miR-146a downregulation

Among the first studies published, Wang et al. observed that in a cohort of 138 hospitalized patients with COVID-19, hypertension (31.2%), diabetes (10.1%), cardiovascular disease (14.5%) and malignancy (17.2%) were the most common coexisting medical conditions [10]. Meta-analysis performed by Li et al calculated an odds ratio of 2.2 for diabetic patients to be admitted to an intensive care unit [11]. In another study, diabetes was found to be associated with the occurrence of ARDS with a hazard ratio of 2.3 [12]. Likewise, 47.6% of patients admitted to the intensive care unit in France and 48% of the patients admissions to intensive care in Spain due to SARS-CoV-2 were obese [13,14]. Furthermore, young patients developing severe forms of the infection, were more likely to have obesity [15]. Patients with hypertension and SARS-CoV-2 infection expressed 2.27- and 3.48-fold higher risks of severity and fatality respectively compared to the COVID-19 patients without hypertension [16]. Results of meta-analysis revealed that circulatory miR-146a was downregulated in T2D samples (PBMCs and whole blood samples) compared with controls [17]. Overweight and obesity, independent of other cardiometabolic risk factors, negatively influence circulating miR-146a, and miR-146a shows significant inverse relationship to body mass index [18]. Hypertension, independent of other cardiometabolic risk factors, adversely affects the circulating miR-146a which is inversely related to both systolic and diastolic blood pressure [19].

miR-146a defficiency is associated with excessive inflammation and modulation of host antiviral response

Accumulating evidence suggests that chronic inflammation underlies obesity, diabetes and atherosclerotic coronary disease. Crucial player in this chronic inflammation is the feed-forward loop involving Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), which increases pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IFN-γ which, in turn, stimulate NF-κB [20]. miR-146a is induced in response to inflammation in order to attenuate inflammation: NF-κB-induces expression of miR-146a which negatively affects IL-1 and TNF-α receptors to attenuate inflammation [21]. Downregulation of circulatory miR-146a or miR-146a deficiency are associated with inflammatory disorders manifested in a various organs: lungs, heart, brain or skin, and underly vascular or autoimmune diseases (Table 1). Recognition of viral infection by pattern-recognition receptors, such as TLRs, initiates the innate immune response which includes changes in miRs expression and leads to modulation, augmentation or suppresion of cytokine responses. miR-146a is considered to be dominant regulator of TLR- downstream signaling [22]. Namely, miR-146a targets and suppresses several downstream TLR- signaling molecules, such as IL-1 receptor activated kinase 1 (IRAK1), interferon regulatory factor 5 (IRF5) and tumor receptor factor-associated factor 6 (TRAF6), in order to avoid excessive inflammation after infection [21]. Given its significance in host antiviral defense mechanisms, it is not surprising that virus could develop mechanisms of interfering with host miRs. In a study by Liu et al, among 28 human miR predicted to target at the SARS-CoV-2 genome, miR-146 was reported as one, involved in immunity modulation [23]. Virus could alter miR activity by binding and sequestering free miR or can alter miR expression and miR-mediated protein expression thus affecting viral replication and host immune responses. For example, IFN-signaling is a critical cascade of events induced by viral infection, leading to upregulation of IFN-stimulated genes that inhibit viral replication. Viruses have developed various mechanisms to evade IFN system, such as through changes in host miR-146a. Namely, enterovirus- EV71, dengue virus, HBV or influenza A virus, by induction of miR-146a in infected cells, could negatively regulate the IFN-signaling [9,24]. Moreover, miR-146a negatively regulates IFN-γ production in natural killer cells (NK cells) by targeting IRAK1 and TRAF6, with subsequent inhibition of the NF-κB signaling cascade. IFN-γ is a critical cytokine produced by activated NK cells which function in immune defense to eradicate both virus-infected cells and tumor cells. However, it is observed that miR-146a suppressing effects occur only after NK cells receive excessive co-stimulation of IL-12 and IL-18 or become super active, suggesting that miR-146a induction would be initiated to "fine-tune" the immune response of NK cells into an appropriate range [25]. Likewise, it is also suggested that miR-146a may also negatively regulate cytotoxicity of NK cells [26]. In line with proposed protective role of miR-146a in SARS-CoV-2, Masselli et al. pointed out that upon SARS-CoV-2 infection, NK cells likely exit the peripheral blood, traffic into to the lung where potentially enhance local inflammation and injury [27]. Thus, miR-146a may, by "fine tuning" of NK cells, contribute to the balance between NK cells- beneficial antiviral and -detrimental pathologic effects in the lungs of COVID-19 patients. Furthermore, miR-146 deficiency observed in diabetes leads to enhanced inflammation (by insufficient inhibition of IRAK1/TRAF6), fibrosis (by fibronectin expression), and increased synthesis of MCP-1 followed by further reduction of miR-146a (by enhancing TGF-β1/ErbB4/Notch1 signaling) [28], systemic effects accompanying severe COVID-19 [1].

Table 1
Association of miR-146a downregulation/deficiency with vascular and autoimmune diseases.

Expression/Function	Association with pathological condition/disease	Reference
Human		
Downregulation of plasma miR-146a	Poor coronary collateral circulation in patients with coronary artery disease	[31]
Downregulation of serum miR-146a	Severe acute ischemic stroke	[32]
Downregulation of serum miR-146a	Acute exacerbation of chronic obstructive pulmonary disease and negative correlation with inflammatory cytokines: TNF-α, IL-1β, IL-6, IL-8	[33]
Downregulation of PBMCs-derived miR-146a	Severe systemic lupus erythematosus and the induction of type I IFNs	[34]
miR-146a-deficient mice		
Knockout of the miR-146a gene in C57BL/6 mice	Myeloproliferative disease (myeloid and lymphoid malignancies) due to a lack of NF-kB suppression	[35]
Mice harboring miR-146a-deficient Treg cells	Impaired function of Treg cells: no restraint of IFN-γ-mediated pathogenic Th1 responses and associated inflammation	[36]
Model of myocardial ischemia and reperfusion injury	Decreased heart function and increased myocardial infarction and apoptosis by targeting Med 1 gene	[37]
Model of Atopic dermatitis	Increased accumulation of infiltrating cells in the dermis, elevated expression of IFN-γ, CCL5 and CCL8 in the skin	[38]

Conclusions

Patients with diabetes, obesity and hypertension are associated with downregulation of circulating miR-146a and this dysregulation may be exacerbated by SARS-CoV-2 infection since virus might interfere with miR-146. Downregulation of miR-146a could be one of the factors underlying severe COVID-19 due to an unadequate host antiviral response, showing more prolonged and excessive cytokine production and lack of feed-back mechanism to limit inflammatory damage of tissues. Future statistical verification of well-designed epidemiological studies is needed to determine correlation of circulating miR-146a deficiency and severe COVID-19 clinical state. Moreover, since miR activity and

function could be modified in patients by pharmacological modulation, investigations should aim also at the possibility of correcting miR-146 deficiency in order to improve host antiviral response in diabetes/obesity and hypertension patients. Noteworthy, recent studies revealed that therapeutic effect of glucocorticoids, drugs which are used in severe COVID-19 treatment, is mediated via miR-146a [29], as well as that exogenous administration of miR-146a to human lung cells augments the effects of these drugs [30]. Having this in mind, it seems that miR-146a could have an impact on therapeutic regime of severe COVID-19 patients by enhancing efficacy of glucocorticoid medications.

Sources of support

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110448.

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