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Multi-receptor mechanism and retinoid signaling disorder in the pathogenesis of COVID-19, (*Discovery of STRA6 and GPCR as a Novel binding receptor of COVID-19*)

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Background

More than two years have passed since the pandemic and despite all the efforts of researchers, the pathogenesis of COVID-19 has not yet been resolved. Multisystem involvement, neuroendocrine involvement, and pathophysiological changes caused by SARS-CoV-2 in peripheral organs have been shown in many studies. However, the molecular mechanism of these pathophysiological changes caused by COVID-19 has not been elucidated. The frequent mutations of SARS-CoV-2 and the change in the interaction of the virus with host cells have further complicated the pathogenetic mechanism in COVID-19. Unfortunately, the mechanism determined at the beginning of the pandemic and based on the single receptor tropism of ACE2 was insufficient to explain the pathogenesis of COVID-19. It is known that SARS-CoV-2 causes retinoid signaling defects and chemosensory receptor disorders and exerts its pathogenic effects through these mechanisms. Multisystem involvement and different clinical presentations in COVID-19 suggest that virus-host interaction develops through multiple receptors and signaling pathways. The previous mechanism described via ACE2, based on single-receptor tropism, was insufficient to elucidate the pathogenesis of COVID-19 due to the absence of ACE2 receptors in most of the affected organs. In addition, there is no satisfactory explanation for the mechanism by which ACE2-free organs are affected in COVID-19. In this regard, we think that ACE2 is not a true binding receptor for the SARS-CoV-2 spike protein. With our recent molecular docking studies, STRA6 and its GPCRs were identified as new binding receptors of the SARS-CoV-2 spike protein. These studies have brought a multi-receptor mechanism to the pathogenesis of COVID-19. The multi-receptor mechanism clearly illuminates the complex pathogenesis of retinoid signaling disorder, systemic organ involvement, neuroendocrine involvement, loss of smell and taste, and many other peripheral symptoms and signs, which are considered an enigma in the pathogenesis of COVID-19. Therefore, we suggest retinoid signaling defect as the main pathogenetic disorder in COVID-19 and STRA6 and GPCRs as the main binding receptors of SARS-CoV-2 spike protein. This new mechanism also clarifies the changing symptoms and findings in COVID-19 with each new variant. In addition, these studies have revealed new signaling pathways and drug targets for the treatment and prophylaxis of COVID-19.

KEYWORDS COVID-19, SARS-CoV-2, Spike protein, Omicron, ACE2, STRA6, GPCR, GnRHR, Anosmia, Multi-receptor mechanism

Introduction

Unfortunately, despite the intense efforts of researchers since the beginning of the pandemic, the pathogenesis of COVID-19 has not been clearly resolved. Without solving the mystery here, the chances of developing vaccines and drugs that could be effective against COVID-19 will also be limited. Unfortunately, the pathogenetic mechanism based on cell and tissue tropism provided by ACE2 and TMPRSS2 in COVID-19 cannot clearly meet the systemic organ involvement, neuroendocrine involvement and peripheral organ involvement of COVID-19 (1). It is known that SARS-CoV-2, like many other viruses, enters host cells via receptor-mediated endocytosis and infects host cells in this way. It is also known that SARS-CoV-2 causes chemosensory dysfunction and exerts most of its systemic effects through this mechanism (2). Looking at the big picture, it should be seen that serious systemic effects of SARS-CoV-2 virus and causing damage to many organs are only possible if more than one receptor and signaling pathways organized in different tissues are affected.

Although ACE2, identified as the major binding receptor in COVID-19, is widely distributed in various human tissues and many of its determinants are well known, organs expressing ACE2 are not equally involved in the pathophysiology of COVID-19 (3). This indicates that other receptors and signaling pathways are involved in the pathogenesis mechanism of virus-host interaction resulting in tissue damage. Although ACE2 expression is frequently seen in the cardiovascular system, lungs, intestines and kidneys, ACE2 expression is absent or very low in the brain, endocrine organs and sensory organs, which are the organs most affected by severe disease (3,4). Moreover, it has been shown that there is no ACE2 expression in other endocrine and peripheral organs, especially in the brain and olfactory neurons, which are most affected by the disease picture in COVID-19 patients (4,5).

Neuroendocrine disorders, hormonal imbalance, olfactory dysfunction, anorexia and retinol deficiency are common symptoms and signs of COVID-19. However, the mechanism of development of these findings cannot be fully explained over ACE2 (3,5). Although there is limited ACE2 expression in some supporting cells in the olfactory epithelium, there is no ACE2 expression in olfactory neurons (5). This shows us that many neuroendocrine disorders, especially the olfactory disorder in COVID-19, develop through some receptors or signaling pathways other than ACE2. The intense expression of STRA6 and GPCR in these organs where there is little or no ACE2 expression suggests that the pathogenetic disorders in COVID-19 develop through these receptors and related signaling pathways. STRA6, GPCRs, and GnRHRs, a type of GPCR receptor, are largely expressed in the brain, endocrine organs, and olfactory neurons (6,7).

Blocking of STRA6 and GPCRs by spike protein with retinoid signaling disorder causes involvement in many other peripheral tissues, especially in neuroendocrine organs (8,9,10,11). Likewise, although the retinoid signaling mechanism and the signal pathways running through STRA6 and its GPCRs seem to be different mechanisms, the retinoid signaling mechanism and the signaling pathways directed by these two receptors are in mutual interaction (10,11). The intense positioning of retinoid signaling (10,11) and GPCRs in the limbic system, which is the center of emotional activity in the brain, and in the thalamus, hypothalamus and pituitary gland, which is the center of neuroendocrine regulation, tells us that the neuroendocrine involvement in COVID-19 shows the retinoid activity disorder in these regions and the spike protein of GPCRs. This suggests that it is due to blocking. SARS-CoV-2 spike protein may cause neuroendocrine, hormonal and metabolic disorders in COVID-19, especially smell and taste defect, by binding to neuroendocrine cells in the brain, olfactory neurons in nasal epithelium and peripheral endocrine tissues via STRA6 and GPCRs (10,11).

Signaling pathways governed by retinoid signaling and STRA6 and its GPCRs are intertwined and interacting mechanisms. Therefore, disruption in the synthesis and functions of STRA6 and GPCRs occurs in the retinoid signaling disorder in COVID-19 (9,10,11,12). The location of STRA6 here is particularly critical, as it facilitates the intracellular transfer of retinol and is at the crossroads of multiple signaling pathways. Likewise, blocking of STRA6 and GPCRs by spike protein may impair retinoid signaling by preventing retinol transfer into the cell (10,11). In COVID-19, the pathogenetic mechanism becomes chaotic due to the fact that many signaling pathways and receptors are affected and their interactions. As a result of these studies, the pathogenetic mechanism in COVID-19 has begun to be clarified with the location of the retinoid signaling defect, STRA6 and GPCRs in the pathogenesis of COVID-19.

ACE2 and multi-receptor mechanism in the pathogenesis of COVID-19

We think that ACE2 receptors do not have a primary role in the pathogenesis of COVID-19. ACE2 receptors alone are insufficient to explain the pathogenesis of COVID-19. STRA6 and GPCRs play the main role in the pathogenetic disorder caused by virus-host interaction in COVID-19 (10,11,21). Angiotensin converting enzyme 2 or ACE2 for short; It is an enzyme bound to the cell membrane on the outer surface of cells in the heart, lungs, arteries, kidneys and intestines (13). Angiotensin II (AngII), synthesized from Angiotensinogen I as a result of ACE2 activity, causes vasoconstriction by activating Angiotensin receptors (AT1 and AT2), one of the GPCR subtypes (14,15,16). Activated AT2 triggers cellular responses by binding to G q/11 and G i/o, respectively from G proteins, activation of phospholipase C and stimulation of protein kinase C via cytosolic Ca²⁺. Activated AT receptors also provide inhibition of adenylate cyclase and activation of some tyrosine kinases (17).

The effects of ACE2 are mediated by GPCRs (AT1 and AT2) (18,19). Blocking of ACE2 by the SARS-CoV-2 spike protein disrupts G-protein-dependent signaling cascades via AT1 and AT2 receptors, a type of GPCR. The disruption of cellular signaling pathways via AT2 and G proteins by the SARS-CoV-2 bound ACE2 complex still cannot fully explain the severe and systemic effects in COVID-19. Likewise, although AT2 is a G-protein-coupled receptor (20) and displays distinctive motifs and signature residues of G protein-coupled receptors, it fails to display most of the classical features of GPCR signaling (20,24,25).

Another virus-host interaction mechanism operating via ACE2 in COVID-19 is that biological parts of SARS-CoV-2 can activate AT2 receptors, causing AT2 to bind with ACE2 and disrupt the signaling cascades in this way (21,26,31). There is also an indirect mechanism that operates in this way between SARS-CoV-2, ACE2 and AT2. The third interaction mechanism, which operates through AT2, is the internalization of SARS-CoV-2 into the cell, which operates through GRK- β arrestin. Interestingly, the complex formed by AT2 and GRK- β arrest after SARS-CoV-2 binding activates the Gi2/Gi3-proteins, leading to the internalization of the virus-receptor complex into alveolar respiratory epithelial cells (22). As seen here, the internalization of SARS-CoV-2 into the host cell is provided by a mechanism mediated by the AT2 receptor, which is also in the GPCR structure.

Smell and taste disorders in COVID-19 develop with the blocking of STRA6 and GPCRs by the SARS-CoV-2 spike protein, as well as systemic organ damage, neuroendocrine disorders, and many peripheral signs and symptoms, as well as retinoid signaling defects (9,10, 11th). In addition, ACE2 receptors are very low or absent in the brain, endocrine organs and olfactory neurons, which are the tissues most affected in COVID-19, while their GPCRs have a very intense expression (23,24,25,29,30). In addition, the virus-host interaction that operates via ACE2 in the pathogenesis of COVID-19, the effects of ACE2 are mediated by GPCRs and G proteins. As can be understood from all these, the signaling mechanism operating via ACE2 in virus and host interaction is insufficient to explain the pathogenesis and multisystemic involvement of COVID-19 (23). In this regard, we think that ACE2 is not a true binding receptor for the SARS-CoV-2 spike protein. We propose STRA6 and its GPCRs as major binding receptors of the SARS-CoV-2 spike protein. In addition to ACE2, the identification of GPCR and STRA6 receptors as new binding receptors of spike protein has brought the multi-receptor mechanism to the pathogenesis of COVID-19. Multi-receptor mechanism with retinoid signaling defect, Type I IFN synthesis defect, which is seen as an enigma in the pathogenesis of COVID-19, provides a full explanation for excessive inflammatory cytokine discharge, immune dysregulation, multi-organ involvement, neuroendocrine involvement and peripheral organ involvement.

GPCRs and neuroendocrine disorders in the pathogenesis of COVID-19

G protein coupled receptors (GPCR) are various membrane receptors and are the largest superreceptor family of genome and signaling proteins (7,25). They also have the nomenclature of "seven transmembrane segments" (7TM) receptors, as they fold through the cell membrane seven times. GPCRs detect extracellular compounds and activate intracellular signal transduction pathways. They do this by binding to G proteins inside the cell (26). Ligands that activate GPCRs include light-sensitive compounds, fragrances, pheromones, hormones, and neurotransmitters. These receptors, which also play a role in many diseases, are the target of approximately 40% of drugs (27). GPCRs that bind to protein G i/o have a wide distribution pattern in the human body and are found in almost all organs and tissues (27,28). G i/o-linked GPCRs are especially high in the brain, hematopoietic system, immune system, lung, gastrointestinal system, endocrine organs, and reproductive system, while they are less common in pancreas, fat, and other soft tissues (7,28). It should not be overlooked that the distribution of GPCRs in tissues is parallel to the organ involvement in COVID-19.

More than 90% of GPCRs are expressed in the brain (29,30,49). They are activated by a wide variety of ligands, including light energy, lipids, sugars, peptides, and proteins (31,32,33) and carry information from the external environment into the cell to mediate relevant functional responses. When ligands bind to GPCRs, they trigger a series of biochemical reactions within the cell by conformational change. These intracellular reactions are involved in sensory functions such as smell, taste, and vision, as well as a wide variety of physiological processes such as secretion, neurotransmission, metabolism, cellular differentiation, inflammation, immune responses, neuronal excitability regulation, metabolism, reproduction, development, hormonal balance, and behavior. controls (34,35,36). G protein-coupled receptors are expressed in many cells in the body. The expression profile shows that GPCRs are expressed in multiple tissues and individual tissues can also express multiple GPCRs (46,49,50). The location of GPCRs as different receptor subunits in many tissues, the presence of different and multiple GPCRs in a single tissue, and their different functions may explain the different clinical signs and symptoms seen in COVID-19 between individuals.

G-protein coupled receptors play a role in many physiological processes. Sight, taste and smell senses, immune system regulation, autonomic nervous system regulation, endocrine and neuroendocrine system regulation, regulation of behavior and mood, perception of cell density, homeostasis, inflammation, tumor growth and metastasis are regulated by the activity of GPCRs (31,32). ,33). G i/o-linked GPCRs show intense activity within the nervous system. These receptors participate in complex brain functions such as memory, learning, and cognition by playing a role in neurite outgrowth, neurotransmitter release, and synaptic plasticity (34). We think that many other neuropsychiatric symptoms, especially the confused state of consciousness and memory problems, which is called brain fog in COVID19, develop largely due to the blocking of GPCRs in the brain by the spike protein.

To date, about 170 GPCRs have been found to be receptors for intercellular mediators such as hormones and neurotransmitters, and 367 genes have been recognized as GPCR-related genes in the human genome (37,38). Many hormone and neurotransmitter receptors are in the GPCR structure and are named differently in different tissues and cells. Although they interact with different naming and different mediators, all of these receptors act on G proteins. GnRHRs are also a subtype of GPCRs. It has been shown that G-protein coupled receptors are adequately expressed in the hypothalamus, pituitary, limbic system and olfactory region, as well as in the thyroid gland and lung (37,38). GPCRs have also been found to act as thyroxine receptors and are responsible for a variety of biological functions such as appetite regulation, cortisol level, olfaction and taste, as well as intracellular

transport of retinol (39,40,41). In this regard, we think that in COVID-19, mainly neurological disorders, endocrine disorders such as diabetes, hypothyroidism, adrenal insufficiency, and menstruation and reproductive disorders are caused by the loss of function of these receptors (GPCRs) due to retinoid signaling defect or their blockage by spike protein.

Chemosensory GPCRs (csGPCRs) are essential receptors for sensory signals perceived from outside the body as odor, taste, or pheromone (42). Peptides, lipids, neurotransmitters, and nucleotides are all examples of endogenous signals to which GPCRs respond (43). The primary function of GPCRs is the conversion of extracellular stimuli into intracellular signals (44). The main feature of GPCRs is that they interact with G proteins. GPCR receptors affect cellular signaling pathways through G proteins (45). The conformational change that occurs in GPCR with ligand binding leads to the activation of G proteins, allowing the signal to be transferred into the cell. Signaling pathways affected include enzymes such as adenylyl cyclase, phospholipase C and D, and ion channels (46). G protein-coupled receptors basically act through two main signaling pathways. These are cyclic adenosine monophosphate (cAMP) and phosphatidylinositol (IP3/DAG) signaling pathways (47). Under normal conditions, inhibitory G proteins characteristically inhibit adenylyl cyclase activity and lower the cAMP concentration (49).

In COVID-19, when the spike protein binds to GPCRs, it creates a conformational change in GPCRs and blocks the binding of GPCRs to inhibitory G proteins. In this way, the signaling pathways that operate through cAMP inhibition and kinase activation may be disrupted. Intracellular cAMP levels may increase with the inhibition of adenylyl cyclase inhibition and rapid induction of the cAMP/PKA pathway. Since GPCRs can bind to different isoforms of G proteins (Gs, Gq/11, Gi, G12/13) in different cells and tissues, spike protein may also affect a number of intracellular alternative signaling cascades (50). Influence of GPCRs on signaling pathways through different isoforms of G proteins in this way may cause different symptoms and findings in COVID-19. This may be the main mechanism underlying the presentation of COVID-19 with different signs and symptoms in a wide range of tissues and organs. The vast clinical presentations and residual diseases in COVID-19 have been the subject of curiosity and research for researchers since the beginning of the pandemic.

STRA6 receptors and retinoid signaling disorder in the pathogenesis of COVID-19

When STRA6 (Stimulated by retinoic acid 6) was first discovered, it was identified as a cell surface receptor for retinol-binding protein (51,52). However, it was later found to be a transmembrane retinol transporter and a cytokine signal transporter. STRA6 has also been described as the first member of a new protein class called cytokine signal transporter (51,52). A key to the retinoid signaling mechanism and many other cytokine pathways, STRA6 is present at high levels in a variety of tissues, including the choroid plexus, brain microvascular space, placenta, spleen, kidney, eye, placenta, and female reproductive system. Surprisingly, however, STRA6 is not found in liver tissue where retinol is primarily stored (51,53). STRA6 mediates cellular uptake of retinol by binding with the retinol-coupled RBP molecule to trigger the release and internalization of retinol, in addition to cholesterol uptake into human cells (53). It has been shown that both retinol and cholesterol decrease in COVID-19 infection (54,55,56,57).

STRA6 is at the center of a complex signaling network and plays a key role (58,59). After the retinol-RBP complex binds to STRA6, it activates the JAK/STAT pathway, enabling the activation of the STAT5 transcription factor. The retinol transporter function of STRA6 and its cytokine signaling receptor function are interdependent processes and interact with each other (59). While activation of STRA6 with JAK2 is required for retinol uptake, STRA6 signal can inhibit JAK2 signal through SOCS3 (60,61). While this interaction regulates the signaling pathways, it also manages the controlled uptake of retinol into the cell. SOCS3, the first protein classified as a cytokine signal suppressor, also played a role in this regulation. SOCS3 inhibits JAK2 activity by binding to JAK2 kinase (61,62). In this respect, STRA6 is also associated with some other cytokine signal suppressors, especially SOCS3. Considering all this, it is likely that STRA6 functions as a vitamin A receptor, transmembrane retinol transporter, and cytokine signal transporter as well as a cytokine signal suppressor. Blocking of STRA6 by spike protein in COVID-19 may disrupt the cytokine signal suppression function of STRA6 and SOCS3, leading to a signaling disorder that may lead to disruption of Type I interferon synthesis in the pathogenesis of COVID-19 (62).

STRA6 determines cell fate by integrating retinoid signaling with numerous signaling pathways such as p53, MAPK/Erk, PI3K/Akt, mTOR, Jak/STAT, Ca-Calmodulin, Wnt/catenin (9,10,65). It should not be overlooked that most of these pathways are related to transcription mediators such as STATs and NFkB, which are essential regulatory mediators for vital functions such as inflammatory cytokine release, apoptosis, cell cycle and cell survival. It has been found that excessive activity of the STAT pathway in COVID-19 is associated with severe clinical pictures (63). STRA6 expression and activity depend on retinoid activity (64). Likewise, adequate and balanced activity of STRA6 is required for normal retinoid activity. STRA6 activity and retinoid signaling activity interact with each other (64).

Retinoid signaling disorder is at the center of the pathogenesis of COVID-19 and causes severe systemic effects in COVID-19 (9). Excessive use of retinol in the synthesis of Type I interferon and suppression of inflammation in COVID-19 causes retinol depletion and retinoid signaling defect (9). In addition, the blocking of the retinol receptor and the STRA6 receptor, which is the transmembrane transporter of retinol, by the spike protein also disrupts the intracellular retinol transfer, leading to a decrease in endogenous retinoic acid levels and retinoid signaling disorder (9,19). As a result, disruption in many signaling pathways and immune system response in COVID-19, Type I interferon synthesis defect and an increase in inflammatory cytokine synthesis and release via the UPS/NFkB system occur (8,9,10).

Disruption of many cellular signaling pathways operating through STRA6 causes dramatic clinical manifestations in COVID-19. Activation of the MAPK/ERK2, AKT, c-MYC or PI3K/AKT pathway via RAR α leads to significant changes in cellular differentiation, proliferation and tumorigenesis (9,10,67). Signaling pathways working depending on RARA activity are highly active signaling cascades in many cells, especially in the nervous system and immune system (68). RAR α , a subtype of RARs, is localized in membrane lipid rafts, such as STRA6, and similarly activates cytoplasmic kinases after binding to the RA ligand, leading to the activation of various intracellular signaling pathways, including PI3K/Akt (68). Signaling pathways such as MAPK/Erk, Jak/STAT, RIG-I, mTOR, GluR1 and Ca-Calmodulin, which are dependent on STRA6 and RARA activity, are highly active signaling cascades in many cells, especially in the nervous system and immune system (69,70). Under normal conditions, GPCR signal inhibits mTORC1 through PKA phosphorylation (66,69). Blocking this signaling mechanism by spike protein in COVID-19 will impair mTOR inhibition via PKA, and cell growth, metabolism and autophagy governed by mTORC1 will also be impaired (71).

In COVID-19, genomic and nongenomic effects controlled by retinoic acids are particularly impaired due to retinoid signaling disorder (68). Activation of functional proteins and enzymes through protein kinase activity is provided by retinoid signaling (69,70). With the disruption of the retinoid signaling mechanism, the synthesis and activation of functional proteins and enzymes are disrupted and cellular functions are also impaired (69,70). If there is enough RA in the cell, kinase activity, protein phosphorylation and associated signaling pathways continue to operate (9,66). In COVID-19, kinase activity and protein phosphorylation are disrupted due to decreased endogenous RA levels and retinoid signaling disorder. When the kinase activity provided by retinoid activity is impaired, Type I IFN synthesis, which occurs through the phosphorylation of IFNs, is particularly impaired (9,10,54).

Type I interferon synthesis occurs through a mechanism in which the genomic and nongenomic activities of RAs are carried out together (9,54). While the phosphorylation of IFNs is provided by the nongenomic activity of RAs, the activation of genes responsible for Type I interferon synthesis via transcription factors is provided by the genomic activity of RAs (8,9). Another mechanism by which Type I interferon synthesis is disrupted in COVID-19 is that the viral proteins of SARS-CoV-2, NSP5, ORF6 and ORF8, block the displacement of STATs or inhibit the phosphorylation of mediator molecules, thereby inhibiting Type I IFN synthesis and JAK-STAT. occurs by disrupting the signaling (72). An imbalance in JAK-STAT signaling has been found to be associated with COVID-19 severity (73). Type I IFN strengthens cellular and humoral immune responses, working like a conductor in regulating the immune system in host defense. Type I IFN synthesis defect in COVID-19 is one of the most important pathophysiological disorders that aggravate the clinical picture together with inflammatory cytokine discharge and has been shown in many studies (8,9,84).

It was found that cAMP-dependent protein kinase (PKA) activity was rapidly up-regulated in NB4 cells treated with the retinol derivative ATRA. Phosphorylation of RARα by PKA via ATRA increases transactivation of RARα (67,68). Decreased RA levels impair kinase activity and phosphorylation of RARα by PKA (67,68,69). GluR1 is a presynaptic receptor and provides the transmission of the sense of smell via glutamate. GluR1 synthesis occurs with the nongenomic effect of RAs and RARα activity in the cytoplasmic compartment (68). Decreased endogenous RA levels cause disruption of RARα phosphorylation, disruption of GluR1 synthesis, and loss of sense of smell in COVID-19 (8,9). In addition to the decrease in the synthesis and activity of GluR1 and GPCRs in COVID-19, the blocking of GPCRs in olfactory neurons by the spike protein is also responsible for olfactory loss (11).

There is also a strong correlation between retinoid signaling and GPCRs. Like STRA6 receptors, GPCRs are synthesized depending on retinoic acids (74). Therefore, the retinoid signaling defect causes the synthesis defect of STRA6 and GPCRs as well as the disruption of signaling pathways controlled by STRA6 and GPCRs. With the disruption of signaling pathways related to STRA6 and GPCRs, serious disruptions occur in the cellular cycle, neuroendocrine system, apoptosis mechanism, immune system regulation and suppression of inflammation (75). In COVID-19, retinoid signaling defect specifically impairs neuronal conduction and neuronal plasticity (9,75). The different location of GPCRs in the brain, endocrine organs and peripheral tissues and their ability to bind to different G protein isoforms may cause organ-specific symptoms and signs of COVID-19 (76). Since the blockade of the STRA6 pathway in COVID-19 causes retinoid signaling defect, we think that disruption of this pathway may be responsible for severe systemic findings in COVID-19, and that the blocking of GPCRs may be responsible for the emergence of some neuroendocrine disorders and organ-specific signs and symptoms.

Intracellular internalization of SARS-CoV-2 and GPCRs in COVID-19

Although GPCRs are important receptors of signal-transmitting lipid mediators, they also played an important role in the internalization of SARS-CoV-2 into the cell via the adenosine-CFTR system (22). Viruses effectively use intracellular signaling pathways for replication and life cycle. Like most viruses, SARS-CoV-2 is taken up by endocytosis via membrane surface receptors to enter host cells (23). It is known that SARS-CoV-2 carries an outer lipid membrane and adheres to host cells with a lipoprotein spike protein embedded in this membrane. However, even if SARS-CoV-2 binds to the ACE2 receptor, it can enter host cells by indirect mechanisms including GPCRs (22,77).

Under physiological conditions, the adenosine-CFTR regulation system is critical for mucosal airway surface protection and regulation of the alveolar surface layer (78). However, in COVID-19, CFTR is also involved in the uptake of SARS-CoV-2 into the host cell together with GPCRs (22,77,78). It is also known that the ACE2-AT2 (GPCR) complex formed by the binding of SARS-CoV-2s to ACE2 is taken into respiratory alveolar epithelial cells by catalyzing the activation of Gi2/Gi3-proteins over GRK- β arrestin (22,79). Based on current findings, SARS-CoV-2 uses three distinct pathways via GPCR to enter host cells. The first of these is the internalization of the spike protein into the host cell via AC2 via AT2, and the other two pathways are provided by the mechanisms provided through the Adenosine-CFTR system and the AT2-GRK β arrestin system.

Although ACE2 appears to be the primary receptor for the entry of SARS-CoV-2 into the cell, it is clearly seen that the mechanism operates through the AT2 receptors in the GPCR structure. Recognition of intracellular viruses by the host immune system is provided by retinoic acid-inducible gene-I (RIG-I), which is the most important cytosolic viral RNA recognizer that initiates the congenital immune system response against cytosolic RNA viruses (80). Interestingly, RIG-I was initially identified as an orphan G-protein coupled receptor induced by retinoic acid and whose ligand is unknown, but later it was determined that viral triphosphate-RNA ends were ligands of RIG-I (81). It is clear that the activity of RIG-I, which is synthesized due to retinoic acid activity, will also decrease due to retinol depletion and retinoid signaling defect. Therefore, the retinoid signaling defect in COVID-19 also renders the RIG I pathway, which is one of the important pathways responsible for type I interferon synthesis, nonfunctional (82,83).

Omicron variant and multi-receptor mechanism

Each new mutation in SARS-CoV-2 causes conformational changes in the spike protein and changes the binding state of the SARS-CoV-2 spike protein to ACE2, STRA6 and GPCR receptors. The conformational change in the spike protein also causes a change in the receptor binding site of the spike protein, resulting in a change in the affinity of the spike protein to ACE2, STRA6 and GPCRs, and binding to these receptors with different strengths or impaired binding to these receptors. Since this affinity and binding change between the spike protein and the host cells also affects the cellular signaling pathways managed by the receptors, it causes a change in clinical signs and symptoms with each new variant in patients.

Omicron, the last variant of SARS-CoV-2 and now the dominant strain on the world, was found to bind to ACE2 receptors twice as strongly compared to previous variants (85). This increase in binding strength caused the virus to spread more quickly and spread the epidemic again. Despite this, severe clinical pictures have started to be seen less frequently with the Omicron variant (84,86). This situation

also shows that ACE2 does not play a leading role in the pathogenesis of COVID-19 and the aggravation of the clinical picture. With the new mutation, the increase in the binding power of the spike protein to ACE2 and the intense expression of ACE2 in the upper respiratory tract mucosa were effective in the increased colonization of Omicron in the respiratory tract and increased transmission (84,87).

Conclusion

The complex pathogenetic mechanism, multisystemic involvement, and different clinical presentations in COVID-19 make us think that the SARS-CoV-2 spike protein interacts with other receptors besides ACE2 in COVID-19. The pathophysiological changes caused by SARS-CoV-2 in the central nervous system and peripheral organs have been shown in many studies. However, the molecular mechanism of these pathophysiological disorders has not been elucidated. The frequent mutations of SARS-CoV-2 and the change in the interaction of spike protein with host cells have complicated the pathogenesis of COVID-19. The pathogenetic view, which was determined at the beginning of the pandemic and based on the single receptor mechanism of ACE2, was unfortunately insufficient to explain the pathogenetic mechanism underlying the severe and systemic involvement of COVID-19.

Previous studies have shown that retinol decreases in COVID-19 in correlation with the clinical picture and is depleted in severe patients. Retinoid signaling disorder that develops with retinol depletion in COVID-19 causes dysregulation in the immune system. The main cause of Type I interferon synthesis defect and excessive inflammatory cytokine discharge in COVID-19 is the dysregulation of the immune system caused by retinoid signaling disorder. This finding also clearly meets the biphasic immunopathogenesis in COVID-19, on which the researchers agree (88). Blocking of the STRA6 receptor by the spike protein disrupts the intracellular transfer of retinol, resulting in decreased endogenous retinoic acid levels and retinoid signaling defect. The blockade of the STRA6 receptor, which is at a junction point in the cellular signaling mechanism, also disrupts important signaling pathways such as janus kinase, mTOR, PI3K/akt, Raf/Mek/Erk, ca-calmodulin and STAT, in addition to the retinoid signal. It is clear that severe systemic effects in COVID-19 occur with the blocking of the STRA6 receptor by the spike protein and the disruption of the signaling pathways provided by STRA6.

Retinol depletion and retinoid signaling defect caused by spike protein blockade of the STRA6 receptor appears to be responsible for the severe and systemic manifestations in COVID-19. In addition, we think that with the blocking of GPCRs by the SARS-CoV-2 spike protein, symptoms and findings mostly occur in the neuroendocrine regulation center and peripheral endocrine organs. Blocking of GPCRs by spike protein can explain the wide spectrum of diseases in COVID-19 because GPCRs are located in many tissues, affect many neurotransmitters and signaling pathways, and act on different G-protein isoforms.

In conclusion, although ACE2 has been identified as the main binding receptor of the SARS-CoV-2 spike protein for host cells, it is understood that ACE2 does not have a primary role in the pathogenesis of COVID-19 and aggravation of the clinical picture. In the pathogenesis of COVID-19, SARS-CoV-2 disrupts cellular signaling pathways by blocking STRA6 and GPCRs of spike protein and invades host cells. Potentially, acute, chronic neurological, endocrine and metabolic signs and symptoms of SARS-CoV-2 occur with the disruption of cellular signaling pathways working due to STRA6 and GPCRs. In COVID-19, devastating systemic involvement and neuroendocrine disorders, olfactory dysfunction, loss of appetite, retinol deficiency, retinoid signaling defect and other metabolic disorders develop through STRA6 and GPCRs. Therefore, we think that the blocking of STRA6 and GPCRs by spike protein plays an

important role in the pathogenesis of COVID-19 and can be used as potential therapeutic targets for the treatment and prophylaxis of COVID-19.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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