SARS-CoV-2 Interaction with Human DNA Methyl Transferase 1: A Potential Risk for Increasing the Incidence of Later Chronic Diseases in the Survived Patients

Abstract
Currently, the COVID-19 pandemic is the most discussed subject in medical researches worldwide. As the knowledge is expanded about the disease, more hypotheses become created. A recent study on the viral protein interaction map revealed that SARS-CoV-2 open reading frame 8 (ORF8) interacts with human DNA methyl transferase1 (DNMT1), an active epigenetic agent in DNA methylation. Moreover, DNMT1 is a contributor to a variety of chronic diseases which could cause some epigenetic dysregulation in infected cells, especially leukocytes, pancreatic beta, and endothelial cells. Regarding the fact that epigenetic alterations have a partial, but not completely reversible phenomena, it raises the question that if this interaction may cause long-term complications such as diabetes, atherosclerosis, cancer, and autoimmune diseases. Accordingly, long follow-up studies on the recovered patients from COVID-19 are recommended.

Keywords: Chronic diseases, COVID-19, DNA Methyl Transferase, epigenetics, SARS-CoV-2

Introduction
SARS-CoV-2 is a novel and sophisticated member of coronaviridae which has currently become the greatest concern of health care systems worldwide. Since late 2019, when China reported the first cases of the disease as "pneumonia of unknown cause", researchers from almost all countries are trying to find out more aspects of the disease. Recent studies on the viral protein-protein interactions (PPI) have revealed at least 332 protein interactions that each potentiates to elaborate the pathophysiology of COVID-19 and pose more complications in the way of the discovery of the appropriate treatment. Among all these interactions, the interaction of viral open reading frame 8 (ORF8) with human DNA methyl transferase 1 (DNMT1) is a special PPI that draws the attention toward the possibility of long-term effects of COVID-19, even in patients recovered from the disease. DNMT1 is a human enzyme acting as an epigenetic agent that physiologically maintains the normal DNA methylation pattern and in mitosis cooperates with the replication machine of DNA to maintain the same epigenetic pattern in the daughter cells. Recent researches indicated that in pathologic states such as diabetes, atherosclerosis, and cancer abnormal DNMT1 expression and function may act as one of the key contributors to such diseases.

This review has been written to raise the hypothesis that SARS-CoV-2 interaction with human DNMT1 may increase the potential risk of chronic disease incidence in the later years of life among the survived patients.

DNMT1 and COVID-19, the possible interactions
Chen et al. presented that certain single nucleotide polymorphisms (SNPs) of DNMT1 are associated with hypermethylated phosphatase receptor type beta (PTPRD) gene and further downregulation of insulin receptors. In another study, they reported that the blood glucose level decreases through inhibiting DNMT1 by aurintricabocylic acid in type 2 diabetes mellitus mice. Chakravarthy et al. regenerated the insulin-producing pancreatic β cells from α cells by inhibiting DNMT1 and Aristaless-related homeobox (Arx) in mice. Hou et al. in their study on the latent autoimmune diabetes of
adults (LADA) patients provided information about the hypermethylation of fork head box P3 (FOXP3) gene by a group of agents including DNMT1 in regulatory CD4 + T cells. On the other side, T-cell global hypomethylation is another epigenetic dysregulation in leukocytes which was reported in systemic lupus erythematosus caused through inhibition of DNMT1 by overexpression of a protein phosphatase in Sunahori et al.\textsuperscript{[10]} study. In the field of atherosclerosis, DNMT1 is more studied and is a subject of interest as a potential drug target for the prevention of cardiovascular disorders (CVD). Researches revealed that hypermethylated DNA regions coding for enzymes such as endothelial nitric oxide synthase (eNOS) in endothelial cells are associated with the overexpression of DNMT1.\textsuperscript{[4]} Moreover, hypermethylation of some DNA regions of macrophages that are responsible for classic activation of macrophages to proinflammatory M1 phenotype, the main cells contributing to plaque formation, are also associated with the overexpression of DNMT1.\textsuperscript{[11]} Furthermore, Zhou et al.\textsuperscript{[12]} reported that endothelial cells exposed to oscillatory shear flow, as a risk factor of endothelial dysfunction and atherosclerosis, express more DNMT1 which leads us to the understanding of the great role of DNMT1 in the process of atherosclerosis. Moreover, insulin receptor dysfunction is also a major player in endothelial dysfunction. Meanwhile, the overexpression of DNMT1 in diabetic status contributes to insulin receptor dysfunction and further insulin resistance in endothelium which leads to atherosclerosis.\textsuperscript{[4]} The most studied aspect of DNMT1 is in the field of oncology in which epigenetics has a considerable effect on tumorigenesis through hypermethylation of tumor suppressor regions and hypomethylation of protooncogene areas of the genome. Although the epigenetic hallmark of cancer cells is the global hypomethylation of the genome, the overexpression of DNMTs, particularly DNMT1, in myelodysplastic syndromes\textsuperscript{[13]} and consequent hypermethylation of tumor suppressor genes lead to consider DNMTs inhibitors such as azacitidine in anticancer treatments.\textsuperscript{[14]}

As epigenetic dysregulations are partially reversible after removing the epigenetic factors,\textsuperscript{[15]} it could be deduced that infection with SARS-CoV-2 may cause or accelerate the incidence of later chronic diseases, particularly, diabetes and atherosclerosis in recovered patients. Moreover, the course of underlying diseases may worsen in diabetic and CVD patients during and after the infection with SARS-CoV-2. Moreover, a 12-year follow-up study on patients recovered from SARS-CoV reported a greater rate of hospitalization and altered lipid metabolism in the recovered patients comparing to the control group. Although the authors concluded that using high doses of corticosteroids was the possible cause of later metabolic diseases in the recovered patients, the role of SARS-CoV infection as the underlying cause for these metabolic malfunctions is not ignorable.\textsuperscript{[16]} Moreover, the recent studies on COVID-19 patients have revealed some alterations in the plasma metabolic and lipidomic profiles which are mainly caused by infection-induced liver dysfunction. The authors indicated that SARS-CoV-2 changes the cellular metabolic pathways for viral replication; in other words, the virus “hijacks the cellular metabolism”. The considerable point is that they reported that patients presented liver dysfunction and altered serum metabolic factors even after recovering from the disease.\textsuperscript{[17]} Figure 1

**Conclusion**

Altogether, COVID-19 may cause or accelerate the occurrence of diabetes, atherosclerosis, cancer, and even autoimmune diseases through interaction with DNMT1 function and consequent epigenetic changes [Figure 1]. Moreover, this interaction in the patients with such underlying conditions may even worsen the course of their
disease during and after the infection with SARS-CoV-2. Accordingly, follow-up studies on recovered patients of COVID-19 are highly recommended to assess this possibility.

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Conflicts of interest
There are no conflicts of interest.

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