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REGULAR ARTICLE

Host Manipulation Mechanisms of SARS-CoV-2

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Abstract

Viruses are the simplest of pathogens, but possess sophisticated molecular mechanisms to manipulate host behavior, frequently utilizing molecular mimicry. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to bind to the host receptor neuropilin-1 in order to gain entry into the cell. To do this, the virus utilizes its spike protein polybasic cleavage site (PCS), which mimics the CendR motif of neuropilin-1's endogenous ligands. In addition to facilitating cell entry, binding to neuropilin-1 has analgesic effects. We discuss the potential impact of neuropilin-1 binding by SARS-CoV-2 in ameliorating sickness behavior of the host, and identify a convergent evolutionary strategy of PCS cleavage and subsequent neuropilin binding in other human viruses. In addition, we discuss the evolutionary leap of the ancestor of SARS-COV-2, which involved acquisition of the PCS thus faciliting binding to the neuropilin-1 receptor. Acquisition of the PCS by the ancestor of SARS-CoV-2 appears to have led to pleiotropic beneficial effects including enhancement of cell entry via binding to ACE2, facilitation of cell entry via binding to neuropilin-1, promotion of analgesia, and potentially the formation of decoy epitopes via enhanced shedding of the S1 subunit. Lastly, other potential neuromanipulation strategies employed by SARS-CoV-2 are discussed, including interferon suppression and the resulting reduction in sickness behavior, enhanced transmission through neurally mediated cough induction, and reduction in sense of smell.

Keywords Host manipulation · SARS-CoV-2 · Neuropilin · CendR motif · Mimicry · Polybasic cleavage site

1 Introduction

Parasitism is observed at all levels of biotic organization, ranging from the molecular to organismal and to human. Evolutionary game theory can be used to better understand commonalities in the different manifestations of parasitism, and contribute to

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a better understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). From a game theoretical perspective, a parasite constitutes a player who obtains a net benefit from a resource holder, in repeated games. A common strategy that a parasite utilizes for achieving this objective is by utilizing deception, a major form of which is deceptive mimicry.

There are two major forms of mimicry found in nature, Batesian and Müllerian, which may be described using the framework of signaling games. In a signaling game, a sender sends a signal to a receiver, which then undertakes an action. The action produces a benefit ('utility') to both sender and receiver. This occurs when the sender and receiver are cooperating with each other given perfect common interest. If the sender and receiver have a conflict of interest, then the sender may send a deceptive signal to the receiver, to manipulate it into undertaking an action that benefits the sender, but not the receiver. A signal is defined as information that is sent that has a strategic purpose, as opposed to a 'cue' which is information that does not. The sender has information regarding its true type, which it may or may not decide to signal to the receiver, this is termed 'information asymmetry'.

Batesian mimicry (Bates 1861) is a deceptive form of mimicry, whereby a species will mimic a signal emitted by another species, in order to deceive a third species as to its true type. An example is provided by the non-venomous drone fly, which possesses a black body with yellow stripes, which mimics venomous bees and wasps (Golding and Edmunds 2000; Casey et al. 2021). Potential predators are tricked into avoiding the non-venomous drone fly, thus losing a valuable meal. Venomous bees and wasps also experience a cost, as the value of their signal of toxicity is diluted by the drone fly free-riding on their signal.

Müllerian mimicry (Müller 1879) is a cooperative form of mimicry, and occurs when two or more species share the same signal, in order to communicate with a third species their true type, to the benefit of all three. An example is again provided by bees and wasps, which share the same signal, a black body with yellow stripes. This is recognized as a signal of toxicity to a potential predator, which will avoid eating the bee or wasp when it encounters the signal. This benefits both the bee or wasp, and the potential predator. The signal is termed an 'honest' signal, as it reveals the true type of both the bee and wasp, that they are venomous. When there are more than two species which emit the same signal to a receiver, then this constitutes a Müllerian mimicry ring.

In the interaction between SARS-CoV-2 and its human host, the human is the resource holder, which the virus needs to utilize in order to reproduce and spread. Resources desirable to the virus include cellular metabolites and mechanisms, and mobility. The host is harmed by infection from SARS-CoV-2 because it loses resources, and so virus and host have a conflict of interest. For this reason, signaling game theory predicts that the virus will use deceptive signaling strategies to exploit the host's resources to its own advantage.

Consistent with this, SARS-CoV-2 utilizes a range of molecular mimicry strategies to manipulate host molecular systems, including the addition of a cap-mimicking structure to viral mRNAs in order to mimic cellular mRNAs (Viswanathan et al. 2020), the use of replication organelles to avoid detection by innate immune

surveillance (Snijder et al. 2020), glycosylation of its surface spike protein to shield epitopes from the immune system (Grant et al. 2020), and a polybasic cleavage site (PCS) located in its spike protein, which mimics an endogenous protease cleavage site (Anand et al. 2020). Recently, deceptive molecular mimicry was formally described in a signaling games context, using SARS-CoV-2 as an example (Casey et al. 2021).

In hosts with a nervous system, neuromanipulation is one means by which a parasite can enhance its transmissability, by influencing host mobility and other behaviors (Hughes and Libersat 2019). Manipulation by parasites may occur at the molecular or sensory level and is employed by endosymbiotic bacteria, microbial eukaryotic parasites, vertebrate parasites, and is a feature of some human personality types (Table 1). Despite its widespread nature, host manipulation has not been well characterized in viruses, however according to the signaling games perspective, viruses would be expected to use host behavior manipulation as well. Indeed, the prediction has been made that SARS-CoV-2 manipulates host behavior to its own benefit (Barton et al. 2020).

Here, potential host manipulation strategies by SARS-CoV-2 are examined with a focus on its binding to neuropilin-1 and the resultant effects on pain suppression. The evolutionary forces that led to neuropilin-1 binding during the evolution of the ancestral bat virus into the new human host are discussed, and examples of convergent neuropilin binding by the surface proteins of other human RNA viruses are described. Given that this has arisen independently on several occasions, there appears a strategic benefit to neuropilin binding, which may have a host manipulation component. In addition, a number of other potential host manipulation strategies deployed by SARS-CoV-2 are discussed. Throughout, the central role of deceptive mimicry is identified, at both molecular and behavioral levels, and signaling game theory used as an explanatory framework that may provide greater insight into the stratagems that the virus employs.

2 Binding of SARS-CoV-2 Spike Protein To Neuropilin-1 and Evidence for Host Behavioral Manipulation

SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) (Wan et al. 2020; Hoffmann et al. 2020a), CD147 (Wang et al. 2020) and neuropilin-1 (Cantuti-Castelvetri et al. 2020; Daly et al. 2020) as host receptors to facilitate viral cell entry. ACE2 binds to angiotensin II as part of blood pressure regulation, and is concentrated in the arteries, lungs, heart, intestine and kidneys (Ghafouri-Fard et al. 2020). CD147 is a metalloprotease with diverse physiological roles and is expressed in numerous cell types (Grass and Toole 2016). Neuropilins are expressed in neuronal, epithelial, immune and hematopoietic cells, and have a role in the development of the nervous and cardiovascular systems (Parker et al. 2012).

SARS-CoV-2 spike protein consists of two subunits, S1 and S2. S1 contains the receptor binding domain (RBD), that binds to ACE2. Upon binding, the S1 subunit is shed, and the S2 subunit facilitates membrane fusion and cellular entry of the virus (Cai et al. 2020). Priming of S2 is necessary for virus entry when utilizing

Table 1 Manipulation of host behavior by parasites from multiple levels of biotic organization

Biotic level	Example	Host	Deceptive strategy	Type of deceptive signal	Effect on host behavior
Virus	Rabies lyssavirus (rabies)	Bats	Rabies glycoprotein is a molecular mimic of acetylcholine and binds to nicotinic acetylcholine receptors (Rustici et al. 1993)	Molecular	Symptoms of rabies infection include hydrophobia, anxiety, hyperactivity, aggression and fearlessness (Bano et al. 2016)
Protozoan	*Toxoplasma gondii* (toxoplasmosis)	Cats	Parasite tyrosine hydroxylase mimics the activity of the host enzyme, increasing the amount of dopamine present in the brain	Molecular	(In rats) increase in exploratory behavior, decrease in neophobia and fear of cats, its primary host (Webster 2007). This is linked with increased dopamine
Fungus	*Ophiocordyceps unilateralis*	Ants	Guanidinobutyric acid and sphingosphine are secreted by the fungus and may affect ant behavior (de Bekker et al. 2014)	Molecular	The infected ant climbs to the tip of a leaf, and then clamps its jaws on it until it dies. Then the fungus bursts out of the head of the ant and spreads its spores
Invertebrate	Hairworm (*Spinochordodes tellinii*)	Grasshoppers	Parasite produces Wnt proteins that appear to be molecular mimics of host proteins (Biron et al. 2005)	Molecular	The hairworm causes the grasshopper to commit suicide by drowning, promoting spread of parasite larvae
Vertebrate	Cuckoo	Nesting birds	Cuckoo chick mimics host chicks, including begging behavior	Visual and auditory	Host bird diverts resources to feed the cuckoo chick. The chick gape is a stimulus that induces the host birds to supply it with food
Human	Psychopaths (described as 'social parasites' (Karpman 1949))	Non-kin members of same species	Affective mimicry (the mimicry of emotions) (Book et al. 2015)	Visual and verbal	Victims are deceived into thinking the psychopath is trustworthy

ACE2 as a receptor and occurs at the S2' cleavage site by the cell surface membrane protease TMPRSS2 (Hoffmann et al. 2020a).

The spike protein also possesses a polybasic cleavage site (PCS), consisting of the sequence RRAR, located at the juncture of the S1 and S2 subunits (Andersen et al. 2020). PCSs are commonly encountered in pathogen membrane proteins, typically increasing their virulence (Braun and Sauter 2019). Consistent with this, the SARS-CoV-2 spike protein PCS is important for the pathogenicity of the virus (Johnson et al. 2021). The spike protein PCS can be cleaved by the protease furin (Hoffmann et al. 2020b), a secretory pathway protease localized in the Golgi (Shapiro et al. 1997), and may also be cleaved by trypsin-like proteases (such as TMPRSS2) and cathepsins (Jaimes et al. 2020). Cleavage of the PCS enhances virus cellular entry (Shang et al. 2020) and may be important for transmissability, given that it promotes the open conformation of the RBD which enhances binding to ACE2 (Wrobel et al. 2020). The exact protease(s) responsible for cleavage of the PCS remains to be determined, which would clarify whether cleavage occurs within the cell or in the extracellular environment.

Cleavage at the PCS may enhance shedding of the S1 subunit prior to receptor binding, which may explain the presence of cleaved spike protein lacking the S1 domain on the virus surface (Cai et al. 2020; Zhang et al. 2020). The S2 rumps form extended spikes, which may act as decoy epitopes (Cai et al. 2020). Decoy epitopes are thought to attract non-neutralizing antibodies, diverting immune resources from neutralizing epitopes (Jin et al. 2018), and can be considered a form of deceptive mimicry.

The virus may be able to modulate which host receptor it binds to by controlling the proportion of PCS-cleaved spike protein on its surface, given that only PCS-cleaved spike protein is able to bind to neuropilin-1. This is because binding is dependent on the presence of a C-end rule (CendR) motif at the C-terminus of the S1 domain, produced by PCS cleavage, described as follows.

Neuropilin-1's endogenous ligands include members of the vascular epithelial growth factor (VEGF), and class III semaphorin families (Parker et al. 2012). VEGF family members are peptides that have the common characteristic of a short basic CendR motif at their C-termini, which is used for binding to the receptor (Teesalu et al. 2009). The motif is generated by proteolytic cleavage of the PCS consensus sequence R/KXXR/K. VEGF family members that bind to neuropilin-1 include VEGF (Soker 1998), placental growth factor 2 (Migdal et al. 1998), and transforming growth factor β1 (Glinka and Prud'homme 2008). Of the semaphorin family, neuropilin-1 binds the class 3 semaphorins 3A, 3B, 3C and 3D (Toledano et al. 2019). PCSs are found in all class 3 semaphorins and are comprised of the consensus sequence KRRXRR (Varshavsky et al. 2008). Thus, the CendR motif is commonly found in neuropilin's endogenous ligands (Teesalu et al. 2009), and is of key importance for binding to neuropilin (Parker et al. 2019; Lee et al. 2003).

Neuropilin-1's endogenous ligands constitute a molecular Müllerian mimicry ring, with the CendR motif a common shared molecular signal recognized by neuropilin-1, the receiver (Fig. 1). The cleaved PCS of SARS-CoV-2 spike protein represents a Batesian invader of the CendR mimicry ring, using deceptive Batesian mimicry to 'trick' the receiver, neuropilin-1, into binding to it. Given that neuropilins

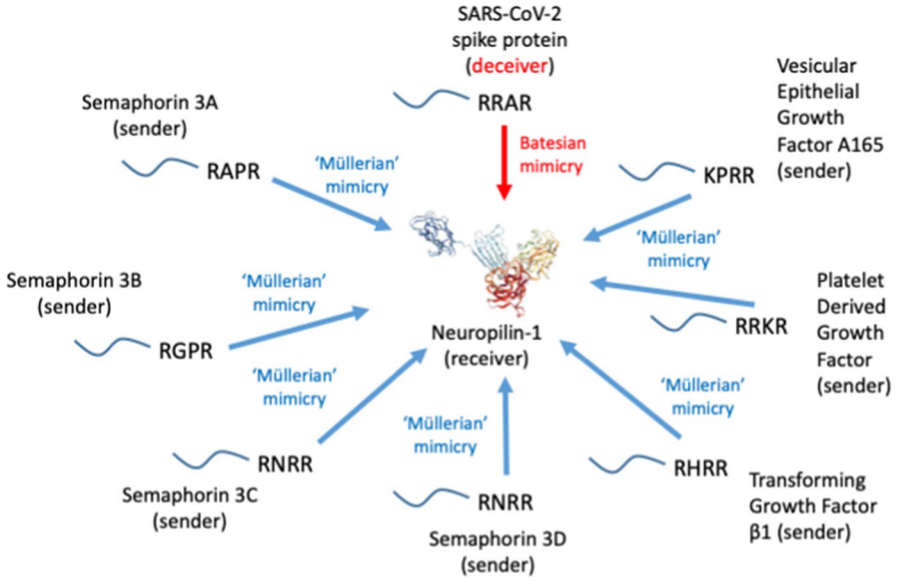

Fig. 1 Müllerian molecular mimicry ring consisting of neuropilin-1 and its ligands, with SARS-CoV-2 spike protein as a Batesian invader. Neuropilin-1 and its endogenous ligands comprise a Müllerian molecular mimicry ring. The ring is formed by the host genes (the senders) that code for endogenous ligands which share a common signal, the CendR motif. The common signal is recognized and bound by neuropilin-1 (the receiver). This is part of normal host physiology and results in a common benefit to all participants of the ring as they have perfect common interest. The cleaved PCS of virus spike protein is a Batesian mimic of the CendR motif, deceiving neuropilin-1 into binding to it. This facilitates entry of the virus into the cell, which is beneficial to the virus, but harmful to the host, hence host and virus have a conflict of interest. Spike protein binding has analgesic effects, which may positively influence the mood of the infected person, promoting transmission of the virus. Given that neuropilin-1 and its endogenous ligands are found throughout the vertebrates, the ring appears to have been stable over hundreds of millions of years, despite the likelihood of repeated invasions by viral Batesian molecular mimics over time. These are indicated by the existence of several human viruses which target neuropilins using molecular mimicry of the CendR motif (Table 2), and may be attributed to the simple nature of the CendR motif, which makes it easy to mimic. A detailed signaling games definition of Müllerian molecular mimicry rings and Batesian molecular mimics is described in (Massey and Mishra 2018; Casey et al. 2021). The PDB identifier for the neuropilin-1 structure is 4GZ9, and the amino acid recognition motifs for each ligand were obtained from the following references: Vesicular Epithelial Growth Factor A165 (Vander Kooi et al. 2007), Platelet Derived Growth Factor (Siegfried et al. 2003), Transforming Growth Factor 1β (Dubois 1995) and semaphorin 3A/B/C/D (Parker et al. 2013)

internalize ligands with CendR motifs through endocytosis (Teesalu et al. 2009), they may constitute an attractive target for viral surface proteins which have undergone PCS cleavage, producing CendR motifs.

The N-termini of semaphorins bind to the a1/a2 domain of neuropilin-1, while the CendR motif of semaphorins binds to the b1/b2 domain (Lee et al. 2003, a review). Likewise, the CendR motif of VEGF binds to the b1 domain (Lee et al. 2003). Thus, it is likely that PCS-cleaved SARS-CoV-2 spike protein, and the array of PCS-cleaved viral surface proteins in Table 2, also binds the b1/b2 domain. Consequently, deceptive molecular mimics of semaphorin and VEGF that bind to the

Table 2 Viruses that bind neuropilin receptors

Virus (viral group in brackets)	Neuropilin receptor	Other host receptor	Virus host-binding protein	Mechanism of binding to neuropilin	PCS involvement
Human T-cell lymphotropic virus type 1 (HTLV-1, retrovirus)	Neuropilin-1 (Ghez et al. 2006)	GLUT1 (Manel et al. 2003)	Envelope protein (Ghez et al. 2006) (Type I fusion protein)	Envelope protein is a molecular mimic of VEGF (Lambert et al. 2009), with a C-end rule motif (Kusonoki et al. 2018)	Furin cleavage is essential for cell entry (Hasegawa et al. 2002)
Epstein-Barr virus (EBV, herpes virus)	Neuropilin-1 (Wang et al. 2015)	CD21 (Fingeroth 1984)	Glycoprotein B (Wang et al. 2015) (Type III fusion protein)	Glycoprotein B possess a C-end rule motif (Wang et al. 2015)	Furin cleavage enhances infectivity (Wang et al. 2015)
orf virus NZ2 (poxvirus)	Neuropilin-1 (Wise et al. 1999)	Vascular endothelial growth factor receptor 2 (VEGFR2) (Wise et al. 1999)	VEGF-like protein (Wise et al. 1999) (part of the Entry Fusion Complex)	VEGF-like protein is a molecular mimic of VEGF (Wise et al. 1999)	Not reported
Human cytomegalovirus (CMV, herpes virus)	Neuropilin-1 (Lane et al. 2020) and neuropilin-2 (Martinez-Martin et al. 2020)	Platelet derived growth factor receptor alpha (PDGFR-α) (Soroceanu et al. 2008) and epidermal growth factor receptor (EGFR) (Wang 2003)	Glycoprotein B (Soroceanu et al. 2008; Wang et al. 2003) (Type III fusion protein)	Remains to be determined	Furin cleavage is important for infectivity (Jean et al. 2000)

b1/b2 domain may have utility in the pharmaceutical treatment of COVID-19, by blocking the deceptive spike protein binding to neuropilin-1 (Daly et al. 2020). A potential problem is that the pharmaceuticals will block the binding of the endogenous ligands of neuropilin-1 that possess CendR motifs, comprising the Müllerian mimicry ring shown in Fig. 1.

In addition to facilitating cellular entry of the virus, binding of spike protein to neuropilin-1 has an analgesic effect, mediated via sensitization of nociceptor activity (Moutal et al. 2021). Social withdrawal is associated with chronic pain (Turk et al. 2016), consequently pain reduction by neuropilin-1 might act to mitigate such withdrawal. This would lead to an increase in the number and duration of social interactions of the infected person, potentially increasing R_o in a population. In this way, the virus may modulate host mood and behavior to its own benefit.

Public health regulations are likely to exert a significant selective pressure on the virus. A focus of public health restrictions only on those who are symptomatic might enhance the effect of analgesia to the virus' benefit. In contrast, some regulations may act to counteract the utility of analgesia to the virus. For example, widespread testing may help to detect persons infected with the virus but who feel well.

Sickness behavior typically results from RNA virus infection, and includes decreased social exploration and libido, depression, lassitude, insomnia and anorexia (Shattuck 2015). RNA virus infection triggers an increase in interferon levels (Nan et al. 2014), and interferon-α has been shown to induce social withdrawal and depression (Lotrich 2009). Sickness behavior is proposed to be adaptive to the host in that it reduces energetic costs, and the risk of predation while debilitated by infection (Shattuck et al. 2015). Thus, interferon suppression mechanisms of SARS-CoV-2 may have the dual beneficial effects to the virus of delaying the immune response allowing the virus to replicate more efficiently, and of countering reduced transmission associated with sickness behavior, by mood manipulation. While virus mediated repression of sickness behavior may be beneficial to the virus in that it may promote transmission, it is expected to be harmful to the host.

3 Evolution of Neuropilin-1 Binding by SARS-CoV-2

The spike protein PCS was acquired by the ancestor of SARS-CoV-2, indicated by its absence in the spike protein of its closest relative RaTG13, isolated from the Intermediate Horseshoe bat *Rhinolophus affinis* (Andersen et al. 2020). Whether the PCS was acquired in bats before the host jump to humans, or if it was acquired in humans after the transfer from bats is unclear, as is the source of the PCS sequence; the PCS may have arisen via recombination with other PCS containing bat coronavirus spike proteins, in the ancestor of SARS-CoV-2 (Zhou et al. 2020). There is also the possibility that the PCS was introduced artificially as part of a lab escape, discussed further below.

PCS cleavage may bring four advantages to the virus:

(1) Facilitation of ACE2 recognition and cell entry
(2) Enabling of neuropilin-1 binding and cell entry

(3) Pain modulation via neuropilin-1 binding
(4) Promotion of the formation of extended spikes, which may act as decoy epitopes, or protect the virus (Cai et al. 2020).

These may contribute synergistically in a pleiotropic fashion to the adaptive benefit of the PCS to SARS-CoV-2 in human populations. PCSs are subject to multiple gain/loss events across the coronaviruses (Wu and Zhao 2021), although they are absent in all other sarbecoviruses, the coronavirus group to which SARS-CoV-2 belongs (Jumgreis et al. 2021). The lack of a PCS in the other sarbecoviruses implies that they do not bind neuropilin, and so the PCS might contribute to differences in tissue tropism between SARS-CoV-2 and other sarbecoviruses. Change in the presence or absence of a PCS in a viral lineage may represent a switch between a single strategy (single receptor binding) and a mixed strategy (multiple receptor binding). Given that the PCS is absent in the bat ancestor RaTG13, then its spike protein would be unlikely to bind neuropilin and modulate pain in the bat host.

The origin of the PCS is interesting, given that recombination occurs only moderately in human coronaviruses (Pollett et al. 2021). The possibility has been raised that the PCS was artificially inserted into the spike protein in a gain of function (GOF) experiment, prior to entry of the virus into the human population (Segreto and Deigin 2020). Indeed, SARS-CoV-1 spike protein has had a PCS inserted in a GOF experiment, albeit in pseudotyped lentiviruses which are safer to use (Follis et al. 2006). With SARS-CoV-2, the GOF scenario is difficult to examine from sequence analysis alone given the short length of the PCS, which means that it effectively 'blends' into the much longer spike protein backbone sequence. Whether introduced by human agency or natural selection, this sequence conformity would act to enhance functional compatibility with the rest of the spike protein. 'No-see-um' approaches leave no trace of artificial ligation as the restriction sites do not remain in the final sequence after ligation; this approach has been used previously for altering the SARS-CoV-1 genome (Baric and Sims 2005). The rationale for using 'no-see-um' approaches for coronavirus genome manipulation are unclear. If the PCS was inserted for malign purposes, this blending effect would have a deceptive role in obscuring its engineered origin, representing a form of deceptive cue mimicry.

In addition to direct genetic manipulation of the virus, another potential GOF scenario is that of serial passage of the virus ancestor through humanized mice (Sirotkin and Sirotkin 2020). One purpose of serial passage experiments is to observe how pathogens might adapt to a new host after an initial zoonotic host jump (Ebert 1998), while the use of humanized mice allows mutations that might lead enhanced infectivity in humans to be identified. For example, in serial passage experiments in humanized mice, simian immunodeficiency virus (SIV) was evolved into HIV (Schmitt et al. 2018). Escape of such an enhanced pathogen has the potential to cause an epidemic, although HIV is less contagious than a respiratory virus.

Mouse strains possessing a genetically modified human like dipeptidyl peptidase 4 (DPP4) receptor have been used for serial passage experiments on Middle East respiratory syndrome (MERS) coronavirus (Cockrell et al. 2017), while transgenic mice expressing human ACE2 have been used for serial passage experiments on

WIV1 coronavirus (Menachery et al. 2016), SARS-CoV-1 (Menachery et al. 2016) and SARS-CoV-2 (Jiang et al. 2020). Serial passage has been described as mimicking natural selection in its effects on viral genome sequences (Sirotkin and Sirotkin 2020), and so is a rather effective method of producing enhanced pathogens that appear to be of natural origin.

While serial passage of the virus ancestor in mice expressing human ACE2 and subsequent lab leak might explain the strong binding of the SARS-CoV-2 spike protein RBD for human ACE2 compared to a range of other mammalian ACE2 receptors, including bat (Sirotkin and Sirotkin 2020; Piplani et al. 2021), the occurence of the PCS is not so explicable under this scenario. If the PCS did arise as a result of serial passage in humanized mice, or another experimental host, then it may be expected that the PCS would confer an evolutionary advantage to the virus in the host used for the serial passage, and that it might be maladaptive in the original bat host given its absence there, and in other sarbecoviruses. In a precedent, PCSs have been shown to emerge in avian influenza strains during serial passage in chicken embryos (Laleye and Abolnik 2020).

The PCS was observed in all 2492 SARS-CoV-2 genome sequences from around the world (Islam et al. 2020) indicating that it is being maintained under purifying selection in the human body. Consequently, whether the insertion occurred naturally or via human agency, the PCS appears to have adaptive benefit in the human body. Ultimately, molecular evolutionary considerations, including of the type discussed here, may help shed light on the origin of SARS-CoV-2.

The observation that the PCS is rapidly lost from passage through cell culture indicates that there is an additional selective pressure present in the multicellular host that maintains the PCS (Lau et al. 2020). The loss of the PCS in cell culture likely reflects the reduced stability of spike protein that results from cleavage at the PCS, which implies that the PCS will have a tendency to deletion unless maintained for an adaptive reason in the human body, which supercedes its decreased stability (Wrobel et al. 2020). From the list above, such reasons may include (3) pain modulation via neuropilin-1 binding (which may manipulate host behavior), and (4) promotion of the formation of extended spikes (which may act as decoy epitopes to the host immune system).

Other viruses that bind neuropilins are described in Table 2. Such binding has evolved multiple times, indicating that the different virus surface proteins independently evolved molecular mimicry of VEGFs and semaphorins via acquisition of CendR motifs resulting from cleavage of PCSs. This is facilitated by the simple nature of the PCS, which is relatively straightforward to mimic due to its short length, constituting a 'cheap' signal. This is in contrast to a 'costly' or 'handicap' signal, which is expensive to produce, and expensive to copy, which has the effect of taming deceptive mimicry (Zahavi 1975). Many other virus surface proteins in addition to those listed in Table 2 have furin cleavable PCSs (Iaaguirre 2019), and consequently are expected to possess CendR motifs after cleavage, however data is lacking as to whether these viruses also bind neuropilin.

The convergent evolution of neuropilin binding by different viruses may have occurred because of the utility of neuropilin's internalization mechanism, because its ligand binding signal is easily mimicked, and/or because neuralgic effects from

binding provide benefits via behavioral modulation of host mobility. These pleiotropic benefits may have led to the widespread occurrence of neuropilin-1 binding in viruses.

4 Other Potential Forms of Host Behavioral Manipulation by SARS-CoV-2

There are other potential forms of host behavioral manipulation used by SARS-COV-2. An example of behavioral manipulation displayed by viruses results from the suppression of interferon alpha, whose expression can lead to mood modulation and social withdrawal, as part of sickness behavior (Seitz et al. 2020). There are a range of interferon suppression mechanisms displayed by SARS-CoV-2 (Xia et al. 2020), indicating its importance to the evolutionary success of the virus. While suppression of interferon has an obvious benefit to the virus due to inhibition of the innate immune response, an additional benefit may be enhanced transmission via suppression of the tendency toward social withdrawal, which is promoted by interferon expression. This may contribute to the selective pressure for the evolution of interferon suppression, thus the benefits of interferon suppression may be pleiotropic, consisting of delaying the immune response, and reducing sickness behavior.

Interferon I suppression appears more potent in SARS-CoV-2 than in MERS or SARS-CoV-1 (Xia et al. 2020). Low levels of interferon may account for the late onset of symptoms in infected individuals, which is held responsible for increased transmissability, and the high frequency of asymptomatic carriers (Chu et al. 2020). An interesting question is whether interferon suppression by SARS-CoV-2 is more potent compared to its bat ancestor, and whether its behavioral effects are more beneficial to the virus in the human host.

An additional factor is that of age, given that interferon production decreases with age in humans (Abb et al. 1984). This might be expected to enhance any advantageous effects on the behavior of the infected individual resulting from interferon suppression and consequent reduction in sickness behavior by the virus. However, there may be a more important factor, that of interferon dysregulation. The increase of interferon dysregulation with age has been linked to the severity of COVID-19 in older people (Lopez et al. 2020). Killing the host is not regarded as advantageous to a pathogen that relies on host mobility for transmission, such as respiratory viruses (Ewald 2004). Thus, any advantage to the virus from interferon suppression might be expected to be countered by the increase in severe disease from interferon dysregulation in older people.

Intriguingly, biomolecular modelling indicates the capacity of the spike protein PCS for binding with acetylcholine receptors (Oliveira et al. 2021), indicating an additional manner in which the spike protein might modulate human behavior. This binding capacity is reminiscent of the rabies virus, which binds to nicotinic acetylcholine receptors (Lentz et al. 1982) (Table 2), and which appears responsible for the drastic behavioral changes that results from rabies infection (Hueffer et al. 2017).

An interesting aspect to SARS-CoV-2 infection is the reduced sense of smell experienced by some patients (Mao et al. 2020). This has been attributed to

neuroinvasion of the olfactory bulb (De Melo et al. 2020), which has been linked to the high level of expression of neuropilin-1 in that tissue (Cantuti-Castelvetri et al. 2020; Mayi et al. 2021).

While the sense of smell in humans is relatively weak, reduction in the sense may have an adaptive benefit for coronavaviruses in bats, possibly increasing risky behavior. Given that spike protein PCSs have been observed in a range of coronaviruses, it would be interesting to determine if the host species of coronaviruses that possess PCSs rely particularly on their sense of smell (Chaverri et al. 2018). A well-known example of a parasite manipulating its host's sense of smell is provided by *Toxoplasma gondii*. Rats infected by *T.gondii*, experience loss of fear of the smell of cats, the parasite's main host, which has been proposed to increase the chance of predation of infected rats and so transmittal of *T.gondii* (Berdoy et al. 2000).

Infection by SARS-CoV-2 is also associated with impaired consciousness, linked with inflammation, vascular damage and neuroinvasion (Losy 2020). It is unclear if this symptom is adaptive to the virus, for example by increasing the probability of transmission via an increase in risky behaviors. This might include a failure to adhere to hand washing and other social distancing measures, in the modern milieu.

Coughing is a protective reflex and a major symptom associated with SARS-CoV-2 infection (Center for Disease Control, CDC). Coughing is partly triggered by sensory neurons in the lungs and is commonly associated with infection by respiratory viruses, promoting viral transmission (Dhand and Li 2020). In SARS-CoV-2, the exact mechanism of cough induction remains to be determined, however it has been proposed that infection is associated with production of the pro-inflammatory peptide bradykinin: this has been termed a 'bradykinin storm' and may cause several of the severe symptoms of COVID-19 (Garvin et al. 2020). Bradykinin activates pulmonary unmyelinated sensory neurons (C-fibers) to induce coughing (Canning 2009). ACE2 cleaves des-arginine(9) bradykinin, a metabolite of bradykinin, while the ACE receptor cleaves bradykinin (Curran et al. 2020). Thus, virus binding to ACE2 is likely to interfere with bradykinin regulation. Interestingly, des-arginine(9) bradykinin has pain suppressing qualities, reducing hyperalgesia in rats (Perkins et al. 1993). This means that a reduction in des-arginine(9) bradykinin cleavage resulting from viral blocking of ACE2 receptors might contribute to pain suppression, in addition to that resulting from neuropilin-1 binding, discussed above.

A mechanical manner of inducing a neuronally-mediated cough reflex is via the production of fluid in the lung. The production of fluid has also been linked with the bradykinin storm (Garvin et al. 2020), and may have adaptive value to the virus, as cough induction will enhance its spread through aerosols and droplets. However, a tradeoff may be expected in that frequent coughing will thwart the ability to mimic a healthy person, essentially acting as an honest signal of infection which may be detrimental to the virus by encouraging isolation of infected individuals. Alternatively, coughing may have utility to the virus by promoting hospitalization, as discussed below.

Lastly, diarrhea is a common symptom of COVID-19 (Guo et al. 2021), and appears to be a transmission strategy of numerous pathogens (Hodges and Gill 2010). While infectious SARS-CoV-2 virus has been recovered from patient stools (Xiao et al. 2020), it is unclear to what degree fecal–oral transmission occurs.

Pathogen-induced diarrhea may be caused by inflammation, or neuronal manipulation via the secretion of neurotransmitters (Hodges and Gill 2010). For example, *Clostridium dificile* and *Entamoeba histolytica* both secret neuropeptides that exacerbate diarrhea (Hodges and Gill 2010). In SARS-CoV-2, the mechanism behind diarrhea induction remains to be determined, likewise the mechanisms utilized by other viruses that cause diarrhea is also unclear (Guo et al. 2021).

5 Asymptomatic Carriers Represent Virus Induced Human Mimics

A feature of a substantial proportion of people infected with SARS-CoV-2 is their mildly symptomatic or asymptomatic nature, which may be considered a form of deceptive mimicry on behalf of the virus, acting to promote transmission. For example, fever is the result of the release of cytokines in response to viral infection (Conti et al. 2004), and a high temperature has been widely viewed as a useful early indicator of potential infection by SARS-CoV-2. However, in January 2021 only 38.9% of individuals assessed in Puerto Rico who had a positive molecular COVID-19 test presented a fever (19th Informe del Sistema Municipal de Investigación de Casos y Rastreo de Contactos, Departamento de Salud, Gobierno de Puerto Rico). This indicates that a high proportion of infected individuals are asymptomatic, which is of strategic benefit to the virus, as it enhances transmission.

There are two aspects to this deceptive mimicry: interpersonal deception (deception of others) and intrapersonal deception (self-deception). Interpersonal deception involves the infected person mimicking a healthy person, so others will be less likely to take precautions when coming into contact with them, promoting spread of the virus. Intrapersonal deception involves the virus manipulating the mood of the infected person, so that they may feel well, which will encourage them to maintain their social interactions, rather than self-isolate. This has an interesting parallel with von Hippel and Trivers' theory of self-deception, which proposes that people deceive themselves in order to better deceive others (von Hippel and Trivers 2011). Neither virus-induced intrapersonal or interpersonal deception are likely to benefit the host, but are beneficial to the virus if they increase viral transmission. Given the ancestor of SARS-CoV-2 evolved in bats, it is not clear if these effects would have been beneficial in these animals.

These perspectives have relevance to the debate as to whether SARS-CoV-2 is expected to evolve to become more or less pathogenic over time. The 'tradeoff' hypothesis proposes that pathogens evolve over time to become less pathogenic, partly by reducing their titer, as prolonged host survival increases the opportunities for pathogen spread (Anderson and May 1982). This would mean that there is an evolutionary imperative to induce an asymptomatic or mildly symptomatic response to infection, which would result in the host effectively mimicking a healthy organism, promoting transmission. This is because the asymptomatic/mildly symptomatic host would be more likely to maintain their social contacts, who themselves would not be likely to take evasive action of the infected individual, due to the lack of alarming symptoms.

However, a refinement to the tradeoff hypothesis was presented by Ewald, who proposed that the degree of pathogenicity evolved by an infective agent depends on its mode of transmission (Ewald 2004). Those pathogens that do not rely on host mobility for transmission have no evolutionary imperative to reduce their pathogenicity, and so instead maximize their titer. These include water-borne, vector-borne and attendant-borne pathogens. 'Attendant-borne' refers to pathogens spread by medical attendants, in hospitals or other medical facilities.

Typically, respiratory viruses depend on host mobility for transmission, so according to Ewald's theory they would be expected to evolve to become less pathogenic over time. However, the hypothesis of enhanced pathogenicity resulting from attendant-borne transmission has particular relevance to SARS-CoV-2, as a significant proportion of infections appear to have occurred in hospitals (Rickman et al. 2021). Consequently, it may be to the advantage of the virus to induce severe symptoms, as this would mean transportation to a hospital, where the virus could be spread via attendants to vulnerable patients. In this scenario, by inducing severe symptoms the virus would be effectively manipulating not the host, but the emergency services, in order to further its spread. In particular, nosocomial transmission to elderly patients, who then return to their care homes and there spread the virus might be expected to reinforce this viral strategy. The success of this would be enhanced by the surprising decision of multiple health authorities worldwide to return elderly hospital patients to their care homes without virus testing or other preventative measures. This is of especial concern given that the emergence of virulent strains of the 1918 "Spanish" Flu has been attributed to transmission between immobile hosts in close quarters at the Western Front (Roes 2018).

6 Parasitic Host Manipulation Across Multiple Levels of Biotic Organization

Parasitism is a behavior found at all levels of biotic organization, from the molecular to the organismal and to human levels. Likewise, strategic host manipulation via deceptive mimicry is universally observed in viruses, bacteria, eukaryotic parasites, invertebrates and humans (Table 1). Considering such a wide scope allows universalities to be identified, which might then provide insights into a particular system, SARS-CoV-2.

Host–parasite interactions are expected to lead to evolutionary arms races, with parasites typically evolving deceptive strategies to manipulate the host, and in response the host evolving counter-strategies. In addition, in humans, society and culture may evolve counter-strategies that combat viral deception.

If the effects of SARS-CoV-2 on the nervous system and behavior are better understood, then society can better design detection, mitigation and treatment strategies. In particular, if the virus is shown to manipulate the host to promote asymptomatic transmission, then this may give additional impetus to the development of technological solutions to better detect infected individuals; these would represent societal counter-strategies to the virus's host manipulation. Interestingly, cultural counter-strategies appear to have arisen in regions of high pathogen prevalence such

as differences in collectivism (Fincher et al. 2008), food preparation (Sherman and Billing 1999), marriage structures (Low 1990), mate preferences (Gangestad and Buss 1993), parenting practices (Quinlan 2007) and moral vitalism (Bastian et al. 2019).

Del Giudice has proposed that the human brain has evolved molecular mechanisms to combat neuromanipulation by microbial parasites, including costly signaling and avoidant sequence change in host receptors (Del Giudice 2019). Such mechanisms may have evolved to combat some of the viral strategies described here, and these host defenses stand in addition to those of the immune system.

In order to complete this purview of parasitic deception in nature, we have included an example of a human personality trait, psychopathy, that has been described as intra-species parasitic behavior, and may be characterized by manipulation of others via deceptive mimicry (Table 1). Using the terminology of non-cooperative games, such human parasitic behavior may be characterized as 'defector' behavior. The impact of such behavior may have had profound effects on our evolution. The Machiavellian intelligence hypothesis proposes that intelligence partly evolved as a need to detect and outwit deceptive rivals, as well as the need to utilize deception per se (Byrne 2018) This is consistent with the existence of sophisticated neurological mechanisms for detecting deception, such as reading facial cues and speech patterns (von Hippel and Trivers 2011). Thus, the phenomenon of parasitism may have engendered not only the evolution of our immune system, but also key characteristics of our behavior, and ultimately of our institutions, resulting from the ubiquity of information asymmetry in nature.

7 Conclusions

We have discussed the capacity for host behavioral manipulation of SARS-CoV-2, which leads to the following conclusions:

1. The use of a signaling games framework allows commonalities to be observed in parasitic behavior across biotic levels. This supports the supposition that RNA viruses in general, and SARS-CoV-2 in particular, should engage in host behavioral manipulation.
2. Analgesia due to neuropilin binding is argued to be beneficial to viral transmission by ameliorating sickness behavior. The evolution of neuropilin binding is shown to be convergent across human RNA viruses, which may partly be driven by this effect.
3. Neuropilin binding by SARS-CoV-2 spike protein is dependent on a recently acquired PCS, and so this ability is expected to be absent in the bat ancestor. The acquisition of the PCS by the ancestor of SARS-CoV-2 may have been partly driven by its effects on human behavior.
4. Additional mechanisms of host behavioral manipulation via neuromanipulation include interferon repression, cough induction, and potentially diarrhea and impaired consciousness. Reduction in sense of smell is not clearly adaptive to the virus in humans but may be in some bat species

5. Asymptomatic or mildly symptomatic people infected with SARS-CoV-2 may represent virally induced mimics, with a selective pressure on the virus to induce this phenotype in the host, to a degree depending on the social environment.

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