Neuropilin Is a New Player in the Pathogenesis of COVID-19

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Abstract—A family of glycoproteins called neuropilins is gaining attention as a new contributor to the pathogenesis of COVID-19. The concept of penetration of SARS-CoV-2 into host cells is traditionally associated with the receptor role of the ACE2 protein. New evidence suggests that it is possible to enhance pulmonary viral infection by involvement of neuropilins. Neuropilins have two prominent features: (a) a wide range of participation in cellular and tissue processes; (b) a concomitant enhancement of effects associated with the co-reception of regulatory proteins. These features determine the special role of functionally disseminated neuropilins in the pathogenesis of vascular system damage, immunothrombosis, and organ damage with comorbid manifestations during COVID-19. However, the presentation of neuropilins as a generalized therapeutic target that has a corrective effect on the affected areas is an ambiguous approach and requires a selective strategy.

Keywords: COVID-19, pathogenesis, neuropilins, host factor, targeted therapy
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INTRODUCTION

The development of the COVID-19 pandemic prompted a large-scale analysis of its pathogenesis. Clinical evidence suggests that the original respiratory distress syndrome caused by the SARS-COV-2 virus acquired a wide range of consequences. This refers to clinical disorders of entire systems, individual organs, tissues, and biochemical processes. The pathogenesis of COVID-19 develops according to inverted (“corrupted”) schemes of pathophysiological processes, which serve as a rationale for determining the likely cellular and molecular targets of therapy.

Among the new findings in the pathogenesis of COVID-19, attention has been drawn to a group of glycoproteins called neuropilins, which for many years has been on the sidelines of the interest of biologists and pathophysiologists. Complementary data from recent years demonstrate a wide range of possibilities for neuropilins in the complex dynamics of pathogenesis. There are two important features of neuropilins: (a) a wide range of participation in cellular and tissue regulatory processes and, accordingly, the implementation of various physiological functions; (b) concomitant enhancement of the co-reception of the leading proteins of the vascular and neurogenic systems of the body.

Consideration of the locus and mechanisms of participation of neuropilins in the complex of pathochemical incidents of COVID-19 is complemented by clinical characteristics: the nature of the pathology, stages of pathogenesis, selective or systemic organ damage, etc. From these positions, the traditional desire to link the mechanisms of pathogenesis with the possibilities of determining targets for therapy can lead to extraordinary interpretations.

NEUROPILINS. THE MAJOR POINTS

Neuropilin was first identified as a transmembrane glycoprotein isolated from the African frog eye tunics. It has also been found in the developing brain and designated as a receptor for axonal development [1]. Accordingly, the substance received the name “neuropilin”, although its role in biological processes now seems to be more multifarious.

The neuropilin isoforms NRP-1 and NRP-2 contain several specialized domains. The chemical structure of the domains has been determined, which is important for interaction with other regulatory molecules, determining the variability of participation in physiological processes [2]. In particular, it was found that NRP-1 is a concomitant component of endothelial growth factor (VEGF) in various forms of angiogenesis and tumor development [3].

NRP-1 subdomains b1 and b2 bind, in addition to VEGF, to placental factor (PLGF), heparin, etc. These subdomains interact with the C-terminal domains of coagulation factors V and VIII. The neuropilin subdomains a1 and a2 contact semaphorin 3A (axonal molecules that guide the growth cone), participating in the control of developing neurons [4, 5].
Neuropilins interact with transducer proteins of intracellular signaling, including phosphoinositide-3-kinase (PI3K), Akt, ERK, MAPK, etc.

PATHOPHYSIOLOGICAL FEATURES OF NEUROPILINS

Research over the past decade has shown that neuropilins can cooperate with a wide range of transmembrane regulatory molecules. NRP-1 functions as a coreceptor for vascular endothelial factor (VEGF), hepatocyte growth factor (HGF), platelet growth factor (PDGF), epidermal factor (EGF), fibroblast growth factor (FGF), insulin-like factor (IGF), etc. Neuropilins are functionally involved in the migration and invasion of various cells, membrane disorders, angiogenesis, etc. As a result, NRP-1 is considered as a hub receptor of biochemical ligands involved in the control of the body's vascular system [6].

Neuropilins are involved in diseases associated with endothelial dysfunction, pathological angiogenesis, immunogenesis, and neurodestructive processes. Clinical data demonstrate damage to the liver, damage to the kidneys, damage to the endocrine system, retinopathy, oncological processes and other diseases associated with NRP-1 expression [7]. According to preclinical studies, NRP-1 is involved in the vascularization and progression of some types of tumors, including lung, prostate, and intestinal cancers [8]. NRP-1 and -2 are related to proteinuric nephropathy when cytokines damage proximal tubular cells [9].

NEUROPILIN FACILITATES CORONAVIRUS AGGRESSION DURING COVID-19

It is believed that the penetration of SARS-CoV-2 into host cells is facilitated by spike proteins due to virus binding to ACE2 [10]. Subsequent events involve damage to vascular endothelial cells caused by cytokine storm, with the development of neuroinflammation and microthrombosis.

The main cellular target of virus aggression is the angiotensin-converting enzyme 2, ACE2, a key factor in hemovascular regulation. Due to its high affinity, coronavirus suppresses the activity of ACE2, disrupting the control of hemovascular and cytoimmune processes. The fundamental point that determines the specificity and intensity of COVID-19 infection is the coincidence of chemical structures, due to which SARS-CoV-2 uses ACE2 as a “Trojan horse” for entry into host cells [11].

The neuropilin family is attracting attention as a new participant in the initiation and development of the COVID-19 pathogenesis. A series of studies considered NRP-1 as a host factor for penetration of SARS-CoV-2 and as a component that enhances its contagiousness [12]. The penetration of SARS-CoV-2 is complemented by the attachment of NRP-1 and conformational changes in the structure of the virus, using the spike protein S to attach to host cells. In the traditional interpretation, the binding domain structures of SARS-CoV-2 interact with the ACE2 receptor; in a new interpretation, the endogenous protease furin forms a bond with the NRP-1 and NRP-2 receptors using the virus fragments S1 and S2. As control evidence, it was found that blocking this interaction with selective inhibitors reduced the infectivity of SARS-CoV-2 in cell culture [13, 14].

In a new formulation of the problem, the effect of the SARS-CoV-2 spike (S1 protein) on the activation of microvascular endothelial cells is considered. Apoptosis of alveolar and endothelial cells infected by the SARS-CoV-2 virus includes signaling with the participation of the Fas receptor, which, by binding to NRP-1, is involved in the cytokine storm activation. Thus, NRP-1, which serves as an infection and amplification factor for the SARS-CoV-2, may be included in subsequent pathogenesis events in other tissues [15].

Until recently, ideas about the penetration of SARS-CoV-2 into host cells were predominantly associated with the role of ACE2 as the main receptor. However, the level of distribution of ACE2 seems to be rather low in the respiratory and olfactory epithelium cells in comparison with other tissues [16]. New data on the accompanying, stimulating role of NRP-1 in these processes suggest that NRP-1 increases the likelihood of penetration of coronavirus into lung cells. Moreover, from this point of view, the lethality of SARS-CoV-2 can be interpreted differently. Since multiple organ manifestations of the disease are an important part of the symptoms of COVID-19, neuropilins can be considered as accomplices of the infectious process at subsequent stages of pathology.

NEUROPILINS AND VASCULAR PATHOLOGY

NRP-1 is expressed in many vascular endothelial cells. Disruption of the endothelium in the pathogenesis of COVID-19 is a key process in the disorder of a complex of interrelated processes: transcellular diffusion, hemostasis, microcirculation, maintenance of vascular tone, and maintenance of systemic arterial pressure. As part of the general conclusion, it is postulated that neuropilins, acting as co-receptors of membrane ligands, affect the processes of vascular permeability, angiogenesis, immune responses, neuronal dysfunction, etc. Apparently, combination with the leading regulators of endothelium-dependent processes is one of the factors in the disseminated pathogenesis of COVID-19 [17, 18]. The severe form of COVID-19 is associated with vascular complications such as dysregulation in the systems of hemostasis and immunothrombosis [19, 20].

As a factor that controls adhesion and permeability of endothelial cells, NRP-1 can be considered as the cause of subsequent damage to endothelial cells, their dysfunction, and coagulopathy. The mechanism of
binding of angiogenic ligands with the b1 domain of NRP-1 to the S protein of the SARS-CoV-2 coronavirus has been proposed [21].

Studies of the “pre-Covid period” show that neuropilins are involved in a wide range of physiological processes. NRP-1 is upregulated in vascular endothelial and smooth muscle cells in response to activation of fibroblast growth factor (FGF) and platelet growth factor (PDGF) [22]. VEGF acts on endothelial cells as a proliferative and migration-stimulating factor, the effectiveness of which is enhanced by NRP-1 according to the feedback rule [23]. These data indicate the involvement of NRP-1 in endothelial barrier dysfunction under conditions of VEGF hyperactivation [24].

The special role of expressed NRP-1 in pathological angiogenesis has been confirmed by the possibility of blockade by inhibitors [25, 26].

PARTICIPATION OF NEUROPILINS IN IMMUNOLOGICAL PROCESSES

A significant amount of information characterizes the role of neuropilins in the complex of immunological processes. An analytical review by Roy et al. described the “multifaceted” role of neuropilins in various types of immune cells in the control of defense and adaptive processes. NRP-1 expression has been described in cellular phenotypes, including macrophages and T cell subpopulations. NRP-1 has been noted to be expressed in bronchial and vascular macrophages, T and B cells, and other phenotypes. In microglia, NRP-2 has been identified in Golgi apparatus compartments [27]. It has been established that NRP-1, as a concomitant component of the connection between the target cell and T-lymphocytes, promotes adhesion and localization of the contact zone. This mechanism indicates the likely role of NRP-1 in initiation of the primary immune response [28].

When evaluating the biochemical signaling pathways that determine the activity of neuropilins during immunogenesis, it was found that NRP-1 knockout abolished interferon-γ (IFNγ)-induced expression of chemokine 10 and the STAT1 transducer protein in brain cells. Blocking NRP-1 reduces the activation of the STAT1-CXCL10 chain, affects the infiltration of lymphocytes, and suppresses the demyelination of neurons. These results indicate the role of NRP-1 in the pathogenesis of inflammatory reactions associated with damage to the blood—brain barrier [29], a situation quite typical for COVID-19.

Cellular inflammation and immune system dissonance are considered significant factors in the pathogenesis of COVID-19. Clinical data document that the severity of COVID-19 is associated with the level of pro-inflammatory cytokines and the cellular immune profile [30]. An important indicator of dysregulation is the distortion in the ratio of neutrophils and lymphocytes, which also serves as a prognosis for development of the severe form of the disease [31]. Cellular inflammation caused by SARS-CoV-2 leads to hypersecretion of cytokines, granulocytes, and macrophages. Pro-inflammatory mediators released by activated macrophages enhance damage to endothelial cells, contributing to the disruption of the vascular structure and the development of a procoagulant status [32].

Henry and colleagues presented the hypothesis of microvascular coagulopathy and immunothrombosis in the pathogenesis of COVID-19 as an association of extreme immune system activity and endothelial cell dysfunction. During viral invasion, activated platelets, coagulation factors, and innate immune effector systems contribute to the formation of clots and multiple tissue lesions [33].

The designation of NRP-1 as a factor enhancing viral infection of the lungs or nasal cavities of the patient allows the presentation of NRP-1 as a likely target for anti-COVID therapy. However, this approach should be considered taking into account the role of NRP-1 in immunosuppression, with pronounced negative and fatal consequences. Post-mortem studies document the role of inflammation in organ damage as a cause of severe cases of COVID-19. Hyperinflammation and organ dysfunction in COVID-19 does not match the tissue and cellular distribution of SARS-CoV-2, demonstrating tissue-specific tolerance. Thus, according to the proposed version, complex manifestations of pathogenesis are primarily due to a disorder of the body’s immune systems [34]. This analysis seems to be important when choosing a therapeutic correction strategy focused on blocking neuropilins. Given its universal involvement in a large number of physiological processes, the assessment of the negative role of NRP-1 as a therapeutic target in COVID-19 seems to be ambiguous (see the section “Neuropilin and the Challenges of Targeting Therapy” below).

COVID-19: BRAIN DAMAGE AND NEUROPILIN

Neuropilin and the brain. NRP-1 is a transmembrane protein that is involved in a wide range of pathophysiological processes. Analysis of NRP-1 expression in the human brain demonstrated its role as an additional mediator of SARS-CoV-2 infection in the central nervous system. Comparison of these data with the results of preclinical studies suggest that NRP-1 may be involved in some forms of neurological disorders and brain damage in COVID-19.

RNA sequencing was used to study NRP-1 in individual structures of the human brain. The level of NRP-1 was determined in endothelial cells, macrophages, neurons, oligodendrocytes, and astrocytes. NRP-1 RNA expression was highest in the hippocampus compared to the olfactory region, basal ganglia, thalamus, hypothalamus, midbrain, cerebellum, and medulla oblongata. This leads to the conclusion that
there are a wide variety of possible neurological manifestations in COVID-19, and that neurotropism of SARS-CoV-2 cells that are associated with the expression of neuropilins is a special concept [35].

Neurons and endothelial cells of brain microvessels express NRP-1 due to control signals: the interaction between cell ligands, Sema3 or VEGF signaling proteins, and individual neuropilin domains provides selective regulation of processes in neuronal and vascular tissues. Previously, in preclinical studies, NRP-1 has been shown to mediate pro-inflammatory levels of endothelial cells in human multiple sclerosis lesions. The involvement of NRP-1 in the infiltration of inflammatory cells and the destruction of the blood-brain barrier was confirmed by knockout manipulation against the background of chemokine expression [29].

**Neuropilin as a “host factor” of the coronavirus.**

Clinical evidence suggests that COVID-19 induces a wide range of symptoms, pointing to lesions of the central and peripheral nervous system. About one third of patients with COVID-19 experience neurological and neuropsychiatric disorders in the acute or late phases of the disease; with symptoms including encephalopathy, impaired consciousness, lesions of the corticospinal tract, and nociceptive reactions.

The “hematogenous pathway” of viral transfection into the brain is associated with disruption of the protective role of the blood-brain barrier: brain endothelial cells exhibit pro-inflammatory responses when exposed to SARS-CoV-2 subunits. In model experiments, how affected cells pass the infection to the brain areas was established [36].

Experimental studies performed with different strains of SARS-CoV showed the possibility of damage to neurons located in the centers of the medulla oblongata [37]. Transferring this information to the current situation, Li and co-authors believe that fatal cases of COVID-19 may be associated with regulatory dysfunction of the cardiorespiratory center of the brain [38].

Analysis of viral invasion pathways in COVID-19 reveals a layered mechanism of neurological complications. Penetration of the coronavirus through the lungs or olfactory bulbs can cause atypical forms of brain damage. The appearance in the field of view of a new factor NRP-1 complements the concept of SARS-CoV-2 neurotropism in addition to interaction with ACE2 [39]. Autopsy analysis of olfactory epithelial cells in COVID-19 patients showed that NRP-1 facilitates the pathway and pathogenic effects of SARS-CoV-2 [40].

This position allows us to state the role of neuropilins in the increasing neurological complications in COVID-19. In patients with previously diagnosed Alzheimer’s disease, an increased expression of ACE2 was found in the neocortex, temporal lobe, and CA1 zone of the hippocampus [41]. Genetic analysis confirms that such patients showed increased expression of NRP-1 compared to the control group. Correspondence between the expression of ACE2/NRP-1 genes and the severity of pathology was established [42].

**NEUROPILIN AND DIFFICULTIES IN IDENTIFICATION OF THERAPY TARGETS**

A review of the material on a new participant in the pathogenesis of COVID-19 allows us to summarize several points related to the unusual role of neuropilin in a wide range of regulatory processes.

(1) A characteristic manifestation of the pathogenesis COVID-19 is acute lung damage with an inverted response of the immune systems. The cytokine storm caused by a viral attack demonstrates a clinical picture of pro-inflammatory etiology with dysfunction of the endothelium and the vascular system as a whole, thrombogenic lesions, and neurological dissonance. Vascular disorders, primarily of the lungs but also of the heart, brain, kidneys, endocrine organs, intestines, etc., are a continuation of immunogenic pathogenesis. Dysfunction of the vascular endothelium, as one of the leading characteristics of the disease, is due to the receptor interaction of coronavirus SARS-CoV-2 with ACE2 protein and due to excessive immune responses.

A special role is played by the accompanying regulatory proteins, which under the conditions of COVID-19 become components of dissonance and amplification of negative processes. Consideration of the information on neuropilin allows us to present a new player in the systemic pathogenesis and, using this example, to designate the complex essence of a targeted therapy strategy.

(2) Recent data indicate that the pathogenesis of COVID-19 has additional enhancing pathways for the penetration of coronavirus into cells. The participation of transmembrane proteins as independent docking sites with virus fragments served to explain the tissue tropism of SARS-CoV-2: selective ligands of the host cell molecules act as infection cofactors in the tissues of the lungs and other organs of the patient [43].

NRP-1 plays a role in the penetration of coronavirus into the alveolar epithelium and endothelium of the lungs. It was assumed that the NRP-1-involving mechanism is a trigger of cytokine storm and initiation of inflammation in cells of various tissues [44]. Neuropilin–mediated infection by SARS-CoV-2 through the olfactory bulbs is one of the causes of neurological disorders in the patient [40].

(3) Analysis of primary preclinical studies provides a generalized picture of cellular processes involving neuropilins. The structural features of NRP-1/2 chemical ligands and interaction with cells of various organs characterize neuropilins as modulators of physiological processes and original integrators of molecular interactions and signal transduction. NRP-1 is expressed in many tissues, primarily in the pulmonary endothelium but also in cells of the immune system, retina, brain, and peripheral nervous system.
These processes determine the specific role of NRP-1 in SARS-CoV-2 infection, including the dissonance of the blood coagulation and fibrinolytic systems, immunothrombosis, and organ damage with comorbid elements of the disease. [21]. In general, a wide range of functions of neuropilins as mediators of biochemical and cellular aspects of pathogenesis indicates the likely significance of these substances in the implementation of multiple forms of lesions associated with coronavirus. Perhaps, this conclusion is important not only in the clinical phase of COVID-19 but also in the difficult-to-understand post-COVID manifestations of various genesis.

(4) The special mission of neuropilins, which is coupled with the expression of other proteins, defines them as a special target of SARS-CoV-2. NRP-1, as a signaling mediator with different potencies, is involved in the control of many cellular and molecular processes. It turned out to be tempting to use data on neuropilins to explain the pathogenesis-stimulating mechanism of COVID-19 and to develop new targets for the anti-COVID strategy. Acting as co-receptors of cellular ligands, NRP-1 promotes the penetration of coronavirus SARS-CoV-2 and is involved in provoking a complex of vascular disorders, including immunoinflammation, immunothrombosis, and multiple organ damage [45].

However, given the polyphony of expression, NRP-1 may turn out to be a generalized target, which affects various systems of the body in terms of their physiological significance. In practical terms blockade of expression or inhibition of NRP-1 ligands turns out to be far from an unconditional therapy. This serves as a basis for criticism that points to the likely side effects of anti-neuropilin correction. Inhibition of neuropilins, knockdown, or blockade can also affect the implementation of other physiological functions. Studies using antibodies to NRP-1 show how these interventions can affect normal cell function, disrupting the vascular endothelium, vascular permeability, BBB status, and immune responses [46].

As a preliminary conclusion, it should be stated that a large-scale orientation towards NRP-1 as a target for correction (therapy) must be controlled, avoiding the involvement of functionally coupled regulations, including the immune, nervous, and other body systems. The strategy of targeted therapy thus acquires limitations and new requirements. The complexity of the biochemical links in the pathogenesis of COVID-19 requires the use of a functionality-based strategy and selective targets for anti-COVID therapy.

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