Effect of DNA methylation on impaired Interferon type I signaling as a strategy to escape of SARS-CoV-2 from innate immune response: a hypothesis

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Dear Editor,

Epigenetic changes play an important role in the immunological response against viruses. In recent years, DNA methylation as an epigenetic mechanism has attracted more attention as a disease biomarker. DNA methylation regulates gene expression in two ways: by recruiting proteins involved in gene repression and by inhibiting the binding of transcription factors to DNA (1). It is interesting to know that many studies have shown that epigenetics regulates interferon (IFN) production as well (2). On the other hand, it has been determined that viral infections can employ an epigenetic mechanism to escape from the innate immune system (3). Type I IFNs (IFN-I) play a key role for host defence against viruses (4). Recent articles described how the SARS-CoV-2 genome encodes accessory proteins, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c and ORF10, which may contribute to immune evasion (5-7). In this regard, it has been determined that accessory proteins ORF3b, ORF6, ORF7a and ORF8 have been shown to be important IFN-I antagonists which in turn lead to disruption of the host's immune response (8). Li et al. also reported that the overexpression of ORF10 significantly inhibited the expression of IFN-I genes and interferon-stimulated genes by SARS-CoV-2-infected HeLa cells in vitro (7). On the other hand, Gao et al. showed that single-CpG-nucleotide methylation is an essential mechanism that controls IFN-I induction and antiviral immunity in both humans and mice. They showed that single-nucleotide methylation can disrupt the recruitment of interferon regulatory transcription factor 3 (IRF3) to the IFN-beta promoter (9). Our hypothesis is that the activity of accessory proteins encoded by SARS-CoV-2 may cause promoter methylation of IFN-I, which in turn results in suppressing the IFN-I response against SARS-CoV-2.

In summary, our study provides a new insight into whether accessory proteins encoded by SARS-CoV-2 can affect IFN-I signaling via DNA methylation. However, further study is necessary to clarify the role of DNA methylation in the regulation of IFN-I signaling in SARS-CoV-2 infection.

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