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Opinion

Inherited and acquired corona of coronavirus in the host: Inspiration from the biomolecular corona of nanoparticles

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ABSTRACT

The family of coronavirus are named for their crown shape. Encoded by the genetic material inherited from the coronavirus itself, this intrinsic well-known "viral corona" is considered an "inherited corona". After contact with mucosa or the entrance into the host, bare coronaviruses can become covered by a group of dissolved biomolecules to form one or multiple layers of biomolecules. The layers acquired from the surrounding environment are named the "acquired corona". We highlight here the possible role of the acquired corona in the pathogenesis of coronaviruses, which will generate fresh insight into the nature of various coronavirus-host interactions.

Introduction

Over the last year, the emergence of a novel infectious coronavirus in humans has resulted in the worldwide COVID-19 pandemic. There are four genera of coronavirus, including *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Belonging to the genus of *Betacoronavirus*, SARS-CoV-1, SARS-CoV-2, and MERS-CoV are able to infect humans and cause severe respiratory syndrome. SARS-CoV-2 has resulted in the ongoing global COVID-19 pandemic. An efficient therapeutic strategy requires a better understanding of the interaction between SARS-CoV-2 and the host [1]. Coronaviruses are a class of enveloped viruses with a positive-sense single-stranded ribonucleic acid (RNA) genome (Fig. 1). There are generally four types of protein in SARS-CoV-2, including the spike glycoprotein (S protein), membrane protein (M protein), nucleoprotein (N protein), and the envelope small membrane protein (E protein). SARS-CoV-2 can be transmitted via respiratory droplets, direct contact of skin mucous membrane and aerosol. In addition to the respiratory organs, genetic matters of SARS-CoV-2 can also be detected in the kidneys, liver, pancreas, gastrointestinal tract, brain, nerves and heart, suggesting that SARS-CoV-2 can access most of the tissues [3].

Coronaviruses are named for their most prominent feature, the "crown of spikes" around the virion ("corona" means "crown" in Latin). This viral "corona" is composed of a lipid membrane and the

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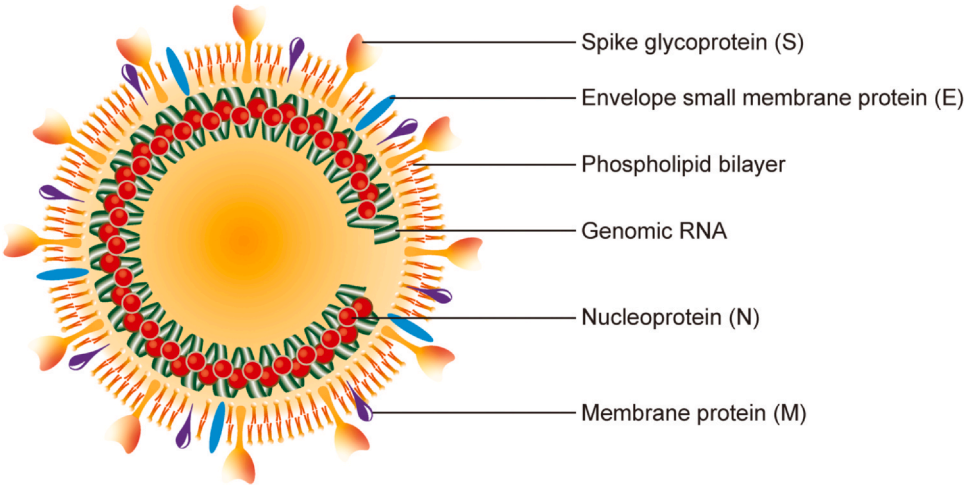

Fig. 1. Structure schematic diagram of coronaviruses.

M, E, and the trimeric S protein. Since this well-known corona is encoded by the genetic material inherited from the virion itself, it can be considered an "inherited corona". This inherited corona undoubtedly has a crucial role in the interaction of the virus with host cells' replication, and the construction of new virions [2]. The S protein mediates the entry of coronaviruses into the host cell through the attachment of the virus to cell receptors. The M protein maintains the structure of the viral envelope, through the interaction with other major structural proteins. As the smallest of the major structural proteins, the E protein is also involved in the coronavirus assembly. It is also involved in other aspects of the coronavirus replication cycle and the host's cellular response to viral infection. All four proteins are critical in the biogenesis of new complete virions after entry into host cells. Through binding to the RNA genome, the N protein's function is to construct the nucleocapsid. In host cells, the N protein is also responsible for the replication cycle and the virion formation.

Role of the host's extracellular soluble biomolecules in virus interactions

The virus-cell interaction can lead to various changes in the host's biology, such as stimulation of the host's immune system and potentially serious clinical symptoms [4]. Dissolved biomolecules in biological fluids are an important part of virus-cell interactions [5]. For instance, the complement protein C4 can inhibit infection through the direct inactivation of viral capsid proteins required for infection [6]. The interaction of soluble proteins with viruses can also enhance viral infectivity. For instance, as a dissolved biomolecule, prostatic acid phosphatase fragments in the semen of a host, can facilitate human immunodeficiency virus (HIV) infection [7]. The interaction between soluble heparin-sulfonated proteoglycan cell surface attachment factors and virions initiates the infection of target cells by the human papillomavirus (HPV) [8]. Soluble biomolecules in host biofluids also play important roles in the response of host cells to the invasion of pathogens. It has been reported that coagulation factor X absorbed onto the surface of a virus could be internalized by macrophages along with the virion triggering innate immune recognition [9]. The interaction of these biomolecules with coronaviruses could modulate the virus-cell interaction or cellular response.

Biomolecular corona of exogenous particles or viruses

As discussed above, some effects of soluble extracellular proteins on the behavior of infectious viruses have been revealed in recent decades. Nevertheless, after entering biological fluids, particles not only absorb a single protein but can also dynamically interact with hundreds to thousands of soluble proteins to form the "protein corona" [10–13]. In addition to proteins, nanoparticles can also absorb other biomolecules, including lipids, sugars, and small molecules such as hormones and metabolites [14–17]. These interactions can form one or multiple layers of biomolecules on the surfaces of the nanoparticles [18], which are known as a "biomolecular corona" [19]. When entering into the natural environment, the binding or coating of biomolecules such as dissolved organic matter (DOM) on the surface of nanoparticles could form biomolecular corona or "eco-corona" [14,17,20,21]. The components of this corona can endow invading particles with properties that are distinct from the intrinsic properties of bare nanoparticles. This affects their environmental behavior, and their interactions with cells, including particle recognition, cellular internalization, stimulation of intracellular signaling pathways, and subsequent biological activities [10,22,23].

As natural particles at the nanoscale, viruses can also interact with groups of molecules in biological fluids simultaneously as discussed above [6–9,24]. Recently, the understanding of the interaction of soluble proteins with viruses has begun to evolve from considering single proteins to encompassing multiple proteins [25]. Ezzat et al. studied the protein corona absorbed onto respiratory syncytial virus (RSV) and herpes simplex virus type 1 (HSV-1) in different biological fluids [25]. Hundreds of proteins were found to absorb onto the viruses, and distinct profiles were observed because of the different surface properties of the two types of virus. This protein corona has important functions in viral infectivity, immune recognition, and induction of amyloid aggregation [25].

Possible role of the "Acquired Corona" in the host-coronavirus interaction

It can be speculated that when coronaviruses are enveloped in different compartments, a dynamic biomolecular corona will form on the surface of the virion. Compared with the inherited corona described above, because this "corona" is acquired, it is referred to as the "acquired corona" (Fig. 2). A vast spectrum of biomolecules can form an acquired corona (or eco-corona) on the surface of coronaviruses in the ambient environment, such as wastewater, inanimate surfaces, and oral droplets (Fig. 3A). In the host environment, the acquired corona could form in different mocosa or pulmonary surfactants (Fig. 3B). Because the altered biomolecular components in different biological fluids, the components of the acquired corona may change dynamically when SARS-CoV-2 is

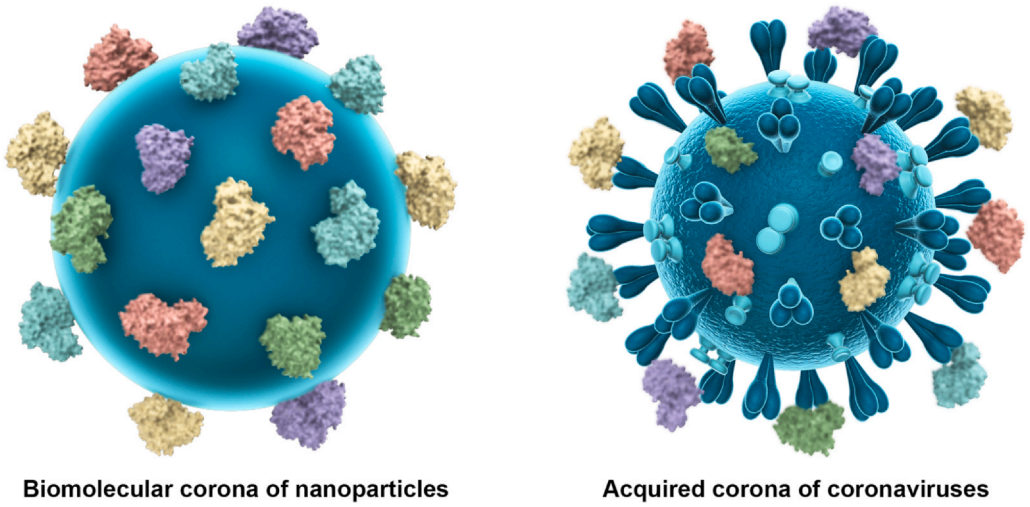

Fig. 2. Forming of acquired corona on nanoparticles or coronaviruses.

enveloped in different tissue microenvironments (Fig. 3C). After entry into the cells, release into the blood stream, and arrival at the target tissue, some biomolecules in the acquired corona of coronaviruses might be exchanged with new biomolecules (Fig. 3C).

The acquired corona is capable of covering the inherited corona, at least in part, which could modify the surface properties of coronaviruses, and the subsequent virus-host interaction. (1) Coronaviruses have the potential to perturb the normal structure of biomolecules in the acquired corona. For example, protein conformation arising from the binding of some viruses can mediate extracellular pathogenesis [25]. Whether coronavirus-mediated alterations of protein could lead to abnormal response is not clear. Meanwhile, the acquired corona may affect the stability of the coronavirus envelope. (2) The acquired corona may perturb or modulate the virus-cell interface. In the lung, the acquired corona may either interrupt the binding of the coronaviruses to the known cell

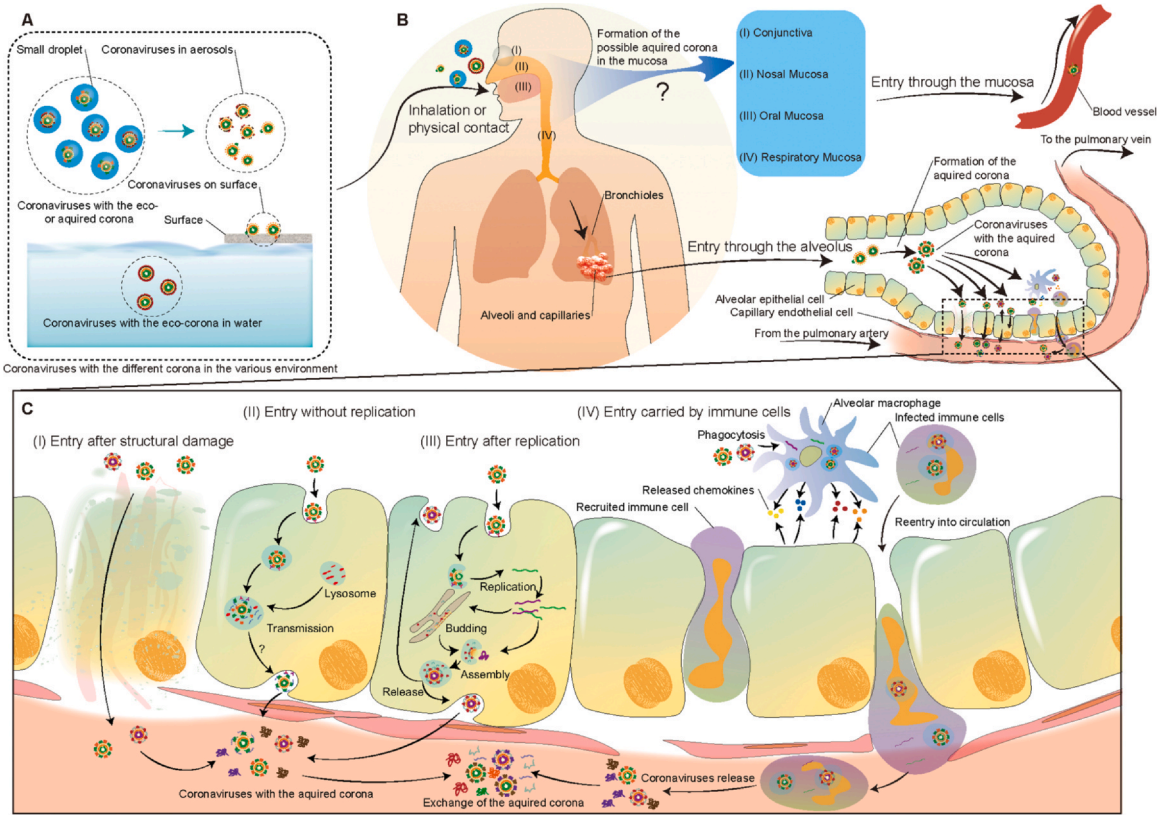

Fig. 3. The formation of acquired corona in different environmental compartments. A, Formation of the an acquired corona in the outside-host environment. B, The incorporation of coronavirus in different types of mucosa, such as the (I) conjunctiva, (II) nasal mucosa, (III) oral mucosa, and (IV) respiratory mucosa. C, an acquired corona forms at the interface between coronaviruses and the lung surfactant after arrival in the alveoli. Coronaviruses may entry the bloodstream across the lung barrier in a replication dependent or independent manner, including (I) entry after structural damage, (II) entry without replication, (III) entry after replication, (IV) and entry carried by immune cells. In the intracellular compartments, some components of the original acquired corona in the alveoli can exchange with the intracellular biomolecules, such as lysosomal enzymes. In the circulation, some components in the intracellular acquired corona may be displayed by different biomolecules in the blood plasma or target organs to form a new mixed acquired corona dynamically.

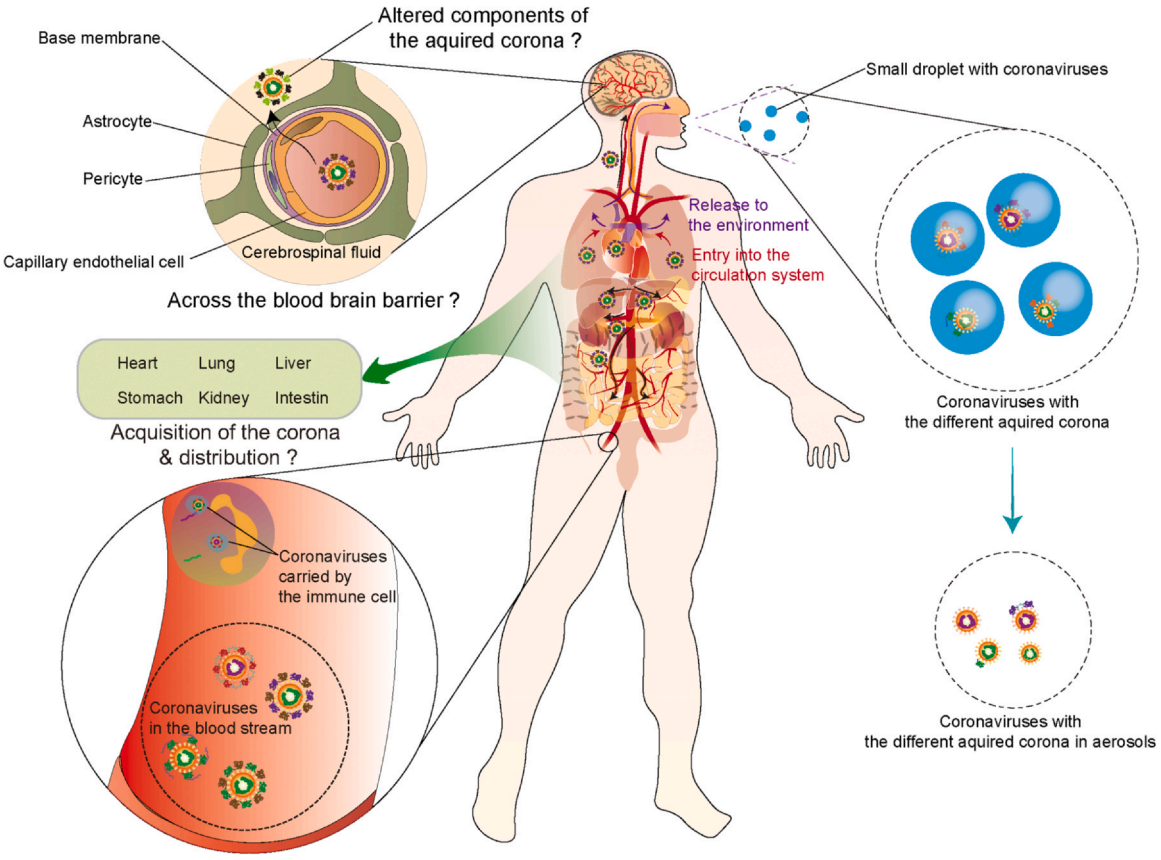

Fig. 4. The spread of coronaviruses with acquired coronas through the bloodstream and entry into the target organs. For example, the acquired corona has a possible role in the penetration of blood brain barrier by coronaviruses. After leaving the host via droplets or other carriers, coronaviruses can take the original acquired corona from the inside-host environment to the outside-host environment. This corona could be partially displaced by the biomolecules in the ambient environmental compartment to form a new acquired corona (eco-corona).

receptors or mediate the binding of virions with the unidentified cell receptors. It has been reported that lung surfactant protein D (SP-D) can interact with the S-protein of SARS-CoV-1. However, as with other collectins, SP-A and mannan-binding lectin in the blood circulation show no interaction with S-protein [24]. The preincubation of S-protein with SP-D increases binding to dendritic cells but not macrophages, suggesting a regulatory function for SP-D in virus-host cell interactions. Therefore, similar to SARS-CoV-1, SARS-CoV-2 may also interact with surfactant and form an acquired corona, which could affect the behavior of SARS-CoV-2 in the host. (3) Although a large number of intracellular signaling pathways, cell-cell interactions, and intercellular communication events have been predicted to participate in the infection syndromes associated with coronaviruses [26], the role of the acquired corona in the multilayer of biological process is not clear. Because of the intracellular translocation of biomolecules in this multi-layered biological process that interact with viruses, the acquired corona may mediate the stimulation of the immune system and the possible poor outcomes in patients. As an acidic membrane-bound organelle, lysosome could digest intruding coronaviruses. However, recent evidence suggested SARS-CoV-2 could lead to the loss of function of the lysosome, allowing the survival and release of SARS-CoV-2 from cells [27]. The role of the acquired corona formed in cytoplasm or lysosome may contribute to the exocytosis of SARS-CoV-2. The interaction of coronaviruses with intracellular biomolecules and the acquired corona as observed in the cellular response should be investigated. (4) After leaving cells, the acquired corona in the blood may affect the spread, penetration of biological barriers, and biodistribution of coronaviruses in different tissues (Fig. 4). When the coronaviruses reach a given tissue, it is still unclear whether the acquired corona is involved in the observed clinical syndromes in different tissues, such as gastrointestinal disease, pinkeye, runny nose, loss of taste and smell, heart failure, and kidney failure [28]. Recently, it has been demonstrated that SARS-CoV-2 can be transport to the nervous system through penetration of the neural–mucosal interface in the olfactory mucosa [29]. Given that SARS-CoV-2 has the potential to attack the central nervous system [30], the acquired corona formed in the mucosa and cerebrospinal fluid in the neural system may have a role in the infectivity of SARS-CoV-2 (Fig. 4). (5) Selective pressures and the instability of the RNA genome drive mutations in the *SARS-CoV-2 genome*, which could generate more variants and alter the inherited corona [31]. Thus, the acquired corona on different coronaviruses may be altered, potentially contributing to variations in symptoms induced by individual SARS-CoV-2 variants.

After leaving hosts, the acquired corona is also an important factor in the environmental behavior of coronaviruses (Fig. 4), which is crucial to the transmission and infectivity of coronaviruses [32–35]. Therefore, the acquired corona should be considered in order to understand in depth the environmental behaviors of coronaviruses under realistic environmental conditions outside the host [34].

Perspective

The components of the acquired corona in different biological fluids or environmental matrices outside the host could be revealed through high-throughput mass spectrometry proteomics, lipidomics, and other target or non-target mass spectrometry. The composition of the acquired corona is highly dependent on the surface properties of virions so could vary in different coronavirus

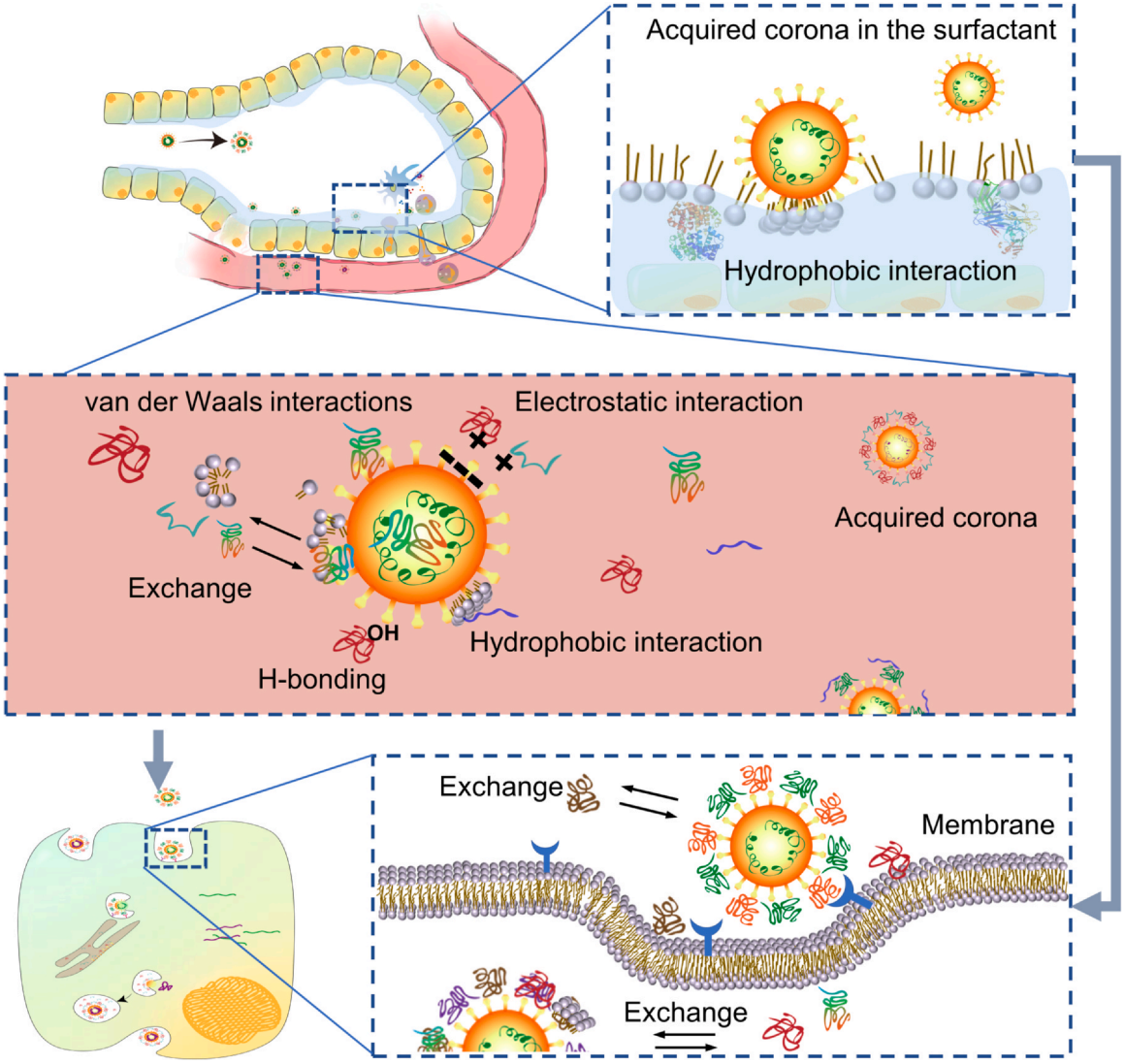

Fig. 5. The possible mechanisms underlying the formation of acquired coronas at different virus-host interfaces. Hydrophobic, ven der Waals, H-bonding and electrostatic interactions may contribute to the formation of an acquired corona.

variants [11,15,36,37]. In the future, with sufficient information on the acquired corona formed on different types of coronavirus obtained, *in silico* models could be established to predict the components of an acquired corona on different novel coronavirus variants. The protein corona may form rapidly upon virus incorporation into biological fluids [38], and the time-resolved dynamics of the interaction between coronaviruses and biomolecule should be evaluated. Because of the differences in the surface properties of engineered hard nanoparticles or other virions, the interface between coronaviruses and the acquired corona is also likely to be different. Better knowledge of the driving forces at the dynamic interface between viruses and soluble biomolecules will help in understanding the dynamic process of acquired corona formation (Fig. 5). In situ coronavirus–biomolecule interactions in suspended biological fluids also need to be studied to differentiate between soft acquired corona and hard acquired corona of coronaviruses [39,40].

Information on the biomolecules that attach to coronaviruses is critical to elucidate the mechanisms underlying their interactions with host cells. This interface is the basis of the interaction between coronaviruses and host cells in vivo. We should, therefore, consider both the inherited and acquired corona in different environments. More detailed knowledge of coronaviruses could pave the way for a deeper understanding of the pathogenesis of coronaviruses, better control of the pandemic, and improved strategies for the development of drugs and vaccines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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