SHORT REVIEW

THE RELATIONSHIP BETWEEN EXPRESSION OF TMPRSS2 AND ANGIOTENSIN II AND PATHOGENICITY OF PEOPLE CAUSED BY THE INFECTION OF SARS COV2

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ABSTRACT

The world is currently in an open battle with an invisible virus of high gravity over the dynamics of life. This study is focused on the description of the structure of SARS CoV2 and on the receptors which play an intermediary role in the viral entry mechanism: TMPRSS2 which activates the ACE2 in order to facilitate the penetration of SARS CoV2 into the cell. The expression of genes encoding transmembrane receptors and its relationship to epigenetic markers including methylation was investigated. The impact of these epigenetic factors on the immune system suggest that the variability of SARS CoV2 is mainly due to environmental, nutritional and age factors which involve forces on our genes via these epigenetic markers. This explains why the variety of the basic viral reproduction rate Ro from one area to another is associated with epigenetic factors including methylation. The level of expression of ACE2 and TMPRSS2 may directly influences the level of severity of infection due to SARS CoV2. Analysis of the studies allowed us to suggest therapeutic targets that may participate in blocking viral spread via the development of specific and pharmacological DNAMT: DNA methyl transferases and may reduce the expression of genes allowing viral penetration and DNAMTs that strongly inhibit SARS CoV2 replication upon viral penetration. It is also suggested that androgen inhibitors represent an effective treatment against SARS CoV2.

Keywords: *SARS CoV2, ACE2, TMPRSS2, angiotensin II, methylation*

1. INTRODUCTION

At the end of 2019, the world witnessed the birth of a new virus in China in Whoan that could have a great impact on the dynamics of normal life activities. Then, it was declared by the World Health Organization (WHO) as a major biological risk can disrupt the health and economic systems worldwide.

The virus belongs to the beta-coronavirus family which requires transmembrane intermediates expressed by angiotensin II converting enzymes ACE2 and the transmembrane serine protease. The entry of SARS COV2 requires the presence of transmembrane ACE2 proteins that are activated by other proteins called TMPRSS2 that are most abundant in the reproductive tissue and less expressed in lung [1].

TMPRSS2 facilitates viral entry into the intracellular environment and the manifestations associated with this entry are reflected in fever, pain in the digestive system, inflammation and acute respiratory syndrome [2]. The knowledge of the structure of SARS CoV2 allows us to better understand the mechanisms of the pathogenicity of this virus.

Generally, the expression of these proteins is different and can vary from one person to another and from one region to another, because of the interactions between the environment and the epigenome reflected by epigenetic markers in particular methylation, acythilation and micro RNA. In this review, we focused on the impact of methylation on gene expression. In fact, methylation reduces the expression of genes which code for factors involved in the process of viral entry into the cell, it also reduces the expression of genes encoding factors which participate in the solidification of our immune system as interleukins and interferents [3]. These epigenetic markers depend on the environment, nutrition and lifestyle of the individual [4] which explains the variability of the viral reproduction rate R0 from one zone to another.

1. Structure and phylogenetic of SARS CoV2

Understanding the structure of SARS CoV2 is very important in determining the viral mode of action and the mechanisms of spread of SARS CoV2, how the virus enters the host cell and also the factors promoting the mechanism of infection.
At the genomic scale, coronaviruses have the largest genomes (26.4 to 31.7 kb) among all known RNA viruses, with G + C contents varying from 32% to 43% [5]. A positive sense single-stranded RNA associated with a nucleoprotein in a capsid is the support of studies aimed at clarifying the structure of SARS CoV2. The structure is presented by projections of cube-shaped glycoproteins, dot glycoproteins, M Nucleocapsid and envelope [5,6].

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An Sg RNA that codes for structural and accessory proteins contains 14 open reading frames encoding 27 structural and non-structural proteins [5-7], this reading frame fills the ORF1 and ORF2 genes of the 5 'terminal region which encode 15 proteins necessary for viral replication [7]. To trigger this replication, there is an ORF1a and ORF1b reading frame shift at which the pp1a and pp1ab polypeptides contribute to the formation of the replicase - transcriptase complex which plays a role in the regulation of viral replication. While the ORF 10 and ORF 11 genes on a third of the SARS CoV genome near the 3-end code for structural proteins [5].

The cryoelectron microscopic structure of the trimer of the ecto domain of SARS-CoV-2 S, demonstrates spontaneous opening of the receptor binding domain and provides a blueprint for the design of vaccine and inhibitors of viral entry [8]. Current research allows us to determine the mode of penetration of the virus from its structure. They show that the binding of the virus to the ACE2 receptor of the host cell is mediated by a furin cleavage site at the border between S1 and S2 [8]. The latter is treated during the biogenesis of SARS-CoV and CoVs linked to SARS via the binding of the S1 protein, which plays a key role in the stabilization of the state of pre-fusion of the S2 subunit anchored in the membrane which contains the fusion machinery [8], with the ACE2 cell receptor for the angiotensin converting enzyme and the priming of protein S2 by cellular protease [6]. Studies on the genome of SARS CoV2 show that there are 380 amino acid substitutions with mutations in the genes encoding the S proteins [7]. These open up a perspective for understanding the mechanism of action and propagation of this virus and its pathogenicity. On the other hand, mutations that affect the site of contact between the ACE2 receptor and glycoproteins make the affinity of SARS CoV2 to ACE2 receptors higher than other members of the same family [7].

2. The expression of TMPRSS2 serine proteases and angiotensin II converting enzyme proteins

At the genomic level and in the context of developing a transcription map for human chromosome 21 (HC21), Paoloni-Giacobino et al use exon trapping from pools of specific HC21 cosmids this study is characterized by the revelation a new gene called TMPRSS2 which encodes a multimeric protein with a serine protease domain. TMPRSS2 (transmembrane protease, serine 2) is a member of transmembrane serine proteases type II, a family of 17 serine proteases characterized by a short cytoplasmic N-terminal domain, a single transmembrane domain and an extracellular C-terminal domain containing the serine domain protease [9].To better characterize the structure of these receptors, they used 3.8 kb TMPRSS2 mRNA via RT-PCR technique to obtain a full-length cDNA encoding a predicted 492 amino acid protein that contains the following domains: a serine protease domain (aa 255-492) of the S1 family which acts as a mediator, inheriting specific between the environment and the cell followed by a cysteine-rich domain of the Scavenger receptor (SRDR, aa 149-242) of the group A; a class A LDL receptor domain (LDLRA, aa 113-148) forms a binding site for calcium; a predicted transmembrane domain (aa 84-106) figure 1 [10-11].

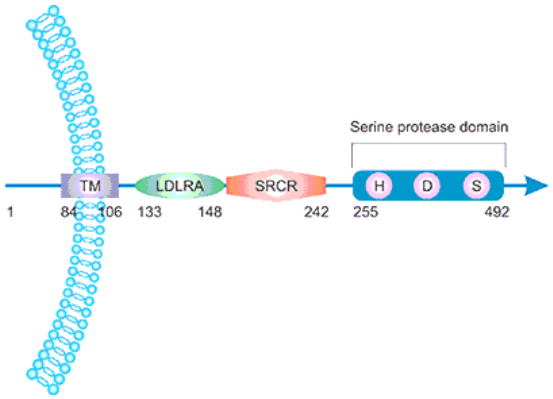

Figure 1: Structure of transmembrane serine proteins.

The relationship between expression of TMPRSS2 transmembrane receptors and the intensity of the immune response induced by SARS CoV2 infection has been well established. According to a study done by Shabir Ossmane's team as part of specifying the mode of viral entry: healthy wild-type mice infected with SARS-CoV develop acute pneumonia and show up to body weight loss to 15%. However, TMPRSS2 knockout -/- mice infected with Synthetic Aperture Radar-CoV do not develop pneumonia or experience any loss in body weight and viral replication is much lower in the lungs of these mice. These results confirm the findings of other study which confirms that the transient expression of proteases in MDCK cells allowed multicycle replication of influenza viruses in these cells in the absence of exogenous trypsin [12].

The TMPRSS2 gene is localized according to bioinformatic studies on chromosome 21: 43000000 and contains relatively 43.6 Kb [13]. Expression of TMPRSS2 has obvious tissue specificity, generally human TMPRSS2 is a type II transmembrane serine protease regulated by androgens which are mainly expressed in the prostate, with a relatively lower level of expression in the lungs, colon, liver, kidneys and pancreas [14]. This expression of TMPRSS2 is regulated by androgens at an exact androgen binding sequence, which is an element of androgen response, the latter is located next to two binding sites for the pioneer factor GATA2 [9]. A single nucleotide polymorphism (rs8134378) in this

androgen response element reduces binding and transactivation by the androgen receptor so it participates in the downregulation of TMPRSS2 expression [9].

The impact of TMPRSS2 on the aggressive intensity of SARS CoV2 is associated with the expression of angiotensin converting enzyme ACE2 receptors on the host cell surface [8].

As part of the identification of the expression level of the ACE2 gene, a study was carried out in this direction using a GTEx RNA-Seq gene expression profiling dataset (RSEM normalized) for 31 normal human tissue from the UCSC Xena project. The expression of ACE2 is linked to elements that promote the production of factors responsible for inflammation during the immune response including T cells CD8 +, the response to interferon, B cells and natural killer cells (NK) reveals the distribution of variation in expression of ACE 2 [8].

In the lungs, colon, liver, bladder and adrenal gland, ACE2 showed moderate levels of expression. studies show that ACE2 proteins have relatively high expression levels in the duodenum, small intestine, gallbladder, kidneys, testes, seminal vesicle, colon, rectum, and adrenal gland. They also showed that the gastrointestinal tract (duodenum, small intestine, colon and rectum), kidneys, gallbladder, and male tissues (testes and seminal vesicle) exhibited high levels of gene expression and the ACE2 protein. This suggests that the infection caused by SARS CoV2 may have impacts on other organs (lungs, digestive system) and functions such as reproduction [15].

According to data collected from the developed work, it is suggested that the relationship between TMPRSS2 and ACE2 may have influences on the degree of viral pathogenicity of SARS COV2. More ACE2 gene expression and TMPRSS2 longer increases the risk of SARS-associated COV2 intensity is high.

3. The variation in the degree of pathogenicity of people caused by the infection of SARS CoV2

Austin Nguyen and his colleagues show that there are differences in DNA that may influence the ability to fight SARS-CoV-2 infection. The SARS CoV2 infection is accompanied by an alarm system that identifies viral invaders and instructs the immune system to send cytotoxic T cells to destroy the infected cells, which slows down infection. However, not all alarm systems are created equal. Humans have different versions of each gene "alleles" some of which are more susceptible than others to different viruses or pathogens. This explains the asymptomatic cases. The origin of this genomic variation which may have influences on SARS CoV2 manifestations and genomic expression remains to be elucidated.

The interactions between our gene and the environment are determined by several studies. In the early 1940s, a new science to study the mechanisms by which the genotype generates the phenotype called epigenetics was proposed by geneticist Conrad Waddington. This new science is, as its name suggests, the heir to the theory of epigenesis of the progressive construction of organisms during embryonic development [16]. This discipline has focused on the activity of the gene which can be transmitted to the son without involving mutations via the intervention of the mechanisms of DNA methylation, a modification of histones, a remodeling of chromatin and an inhibition of genes by non-coding RNA [17].
Current research shows that there are epigenetic traits established during development, and/or acquired under the influence of nutritional, ecosystem, or other environmental factors that can impact the interactions between genes and the environment, which confirms the close relationship between these genes and our ecosystem [17]. The cell constantly receives all kinds of signals informing it about its environment, so that it specializes during development, or adjusts its activity to the situation. These signals, including those linked to our behavior (diet, smoking, stress, etc.), can lead to changes in the expression of our genes, without affecting their sequence. Multiple environmental factors such as diet, exposure to xenobiotics, climate, microbial exposure and / or stress may influence the development of the host's immune system and mucosal barriers very early on, in particular via modifications epigenetics [4]. It is suggested that these epigenetic markers may influence the degree of gene expression of TMPRSS2 and ACE2 (Figures; 2) as they have the potential to influence the quality of immune response from one area to another and from one person to another.

The most common epigenetic marker in the literature is methylation, which is a common modification that decorates the majority of cytosines at the level of promoters and enhancers of inactive genes, repeating elements and in transcribed gene bodies. Its presence at the promoter level is dynamically linked to gene activity, which suggests that it could directly influence gene expression patterns and cell identity [18]. On the other hand, the degree of methylation explains this variety of spread of SARS CoV2 from one person to another according to the behavior of the patient which can have consequences on the level of plasma cytokines and the mediators of inflammation caused by viral infections. In these subjects via changes in overall and gene-specific DNA methylation patterns potentially associated with peripheral immune deregulation [19]

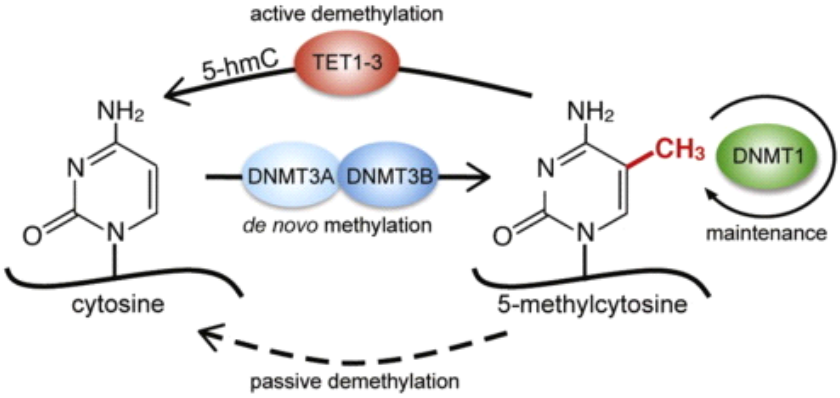

Figure2: Mechanism of DNA methylation [18]

Methylation prevents the binding of transcription factors which reduces the ability of the gene to express itself normally [20]. This aspect has two sides, one negative, reflected in the impact on the expression of the gene containing essential functions for a good quality of life but also has therapeutic aspects for many diseases. From previous studies, it is suggested that methylation of the TMPRSS2 gene reduces the expression level of the receptor transmembrane protease which immediately reduces the activation rate of ACE2 and therefore prevents entry of SARS CoV2 into the host cell. The degree of methylation varies with environment, behavior and diet, and can be considered as one of the factors that explain the variety of the viral reproduction rate of SARS CoV2 R0 which is defined by the number of cases which describes the one of the characteristics of an epidemic. This is a relatively intuitive measure that can tell how many people on average will be infected by an infected person.

5. CONCLUSION

The expression of genes that encode proteins involved in SARS CoV2 infection including TMPRSS2 and ACE2 is a critical aspect in viral spread. On the other hand, the level of expression of these genes can be influenced by epigenetic marks which are linked to environmental, nutritional and age factors. This shows the variability in the intensity of SARS CoV2 between people and space. These epigenetic factors are defined as a two-way capital one translated by the reduction of the expression of the genes which code for factors involved in the immune response which increases the intensity of the infection associated with SARS CoV2, this strongly explains the increase in mortality among the elderly. The positive meaning of these epigenetic marks is to reduce the expression of genes causing viral entry into the cell including TMPRSS2 and ACE2 thus causing mild viral manifestations.

Analysis of the studies allowed us to suggest therapeutic targets that may participate in blocking viral spread via the development of specific and pharmacological DNAMT: DNA methyl transferases and may reduce the expression of genes allowing viral penetration and DNAMTs that strongly inhibit SARS CoV2 replication upon viral penetration. It is also suggested that androgen inhibitors represent an effective treatment against SARS CoV2. During viral infection, the expression of the ACE2 genes is remarkably reduced therefore the development of a pharmacological ACE2 with a higher affinity by supply to the ACE2 receptors. Other studies have shown that IL6 plays a major role in SARS CoV2 infection and leads to death when exceeded 163.4 pg/ml so anti IL6 antibodies may reduce death rates. However, anti S viral glycoprotein antibodies can prevent viral attachment to ACE2 receptors.

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