Letters

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The Relevance of Epigenetics in the SARS-CoV-2 Infection and COVID-19 Disease

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Introduction

Almost 45% of the human genome is comprised in transposable elements, including endogenous retroviruses (ERVs). (Hurst and Magiorkinis, 2017). Although this seems to be limited to particular tissues and times, also in normal physiology, there is a real need for human endogenous retroviruses (HERV) expression (Manghera et al, 2016). HERVs ERVs belong to a number of distinct families that integrated independently during evolution (Tristem, 2000).

HERVs have the common provirus structure of coding open reading frames (ORFs) flanked by two long-terminal repeats (LTRs). LTRs are an important site for epigenetic modifications to control HERV and human gene expression. During the course of evolution and because of host defense mechanisms, most of the sequences contain INDELs or have been reduced to single LTRs by recombination (Hurst and Magiorkinis, 2017).

LTRs function as promoters both in sense and antisense orientations and can alter the expression of host genes (Dunn et al, 2006). These repeats have strong RNA Polymerase II regulatory sequences and can bind nuclear transcription factors (Thompson et al, 2016). More recently, it has been shown that LTRs are responsive to pro-inflammatory cytokines (Laurent et al, 2013). They have a pivotal role as controller of pluripotency and malignancy processes, suggesting that they regulates the expression of long-non-coding RNAs in addition to protein-coding genes, and are important sites for epigenetic modifications too. Epigenetic regulation includes the modification of both DNA and histones around which DNA is wound to create chromatin (Brookes and Shi, 2014).

These mechanisms keep often HERVs silenced, but they also could reserve unexplored functions. While histone deacetylation alone is not responsible for HERV repression, more findings underlie the importance of other factors, particularly CpG methylation, in silencing HERVs (Laska et al, 2002). The methylation of CpGs is carried out by DNMTs, with DNMT1 being the maintenance methyltransferase which is important for fidelity of methylation during DNA replication.

A microarray study analysing HERV families throughout the genome found that HERVs are heavily methylated in normal tissues. Further, the age of the HERVs correlates with their methylation status, with a loss of methylation appearing in older families (Szpakowski et al, 2009).

Krüppel associated box zinc finger proteins (KRAB-ZFP) are identified to contribute to histone methylation and heterochromatin formation early in the embryo (Thomas and Schneider, 2011).

The majority of human KRAB-ZFP binding sites were located within transposons, mainly retrotransposons including HERVs. The KRAB-ZFP bind to HERVs and silence them by burying them in heterochromatin (Imbeault at al, 2017).

Different groups of viruses will target both similar and distinct host pathways to manipulate the immune response and improve infection. Menachery et al. examined differential regulation of IFN-γ-dependent genes following infection with robust respiratory viruses, including coronaviruses. The results indicate a common mechanism utilized by H5N1-VN1203 and MERS-CoV to modulate antigen presentation and the host adaptive immune response. Particularly, epigenetic analysis suggested that DNA methylation, rather than histone modification plays a crucial role in MERS-CoV-mediated antagonism of antigen presentation gene expression; in contrast, H5N1-VN1203 likely utilizes a combination of epigenetic mechanisms to target antigen presentation (Menachery et al, 2018).

2. SARS-CoV-2 ad ACE2

SARS-CoV-2 belong to the Beta-coronavirus family, together with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) (with 80% and 50% homology, respectively). Compared to other RNA virus, it is characterized by the production of transcripts encoding unknown ORFs with fusion, deletion, and/or frameshift. Therefore, in addition to the canonical genomic and nine subgenomic RNAs, SARS-CoV-2, shows a highly complex transcriptome. 41 RNA modification sites, with most frequent motif, AAGAA, were identified on viral transcripts using direct RNA sequencing techniques. Modified RNAs have shorter poly(A) tails than unmodified RNAs, suggesting a link between the modification and the 3' tail (Kim et al, 2020).

The genome sequence of SARS-CoV-2 is 82% identical to SARS-CoV. Angiotensin converting enzyme II (ACE2) was identified as the cell entry receptor for the SARS-CoV-2 spike glyco-protein, allowing the viral infection of humans, similar to SARS-CoV.

ACE2, which is located on the X chromosome, is highly expressed on the surface of lung epithelium cells. It belongs to the angiotensin-converting enzyme family and catalyzes the cleavage of angiotensin II into the vasodilator angiotensin (Shyh et al, 2020).

3. Epigenetics in SARS-Cov-2

SARS-CoV-2 infection is mild in the majority of individuals but progresses into severe pneumonia in a small proportion of patients. Cancer has been identified as an individual risk factor for COVID-19 severity. Likewise, ACE2 is resulted aberrantly expressed in many tumors. A bioinformatic assay showed that ACE2 overexpression and hypomethylation are present in many types of cancer, pointing out the relevance of the epigenetic factors in modulating the SARS-CoV-2 infection and outcome (Chai et al, 2020).

More generally, it has been observed that subjects with compromised immune system result more susceptible to a severe outcome of the COVID-19 disease. For example, it has been suggested that patients with systemic lupus erythematous can develop more severe COVID-19 symptoms. Also in this case, hypomethylation and overexpression of ACE2 are candidate to be responsible of this worse response (Sawalha et al, 2020). Finally, the analysis of over 700 lung transcriptome samples of patients with comorbidities associated with severe COVID-19 showed high expression of ACE2 compared to controls. The network analysis correlated ACE2 overexpression in the human lung to genes related to histone modifications, reinforcing the idea that epigenetic mechanisms can have a role in the modulation of the disease (Pinto et al, 2020).

Adults over 65 years of age represent 80% of hospitalizations due to the COVID-19 disease showing a 23-fold higher risk of death respect to younger people. As above discussed, comorbidities worsen the outcome of the disease, but are not sufficient to explain the role of age as an independent risk factor. Epigenetic hallmarks of aging are known to influence health span in older adults, possibly via mechanisms regulating the immune

system (Salimi and Hamlyn, 2020). Therefore, the well-known aging-associated changes in the epigenome may be taken into consideration in the attempt to explain the age effect in the COVID-19 course (Mueller et al, 2020). Taken together, the increased severity observed in individuals with co-morbidities and in the elderly suggests for an initial defect in the anti-viral host defense mechanisms. The long-term boosting of innate immune responses, the so-called "trained immunity," induced by live vaccines has the potential to induce protection against further infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells (Netea et al, 2020).

Moreover, previous studies in our laboratories evidenced that the expression of IL-6, the main player in the so-called "cytokine storm" occurring in the most severe COVID-19 patients, is modulated by the methylation of its genes promoter (Dinicola et al., 2017). This observation suggests a further mechanism by which the epigenetics can crosstalk with the virus.

Although the studies on the SARS-CoV-2 infection and on the COVID-19 disease are still at the beginning, these observations make room for the possibility that epigenetic mechanisms can have a role both in the susceptibility to be infected and in the severity of the disease's outcome. In particular, the epigenetic control of the ACE2 gene expression seems a promising target for prevention and therapy in COVID-19.

The authors declare no conflict of interest.

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