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Review Article

Is SARS-CoV- 2 Infection a Predictive Factor for Progression of Cervical Intraepithelial Neoplasia to Cervical Cancer? Hypothesis

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Abstract

Cervical Intraepithelial Neoplasia (CIN) is one of the most frequent pathologies in women, capable of inducing in situ cervical cancer according to the degree of CIN progression. The high association of these neoplasms with human papillomavirus (HPV) infection defines these neoplasms as an example of microbiologically induced neoplasms. In this regard, the association of SARS-CoV-2 with thyroid sarcoma and the presence of infection by this virus together with cervical neoplasm involving the expression of the MDM2 oncogene, autophagy, and VEGF signaling pathways have been reported. The current pandemic caused by SARS-CoV-2 infection, exposes the world population to be infected by this virus. The possibility that women affected by cervical neoplasms could be contaminated by a second virus is high. The aim of this article is to highlight the microenvironment of cervical tissue as a possible suitable medium for SARS-CoV-2 infection and to hypothesize the possible role of this in situ infection in the progression of CIN. CIN expresses various molecules that make this neoplasia susceptible to infection by SARS-CoV-2. Molecules such as TMPRSS2 (Transmembrane Protease Serine 2), Cathepsin-L, and the components of the renin-angiotensin system including ACE2 (receptor for SARS-CoV-2) would facilitate the entry of SARS-CoV-2 into the neoplastic tissue. This article examines the possibility that SARS-CoV-2 infection could accelerate the progression of CIN.

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is one of the most common diseases in women. This neoplasm is highly linked to human polyoma virus (HPV) infection, which is of high incidence [1,2]. Because we are living in the presence of a SARS-CoV-2 pandemic, the possibility of patients with CIN becoming infected with this virus is high. There are no reports associating these two viral infections and the effect that SARS-CoV-2 infection could have on the evolution of CIN. It has been reported that CIN has all the elements necessary for SARS-CoV-2 to invade the cervical neoplasia, such as the presence of the enzymes TMPRSS2 (transmembrane protease serine 2), cathepsin-L and all components of the renin-angiotensin system (RAS), including ACE2, the receptor for this virus [3-7]. As previously hypothesized, SARS-CoV-2 infection may be linked to the increased likelihood of inducing progression of CIN [8]. According to this hypothesis and because one of the mechanisms of damage production in SARS-CoV-2 infection is the excessive proinflammatory function of Angiotensin II (Ang II) [9], and that inflammatory activity is associated with the induction of cancers [10-12], it is reasonable to hypothesize that the proinflammatory process of Ang II induced by SARS-CoV-2 could be related to the induction of CIN progression. Therefore, the aim of this review was to analyze the possibility that SARS-CoV-2 cervix infection may influence the acceleration of CIN progression.

The Hypothesis/Theory

The present article aims to set the medical hypothesis of potential impact of SARS-CoV-2 infection on female genital tract status as well as its impact on progression of cervical epithelial neoplasia. The pathogenic mechanism of SARS-CoV-2 infection is still unclear; however, the role of RAS has been involved.

Overview of the Renin-Angiotensin System

The renin-angiotensin system (RAS) is a complex of hormones and enzymes, which play an important role in bloods pressure regulation and fluid and electrolyte homeostasis, through coordinated effects on the heart, blood vessels, and kidneys [13,14].

Angiotensin II (Ang II) is the primary effector of this system that can act either as a systemic hormone or as a locally produced factor in tissues. Cells of the renal juxtaglomerular apparatus synthesize an aspartic protease called renin [15], a very specific

enzyme, which acts on the angiotensinogen synthesized in the liver, thus catalyzing the first step in a biochemical cascade of enzymatic processes. By acting on the angiotensinogen, renin gives rise to the angiotensin I (Ang I), decapeptide, which is subsequently converted into the Ang II, octapeptide, through the action of the angiotensin I converting enzyme (ACE1), Cathepsin D and E and chymase [16].

Ang II exerts its physiological actions mainly through two different receptors: the angiotensin II receptors type 1 (AT1) and type 2 (AT2). Although Ang II binds with similar affinity at both receptors, most of the functions of Ang II are mediated by binding to the AT1 receptor [17]. Binding of Ang II to AT1 receptor activates a series of signaling cascades that lead to tissue remodeling, acute vasoconstriction, and water and salt reabsorption. While binding to the AT2 receptor is believed to have opposite effects, as it has been reported to inhibit and antagonize AT1 receptor-mediated functions [18].

In the year 2000, the angiotensin converting enzyme type 2 (ACE 2) was first reported, and since then, compensatory pathways of RAS have been described [19]. ACE-2 cleaves Ang I to generate Ang 1-9, which is then converted into the vasodilator peptide Ang 1-7 by the action of ACE -1 or other peptidases. More efficiently, ACE-2 also metabolizes directly to Ang II to form Ang 1-7. This heptapeptide has opposite properties to Ang II, promoting vasodilation and exerting anti-proliferative and anti-hypertrophic effects by acting through the Mas receptor (MasR) [20]. Some reports have also described the binding of Ang 1-7 to AT2 receptors [21]. In addition to the above components of RAS, Ang II is additionally metabolized to Ang III (Ang 2-8) by the action of aminopeptidase A, and then converted to Ang IV (Ang 3-8) by the action of aminopeptidase N. By direct action of dipeptidyl-aminopeptidase I-III, Ang II can be transformed in Ang 3-8 [22]. Ang II can also be converted into angiotensin A (Ang A) by the enzyme aspartate decarboxylase derived from mononuclear leukocytes, leading to the formation of Alamandine, which has been shown to bind to the Mas-related D-receptor coupled to G-protein (MrgD receptor) [23,24]. Ang A and Alamandine have antagonistic effects. The first induces vasoconstriction and cell proliferation, while the second triggers opposite effects. Alamandine can be generated both from Ang A and from Ang 1-7. This constitutes an additional axis that modulates the regulation of peripheral and central blood pressure and cardiovascular remodeling in the complex structure of the RAS (Figure 1) [23].

Cervical Intraepithelial Neoplasia and Cervical Cancer

Cervical intraepithelial neoplasia (CIN) is the most common pre-invasive lesion of the cervix. Atypical squamous changes occur in the transformation zone of the cervix with mild, moderate, or severe changes according to the depth (CIN1, CIN2, CIN3), these lesions can progress to cervical cancer [1]. Human papillomaviruses (HPV) are a group of more than 100 DNA viruses that infect human epithelial cells. Approximately 15 of these viruses can cause intraepithelial lesions and cervical cancer. Pre-invasive disease of the cervix has risk factors like cervical cancer [2]. HPV is a necessary but not the only factor for progression to invasive cancer. HPV infection can interact with the immune response and influence the progression of the neoplasm [25]. Therefore, CIN is initially asymptomatic, remits spontaneously or can progress to cervical cancer [1].

Cytokines are low molecular weight proteins which have a complex regulatory influence on inflammation and immunity. They have a role in development of immune and inflammatory response involving hematopoietic cells, lymphoid cell, and various pro-inflammatory and anti-inflammatory cells [26]. *In-situ* upregulation of cytokines in the cervical tissue plays an important role in the progression or in the remission of cervical neoplasia. These cytokines can generally be expressed in conjunction with other cytokines and their interaction can be linked to a result regarding the evolution of cervical neoplasia. Host factors are critical in regulating tumor growth by expressing different modulating factors including immune response [10]. In this regard, neoplastic tissue can produce chemokines that induce the infiltration of leukocytes, which can produce various types of cytokines that modulate the neoplasm progression [11,12]. In addition to inflammation, immunity and infections, cytokines have now expanded their domain to atherosclerosis and cancer [27]. Chronic inflammation is associated with cancers including cervical cancer. During the inflammation, the upregulation of cytokines and the presence of immune cells in cervical tissue modulate the incidence of inflammation and the progression or regression of cervical dysplasia [28]. The production of cytokines by cervical cells and by infiltrating leukocytes can be triggered by antigenic stimuli, including HPV infection. In this regard, significantly lower levels of IL-1α, IL-2, IL-4 and TNF-α are detected in cervical samples obtained from HPV infected patients with low-grade dysplasia when compared to samples obtained from high-grade dysplasia [29]. HPV can induce down-regulation on the expression of interferon and upregulation of IL10 and transforming growth factor (TGF-β1) to produce a local immunosuppressive environment, which, along with altered tumor surface antigens, forms an immunosuppressive network that inhibits the antitumor immune response [30]. Immunological *in situ* events can be reflected in the microenvironment, since high levels of IL-12p40, IL-10, TGF-β1, TNF-α and IL-1β have been found in cervicovaginal washing fluid from patients with cervical cancer infected by HPV [31].

In general, the production of cytokines in the cervical tissue during the malignant transformation can induce, suppress, or have both effects on the progression of the neoplasia (Figure 2). It will be discussed further, how alterations of cervical microenvironment by SARS-CoV-2 infection may have relevance in determining early progression to cervical cancer.

Role of Renin-Angiotensin-System in the Pathogenesis of SARS-Cov-2 Infection

The coronaviruses are a family of viruses capable of producing diseases in humans and animals affecting different systems

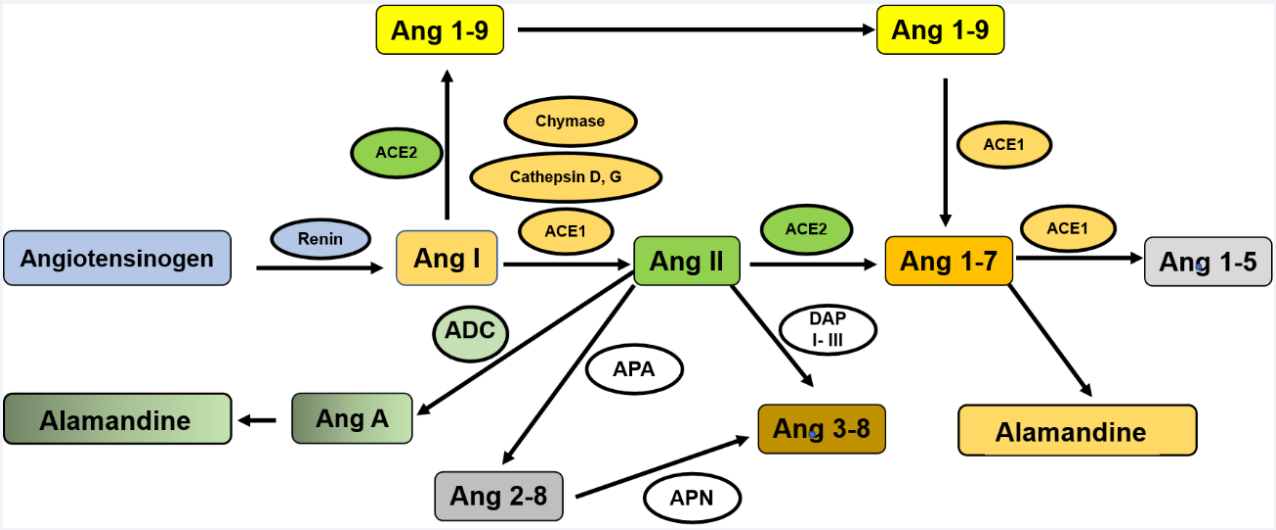

Figure 1 Renin angiotensin system. The angiotensinogen is transformed into Ang I by the action of the enzyme renin. Ang I is transformed into Ang II by the action of ACE 1, cathepsins D and G or by chymase. In addition to, Ang I can be converted into Ang 1-9 by ACE2 that under the action of ACE 1 converted into Ang 1-7. Ang II can also be converted into Ang 1-7 by ACE2 which under the action of ACE 1 can be transformed into Ang 1-5. Various aminopeptidases can act on Ang II to produce Ang 2-8 and Ang 3-8. ACE 1: angiotensin converting enzyme-1; ACE 2: angiotensin converting enzyme-2; DAP I-III: Dipeptidyl-aminopeptidase I-III; APA: aminopeptidase A; APN: aminopeptidase N; ADC: aspartate decarboxylase; Ang I: angiotensin-I; Ang II: angiotensin-II; Ang 1-5: angiotensin-1-5; Ang 1-7: angiotensin-1-7; Ang 1-9: angiotensin-1-9; Ang 2-8: angiotensin-2-8; Ang 3-8: angiotensin-3-8; Ang A: angiotensin A.

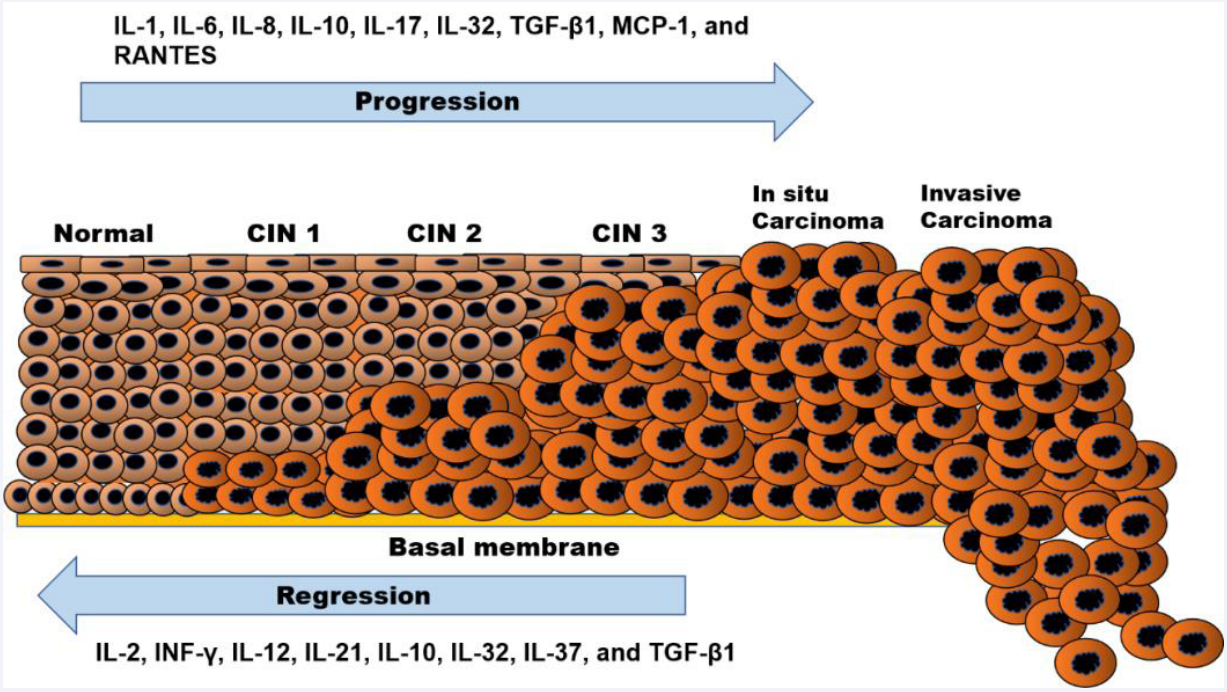

Figure 2 Effect of cytokines on the progression of cervical neoplasia. In general, cytokines have the effects of slowing or preventing the progression of the neoplasm, inducing its progression, or having a dual effect according to the circumstances. Cytokines that prevent progression of the malignancy include: IL-2, INF-γ, IL-12, IL-21, IL-10, IL-32, IL-37, and TGF-β1; those that induce progression: IL-1, IL-6, IL-8, IL-10, IL-17, IL-32, TGF-β1, MCP-1, and RANTES; and those that may have a dual effect: IL-10, IL-32, and TGF-β1.

of the body. A beta coronavirus is responsible for Covid-19 (coronavirus disease 2019), which has become a pandemic [9]. The coronavirus named SARS-CoV-2 has been responsible for this pandemic that began in Wuhan, China at the end of 2019 [32-34]. SARS-CoV-2 uses the renin-angiotensin system to enter, replicate, and produce damage in the body. Since ACE2 a member of the RAS represents a SARS-CoV-2 receptor, this enzyme plays an important role in the pathogenesis of this virus [35]. This viral infection causes a disease with multiorgan dysfunctions involving the respiratory, renal, cardiovascular, central nervous and gastrointestinal systems, among others.

Structurally SARS-CoV-2 is a spherical virus covered by a lipid envelope. Its genome formed by one RNA chain in positive direction, is covered by a nucleocapsid. Externally, this virus presents important proteins for its pathogenesis. The S protein (spikes) which is important for the binding to its ACE2 receptor, M protein which provides structural support, E protein necessary for the assembly of the virus and a hemagglutinin esterase [36,37]. The viral S protein binds to ACE2 after proteolytic modification of both. Prior to protein S/ ACE2 binding occurs, protein S is proteolytically modified by several proteases, especially TMPRSS2 (transmembrane protease serine 2), cathepsin L and cathepsin B, but other proteins as trypsin, factor X, elastase and furin, can also be involved [38-40]. The linkage of the modified S protein to ACE2 facilitates the virus entry into the cell and decreases ACE2 expression on the cell surface [41,42]. The virus attached to ACE2 is introduced into the cell by endocytosis [43]. Initially ACE2 plays a protective role to the deleterious effects of Ang II (inflammation, fibrosis, ROS, vasoconstriction, cancer) through transforming Ang II into Ang 1-7, which acting on its receptor Mas generates effects contrary to Ang II [20]. The cellular internalization of virus/ACE2 complex leaves an increase in the activity of Ang II and represents a stimulus for the expression of ADAM17 (disintegrin and metalloproteinase 17) on the cell surface. ADAM17 has a proteolytic action on ACE2 decreasing even more the expression of this molecule on cellular surface [44]. As a result of increased Ang II activity on its AT-1 receptor and through the nuclear translocation of NF-kB [45], Ang II induces the production of pro-inflammatory cytokines, oxidative stress (ROS), fibrosis, vasoconstriction, and increases activity of ADAM17 [46], among other deleterious effects. ADAM17 has a proteolytic action on cellular membrane pro-TNF-alpha, transforming it into the active form of the molecule, which when released into the extracellular medium, interacts with its receptor in an apocrine manner and induces the production of additional ADAM17 [47,48]. As a result of the increased activity of ADAM17 on ACE2 and the internalization of the virus/ACE2 complex, there is a drastic reduction of ACE2 on the cell surface and an increase of this molecule in the extracellular space [44]. Soluble ACE2 can interact with viral S protein, blocking the interaction of the virus with ACE2 still expressed on the cell surface. This process leads to an exaggerated function of Ang II by impaired conversion of Ang II into Ang 1–7 leading to inflammatory effects and drastic increase in the production of cytokines with the consequent deleterious effects mediated by RAS (Figure 3) [44]. In addition to the role of RAS in this inflammatory process, Sars-CoV-2 infection induces an imbalance in regulatory cell function (Th17/ Treg) leading to hyperactivity of immune cells with consequent overproduction of pro-inflammatory cytokines [49,50].

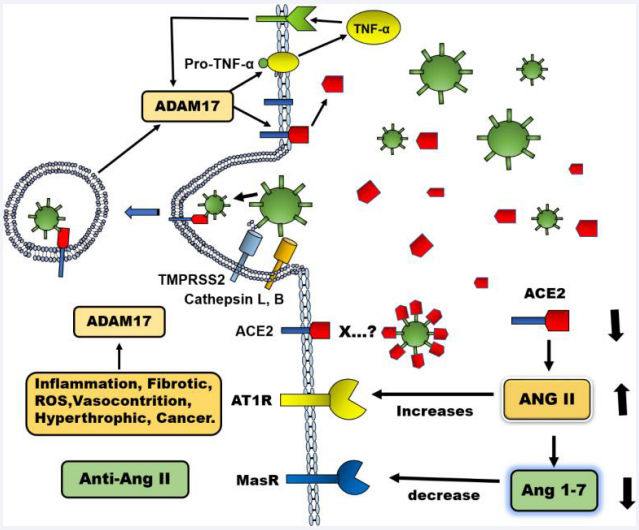

Figure 3 Renin angiotensin system in the pathogenesis of SARS-CoV-2 infection. The viral S protein binds to ACE2 after proteolytic modification by TMPRSS2 (transmembrane protease serine 2) and Cathepsin L. The linkage of the modified S protein to ACE2 facilitates the virus entry into the cell and decreases ACE2 expression on the cell surface. The cellular internalization of virus/ACE2 complex decreases ACE2 and increases Ang II activity and the expression of ADAM17 (disintegrin and metalloproteinase 17) on the cell surface, which by acting on ACE2, decreases even more the expression of this molecule on cellular surface. Increased Ang II activity on AT-1 receptor induces the production of pro-inflammatory cytokines, oxidative stress (ROS), fibrosis, vasoconstriction, and increases activity of ADAM17. ADAM17 also acts on membrane pro-TNF-alpha producing the active molecule that interacts with its receptor and induces the production of additional ADAM17. The activity of ADAM17 on ACE2 and the internalization of the virus/ACE2 complex reduce ACE2 on cell surface and increase this molecule in the extracellular space. This process induces increased Ang II activity by impaired conversion of Ang II into Ang 1–7 leading to drastic increase in the production of cytokines with the consequent deleterious effects.

SARS-CoV-2 Infection and Cervical Neoplasia

Previous studies reported the presence of SARS-Co-V-2 particles in thyroid sarcoma cells, raising the question of whether it was an incidental finding or whether the virus was the cause of neoplastic transformation. It was hypothesized that the virus-sarcoma relationship was synergistic, favoring both virus persistence and neoplastic proliferation [51]. The presence of SARS-Co-V-2 in sarcomatous tissue may be due to the expression of the MDM2 oncogene, capable of inhibiting the expression of p53, a molecule with antiviral activity. It is believed that SARS-Co-V-2 through papain-like-proteases stabilizes MDM2, creating a favorable environment for both the virus and tumor growth. Because of this, it has been proposed a treatment against COVID-19 by blocking MDM2 allowing the antiviral action of p53 [52-55]. These findings indicate the possible relationship of SARS-Co-V-2 with neoplastic cells.

The relationship of SARS-Co-V-2 with cervical neoplasia has also been previously documented. The role of autophagy

in both SARS-Co-V-2 infection and cervical neoplasia has been documented [56]. Autophagy has an important role pro-viral in SARS-CoV-2 replication and autophagy-blocking therapies have been proposed as anti-SARS-CoV-2 treatment [57]. A close association between autophagy and SARS-CoV-2 infection has been reported. In this regard, the phosphorylation induced by SARS-CoV-2 regulates several signaling pathways that include autophagy [58], and autophagy-related genes are essential for virus replication [59,60]. In relation to cervical neoplasia, it has been reported that autophagy controls the transition from epithelial to mesenchymal cells through the regulation of the intracellular domain of NOTCH1 [61].

Another factor linking SARS-Co-V-2 infection with cervical neoplasia is VEGF signaling pathways. The importance of VEGF in the pathogenesis of COVID-19 and the advantages of VEGF inhibition as a therapy for this infection has been reported [62-64]. VEGF regulates several angiogenesis signaling pathways controlling cervical cancer proliferation and apoptosis [65-67]. According with these data both autophagy and VEGF signaling should be common targets in the therapy of patients with cervical neoplasia infected with SARS-Co-V-2 [56].

Events Suggesting a Possible Role for SARS-Cov-2 Infection in the Progression of Cervical Neoplasia

There is evidence to indicate that COVID-19 is more severe in cancer patients [68], therefore special precautions need to be taken when these two entities are present [69-71]. Although neoplasms of the cervix are initially slow-growing and do not warrant emergency surgery treatment [69], the presence of COVID-19 in these patients could alter the biology of this neoplasm.

Neoplasms of the cervix can express molecules that make this tissue more susceptible to SARS-CoV-2 infection. The expression of ACE2 (receptor for SARS-CoV-2) has been reported in many cancerous tumors including cervix carcinoma [3,5]. In addition to ACE 2 expression, cervical neoplasm expresses transmembrane protease serine 2 (TMPRSS2) and cathepsin L (CATL) [6], important mediators in SARS-Cov-2 infection [35]. These *in vivo* findings are reflected in cell lines of cervical neoplasms. In this regard, Hela cells express both ACE2 and TMPRSS2 [7]. Cervical neoplasia also expresses all the components of RAS, a system that SARS- Cov-2 uses to induce pro-inflammatory processes [3]. The presence of these components in cervical neoplasia may be make this tissue prone to infection by the virus and to trigger in the pre-existing neoplasia, additional inflammatory and pro-neoplastic processes that may modify the biology of cervix neoplasia. In this regard, Ang II induced an increase in the production of vascular endothelial growth factor (VEGF) in cervical neoplasia, a finding accompanied by an increase in the expression of the AT1 receptor, suggesting an important role in the progression of the neoplasm by this peptide [4,11]. Therefore, entry of SARS-CoV- 2 into the cell through ACE2, induces decreased cellular expression of ACE2, accompanied by increase of Ang II and decrease of Ang 1-7. These effects induce increased Ang II pro-inflammatory, pro-fibrotic and pro-oncogenic effects, mediated through the nuclear factor kappaB (NF-kB) pathways. Since via ACE2/Ang(1–7)/MasR pathway Ang 1-7 decreases the effect of Ang II, decreased Ang 1-7 is related to increased expression and activity of Ang II [72]. There are evidence that Ang II may play an important role in inflammation, angiogenesis, proliferation, and cellular migration, all of them associated to carcinogenesis [3,73-75]. The expression of Ang II and its AT1 receptor related to the progression of cervical neoplasia by increasing proliferation and secretion of VEGF has been documented [4,76]. VEGF is an important cytokine in the progression of cervix neoplasia [11]. These effects of Ang II probably are mediated by the translocation of NF-kB to the nucleus. In this regard, increased expression of NF-kB and molecules such as RAS, EGFR, PGF, HER2 (NF-kB signaling molecules) involving in the progression of CIN III and cervical cancer have been reported [77], suggesting that NF-kB may be the pathway used by Ang II in cervix neoplasia. In the natural evolution of the intraepithelial neoplasia, initially the HPV decreases the expression of the NF-kB to be able to replicate itself, but as the neoplasia progresses, the expression of the NF-kB increases [77,78], suggesting an increase in its activity. Infection by another virus such as SARS-Cov-2 with the ability to induce activation of NF-kB may activate the inflammatory processes early and induce an earlier neoplastic progression. On the other hand, the capacity of ACE2 to regulate the biology of tumors has been previously reported. In this regard, angiogenesis by suppression of VEGFa/VEGFR2/ERK pathway and cellular migration of neoplasia can be suppressed by ACE2 [79]. The decrease of ACE2 by Sars-Cov-2 infection can reverse this process and abolish the suppressive effect of ACE2 on VEGF expression and migration of neoplastic cells, contributing to the progression of cervical intraepithelial neoplasia.

Considering the mentioned factors, SARS-CoV-2 infection in patients with cervical neoplasia could induce an accelerated state of neoplasia progression mediated by decrease of ACE2, increase of Ang II activity, decrease of Ang 1-7, and increase of angiogenesis and cellular proliferation of cells in the cervical uterine tissue (Figure 4).

To summarize, given the fact that the complete pathogenic mechanism of SARS-CoV-2 infection is still unclear while it has been found that the viral genetic material is detected in various anatomical sites of the host, it seems that there is much place available for studies examining whether SARS.CoV-2 genetic material can be detected in cervical cytology samples and correlated with the progression of cervical intraepithelial neoplasia. Therefore, it could verify if cervix may belong to the group of organs that are invaded and infected by SARS.CoV-2 and if there is any potential interaction with CIN.

Evaluation of the Hypothesis/Idea

The hypothesis presented in this article is related to the possible effect of SARS-CoV-2 infection on the progression of CIN. This hypothesis is based on the fact that the cervical epithelial cell (including the neoplastic cell) has the necessary elements for

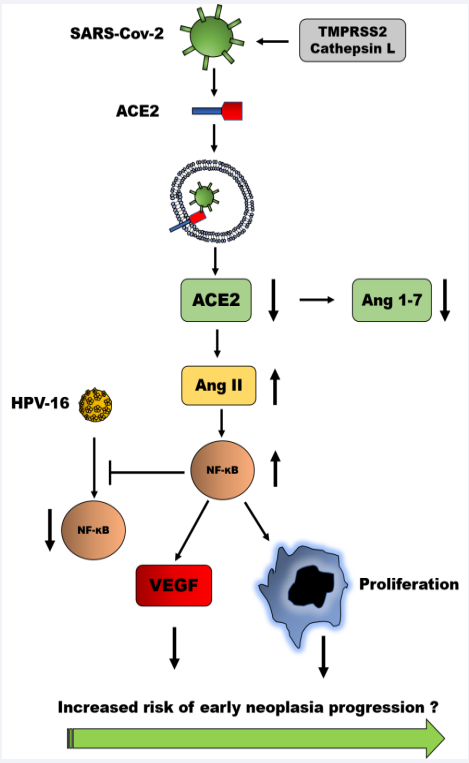

Figure 4 Possible effects of SARS-Cov-2 in cervical intraepithelial neoplasia. Several molecules associated with SARS-Cov-2 infection are expressed in cervical intraepithelial neoplasia, such as TMPRSS2 (transmembrane protease serine 2), Cathepsin L and the Renin-Angiotensin System including ACE2.These molecules make the cervical intraepithelial neoplasia more susceptible for SARS-Cov-2 infection. After binding of the virus to its ACE2 receptor, the complex is introduced into the cell by endocytosis, resulting in decreased expression of ACE2 on the cell surface, with decreased Ang 1-7, which acts as an antagonist to Ang II. This process induces increased Ang II expression and activity that can induce cell proliferation and angiogenesis through the production of vascular endothelial growth factor (VEGF). The increased translation of the nuclear factor kappa B (NF-kB) due to increased activity of Ang II, may block the inhibitory effect of human polyoma virus (HPV). Events that could accelerate the progression of cervical intraepithelial neoplasia.

the penetration and replication of SARS-CoV-2, including its ACE2 receptor, and various compounds of the RAS system. Once the virus invades the cervical cell, the pro-inflammatory action of Ang II may or may not be coupled with the action of HPV to accelerate or promote the onset of CIN. In reference to this, the Ang II AT1 receptor has been demonstrated in epithelial carcinoma cells [80]. These arguments are supported by the events previously described in this article. Against this hypothesis is the lack of evidence for the presence of SARS-CoV-2 antigens in uterine cervical tissue, but in view of the multi-organ activity of this virus it is expected to be found in the uterine cervical tissue of women infected with this virus. There are also no clinical trials to proof this hypothesis.

Several analyses to demonstrate this hypothesis are needed, these include:

1) Analysis of the presence of cervical intraepithelial neoplasia lesions comparing women who have been affected by SARS-CoV-2 with unaffected individuals.

2) Determining in uterine cervical tissue the presence of SARS-CoV-2 virus and associating it with the degree of CIN and Ang II overexpression.

3) Coculture SARS-CoV-2 with normal uterine cervix cells and with cervical neoplasia cell lines such as Hela and with primary cultures of neoplastic cells to determine the effect of this virus on cellular biology regarding to neoplasic events and determine the Ang II production.

4) Coculture SARS-CoV-2 and HPV with normal uterine cervix cells and with cervical neoplasia cell lines such as Hela and with primary cultures of neoplastic cells to determine the effect of those viruses on cellular biology regarding to neoplasic events and determine the Ang II production.

There are no empirical data on the possible role of SARS-CoV-2 infection and CIN progression. However, the presence of CIN 1 lesion has been reported in a patient with a previously healthy cervix who became infected with SARS-CoV-2, suggesting a role of this virus in the finding [81]. The potential presence of SARS-CoV-2 in the cervix has two important clinical implications. 1) The virus being in the tissues and having all the molecules that could facilitate its replication and induce pathophysiological alterations. 2) The possible interaction of SARS-CoV-2 with HPV could lead to alterations in the follow-up of preinvasive lesions and in treatment. Therefore, it would not be an exaggeration to hypothesize that patients with some degree of CIN and SARS-CoV-2 positives should be followed- up more regularly to optimize early detection of lesions.

CONCLUSION

The hypothetical assumption that SARS-CoV-2 infection could accelerate the progression of cervical intraepithelial neoplasia may be important for gynecologists. This possibility could have relevance in patients with CIN infected by SARS-CoV-2 and would require *in situ* studies looking for the neo-expression of cytokines associated with the progression of the neoplasia. Also, the general inflammatory state during the COVID-19 can be an influential factor on the cervical neoplasia together with the *in situ* effect of the virus. The proposed mechanism opens the possibility to use pharmacologically relevant compounds based on the blockade of Ang II synthesis or action as well as the use of Ang II antagonists as Ang 1-7 [77,81].

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