Journal of Ideas in Health

e ISSN: 2645-9248 Journal homepage: www.jidhealth.com Open Access

Viewpoint Article

Understanding SARS-CoV-2 features of infectivity, aggressiveness, and transmissibility: an insect-vector theory for SARS-CoV-2 dissemination

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a ribonucleic acid–based (RNA-based) lineage B β-coronavirus characterized by 10-20 times higher infectivity and transmissibility even across species than previous coronaviruses. The significant infectivity rate of SARS-CoV-2 is due to its different host cell entry mechanisms that are mainly via angiotensin-converting enzyme 2 (ACE2) receptors contrasting earlier coronaviruses that used mainly the endosomal route. Due to the widespread distribution of ACE2 receptors throughout our body, various routes of infectivity are possible, highlighting the necessity of employing multiple forms of protection besides face masks to limit inter-human transmissibility. SARS-CoV-2 exhibits other remarkable features such as the ability to escape the immune system repeated genomic mutations that make it difficult to design a vaccine to address all viral strains and form huge host cell syncytia leading to massive tissue destruction. If we accept SARS-CoV-2 primary reservoir from bats, we should investigate the routes of viral inter-species propagation. In this article, a new theory is proposed- that the dissemination of the virus from the bats to other species and humans could have been possible via an insect vector, as insects possess significant amounts of both ACE2 receptors and a disintegrin and metalloprotease 17 (ADAM-17) enzymes that are essential for virus infectivity.

Keywords: SARS-CoV-2, ACE2, ADAM-17, COVID-19, Infectivity, Insect Vector, Romania

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a ribonucleic acid-based (RNA-based) lineage B β-coronavirus, similar to other genetically related coronaviruses such as severe acute respiratory coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS), and several bat coronaviruses, that has currently become the major world health problem. Contrasting SARS-CoV and MERS that generated pandemics in 2002-2003 and 2015, SARS-CoV-2 is far more aggressive, characterized by 10-20 times higher infectivity and transmissibility even across species and devastating mortality rates [1-4] that left humanity without efficient solutions and resources. The outstanding aggressiveness of SARS-CoV-2 contrasting previous SARS viruses is due to several mutations that have provided this virus with the incredible ability to recognize ACE2 receptors in host cells and mediate its cell entry via this route [5,6], gaining a key that opens all doors. This way of cell entry is unique for SARS-CoV-2, as previous SARS coronaviruses mainly used the endosomal pathway of cellular entry, a less efficient route because it triggers a defensive and offensive host immune response. Instead, cell entry via ACE2 receptors is far more insidious as virus entry is mediated, "invited" by its apparent acquaintance to host ACE2. ACE2 entry route is a very advantageous modality as these receptors are extremely abundant throughout the body, being present on all vascular endothelial cells, not only pulmonary but of all organs (heart, kidney, liver, testicular, etc.). ACE2 is also expressed on epithelial cells- alveolar cells type I and II, but even red blood cells, digestive tract cells (from mouth cavity throughout digestive tract), mucosae (important quantities on nasal mucosa or cornea) [7-9]. This impressive expression of ACE2 receptors throughout our body explains the possible ways of human infectivity via respiratory or corneal pathways and putative digestive, fecal-oral contamination, as described in bats or by contact with contaminated blood or urine. The high corneal density of ACE2 receptors highlights the necessity of wearing protective eyeglasses to prevent another important route of

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inter-human infectivity, maybe as important as the wear of a face mask.

Moreover, the finding that there is a high density of testicular ACE2 receptors in humans [4] brings into question an additional putative sexual transmission route of infection and the post-COVID-19 risk of male infertility that should be addressed by future research in extended studies. The SARS-CoV-2 features of aggressiveness and escape from the human immune system. Besides the increased affinity towards the ACE2 receptors, another feature of aggressiveness that distinguishes the SARS-CoV-2 from previous coronaviruses is its ability to form huge cell syncytia. This process leads to important host tissue loss and inflammatory immune response. The positive feedback in the inflammatory loop supplementary increases virus-mediated destruction and leads to subsequent fibrotic sequelae [5].

Additionally, in SARS-CoV-2 disease, host immune response and developed antibodies are not efficiently protective, and SARS-CoV-2 hijacks immune cells to disseminate throughout the body. Even in this feature, SARS-CoV-2 outstands as it can exploit host immune response- the antibodies-to increase its entry into immune cells, such as macrophages and probably lymphocytes – a process that is called antibody-dependent enhancement of coronavirus entry [8]. In this mechanism, antiviral antibodies do not destroy the pathogenic agent, but after being linked to the virus, they mediate its entry into the immune cells via Fc-receptors [6]. The SARS-CoV-2 antibody-dependent enhancement of coronavirus entry into the host cells explains why an effective vaccine is difficult to be developed in the near future. The possibility of an effective vaccine design for all the SARS-CoV-2 strains in the near future is also pale as this type of coronavirus has a huge registry of immune escape possibilities. This type of virus acquires systematic, repeated genomic mutations in time, between geographic regions, between individuals, and intra-individually, across time, 103 recent SARS-CoV-2 genomes being already described [4, 6]. This feature is similar to the hepatitis C virus (HCV), a virus against which, despite time, no vaccine has been designed. Therefore, SARS-CoV-2 disease is a serious global health problem of present and future from several points of view: high associated mortality rates, unpredictable effects in apparently cured people, and the possibility to reemerge in the future in even more aggressive forms, the result of additional genomic mutations and evolutionary selection of genes.

Naturally, as SARS-CoV-2 escapes and is even enhanced by immune system mechanisms, being ultimately harbored in immune cells such as macrophages and lymphocytes, a major concern of humanity is the possibility of insidious viral survival in human cells of apparently healed individuals and of systematically reemerging (apparent reinfections). The subsequent reinfections, paralleled by a decrease in the host immune cell number, would ultimately lead to the infected individual's death, just like in the progression of an HIV infection. The SARS-CoV-2 transmission routes across species
Knowledge of SARS-CoV-2 transmission routes across species and between individuals is essential for effective prevention and surveillance of the population, especially those at increased risk due to their comorbidities, such as cardiovascular and metabolic diseases.

Currently, there are persisting controversies on SARS-CoV-2 initial origin and dissemination across species. Some authors consider that SARS-CoV-2 features that are at the base of its infectivity are unlikely to be determined by spontaneous evolutionary viral gain, although others disagree in this matter [5]. If natural selection and genomic mutations represent the actual mechanism behind SARS-CoV-2 evolution, it should normally result from a very prolonged period, not only a few months. Many of us would have already been infected in this scenario, and any person could be patient zero. However, others have suspected that SARS-CoV-2 could be the product of human refinement, appearing like an engineered entity based on an original vector that received genomic insertions to overcome the human body's important defense barriers.

In this regard, SARS-CoV-2 acquired features that distinguish it from SARS-CoV, MERS, and bat coronaviruses and render it possibilities for infectivity a cross-species, such as genomic sequences similar to HIV Ebola, HCV viruses and gain towards recognizing ACE2 receptors with the high affinity. These features appear as too evolved mechanisms to arise by random selections and create a pandemic in only a few months. If we accept the initial origin of SARS-CoV-2 from bats that are known to be natural concentrated reservoirs of various extremely dangerous viruses (coronaviruses, hepatitis C viruses, HIV), because these bats live in crowded communities where inter-individual viral transmission is easy, still we cannot explain the transmission of such a virus to humans or other animals (rodents, cats, dogs, etc.) [1,5,10-14].

Until now, the SARS-CoV-2 has been isolated from many animals besides humans and bats, such as domestic (dogs, cats) and farm animals (pigs, chicken, duck, wildlife (birds, exotic animals (many consumed in Chinese cuisine) such as snakes, cats, Chinese bamboo rats, raccoon dogs, civet cats, monkeys but the transmission mechanisms between species are unknown yet [14,15]. The putative animal vectors incriminated up to now (snakes, pangolins, civet cats, and raccoon dogs that represent exotic food in China) have been exonerated afterward. In this setting, our opinion is that the virus's putative initial carrier across species could be an insect. Insects have important numbers of ACE2 receptors (evolutionarily conserved proteins, although insufficiently described) [16-19], but also of ADAM-17 enzymes, essential for the viral and ACE2 activation [20]. Considering their important extension and numbers (there are hematophagous parasitic insects even on bats), insects could contribute to viral dissemination across species. Warm weather, such as in subtropical Wuhan, could have initially contributed to insect cycle progression, human dissemination of the virus, and a higher infectivity rate observed in certain countries contrasting others.

An insect-vector-driven virus theory could explain why malaria-endemic countries and the degree of SARS-CoV-2 infectivity are lower than expected [21,22]. Although anti-malarial medicines have not been found to have definitive positive effects on COVID disease, people use insect repellants more frequently, contrasting with other geographic regions in these countries. Currently, there is a persistent global apprehension regarding the vector-borne diseases of zoonotic origin that can acquire mutations and repeatedly reemerge, creating pandemics. It is already acknowledged that insect vectors such as mosquitos, ticks, blackflies, sandflies, tsetse

flies, fleas, lice, triatomine bugs are responsible for many feared infectious diseases, including malaria, dengue, chikungunya, Zika virus, yellow, West Nile fever, Japanese encephalitis, tick-borne encephalitis, leishmaniasis, Chagas disease (around 700,000 human deaths each year) [23]. Therefore, these insect vectors can transmit viruses, bacteria, protozoa, fungi, and parasites to humans, domestic and wild animals. The transmission can be biological, blood-borne (for bloodsucking insects), but also mechanical, where the insect acts as a carrier (on its legs, mouthpart, feces, vomit, hairs), although it never develops the infection [13].

There are reports that the house flies (Musca domestica Linnaeus) can mechanically transmit coronaviruses (such as turkey coronavirus, the agent of a very severe enteric infection of turkeys; pig coronavirus - agent of pig gastroenteritis) being therefore responsible for the viral dissemination within the same species, but putatively also across species. In fact, house flies can act as vectors for more than 30 infectious diseases (viral, bacterial, and protozoan)[15,24]. Besides coronaviruses, it is known that flies can also act as carriers for avian influenza viruses H5N7 and H7N1, which can persist in their alimentary tracts [25]. Also, the housefly can transport on its body the Newcastle disease virus, and it can harbor it for up to 96 hours [26]. Therefore, further research studies on this aspect should take into consideration that in many insect vectors, the viruses do not persist for extended periods, and the efficient time window for the study is limited. This ability of the house fly to act in the mechanical transmission of diseases has several explanations: their ubiquitous presence in large numbers (in the human houses, farms, domestic animals feeders and drinkers, but also in the wild environment); feeding behavior- flies frequently defecate and regurgitate/vomit while feeding; their common food is represented by putative coronavirus reservoirs such as human and animal feces, dried and fresh blood, sputum, respiratory secretions, dead birds, various corpses; also, carriage of the viruses via housefly exoskeleton; the constant movement of flies across food- surfaces- humans- animals; important areal- capable of covering up to 11.8 km in 24 hours.

The turkey coronavirus (earlier coronavirus) can persist in a viable form in the housefly's crop for an important period of 9 hours, creating a time window when it can further transmit the virus [27]. Even more, flies do not develop the infection, making them capable of transporting the infective agents along their life cycle [15, 25-27]. Some authors also consider cockroaches as putative vectors for coronaviruses by similar mechanisms to houseflies [13]. Mosquitos are also known to transmit to humans many single-stranded RNA viruses. As they feed on multiple species, including bats known as coronaviruses reservoirs, they could potentially play a role in disseminating coronaviruses and other types of feared viruses (e.g., Yellow fever; equine encephalitis, where the mosquitos transmit the infective agent from birds) across species. Even more, many of the arthropod-transmitted viruses express an important capacity to undergo mutations and gain specific host virulence [24]. Other authors have found earlier coronavirus-derived RNA and proteins in the midgut of the domestic cat flea (Ctenocephalides felis) (which is a known vector for many feared pathogens (Yersinia pestis, Rickettsia typhi, Bartonella spp., tapeworms, and filarial nematodes). This suggests that the coronaviruses could persist and replicate into fleas and act as biological and mechanical vectors of the disease across an important range of species, including the initial transmission from bats to other species. Also, a coronavirus-like agent was isolated in the tick of seabirds, responsible for the fatal peritonitis in cats [19]. Even moths could act as vectors for the coronaviruses, although studies on this aspect are currently missing. These data clearly suggest that insects can transmit earlier coronaviruses across animal species. Therefore, it is logical to suspect that they could have acted/ could still act as vectors for the SARS-CoV-2 and disseminate it across the animal species and humans.

The increased need for SARS-CoV-2 dissemination preventing strategies in front of the lack of efficient and specific therapies

Various types of therapies have been proposed for SARS-CoV-2 disease. However, none of them is specific for SARS-CoV-2 treatment, nor has it led to definitive and clear beneficial results [13]. As SARS-CoV-2 does not use the same mechanism of cell entry as other well-described viruses and there is an antibody-mediated enhanced viral entry into the host cells, most of the proposed drugs appear not only to be inefficient but even potentially dangerous. Unless human plasma of cured patients contains an impressive titer of antiviral antibodies, an average, variable in time antiviral antibody titer (sub-neutralizing titer) would potentially become harmful. Moreover, if we consider the antibody-dependent enhancement of coronavirus entry into the host cells, a vaccine could increase viral infectivity [8]. Anti-malarial drugs, especially Artemisia-based ones, appeared at a certain point to be more promising, as they destroyed big foreign particles already entered into the cell by a partially described mechanism [28]. However, the results are mixed as these drugs do not appear to prevent cell infection and massively destroyed infected cells containing the viruses trigger a massive inflammatory immune response overpassing the biological resources in severe cases. Also, the design of an efficient, specific therapy is difficult because the exact detailed mechanism of viral infectivity is insufficiently understood, including knowledge on the exact protease to activate the SARS-CoV-2 [29]. Facing these therapeutic limitations and in front of the many uncertainties regarding the detailed mechanism of SARS-CoV-2 infectivity, knowledge of the inter-human and across species viral dissemination would become an extremely powerful tool in the control of the COVID-19 pandemics [13]. In this light, the prevention/decrease of human exposure to various insect-vectors, including fleas, ticks, mosquitos, houseflies, and cockroaches, may spread various infective pathogens coronaviruses via various control methods (mechanical, physical, and even chemical) appears as a logical necessity.

Conclusion

In conclusion, a potential vector to disseminate the SARS-CoV-2 across species can be insects, as insects express extraordinary amounts of ACE2. In this context, future dedicated investigation of a putative insect-vector transmission route possibility appears essential. As the origins of SARS-CoV-2 remain enigmatic, subject of debates and suspiciousness, understanding the exact mechanism leading to infection propagation across species could bring unexpected promising therapeutic perspectives, including public infection prevention

and control. Also, previous studies have not investigated all the putative ways of infectivity across individuals.

Naturally, as SARS-CoV-2 escapes the immune system mechanisms, a major concern of humanity is the possibility of insidious viral survival in human cells of apparently healed individuals and of systematically reemerging (apparent reinfections), ultimately leading to the extinct of the infected individual. In the absence of a therapeutic escape, our future (not only for one-two years) is uncertain, as the intelligence of this type of virus and its evolutionary features imply that it could recur in repeated pandemics, under more and more aggressive forms, but over a world that is more and more depleted of human and material resources.

Abbreviation

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; MERS: The Middle East Respiratory Syndrome Coronavirus; COVID-19: The Coronavirus Disease 19; ACE2: Angiotensin-Converting Enzyme 2; ADAM-17: A Disintegrin and Metalloprotease 17, also known as TACE (Tumor Necrosis Factor-Alpha -Converting Enzyme); HCV: hepatitis C virus; RNA: ribonucleic acid.

Declaration

Acknowledgment

None.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials

Data will be available by emailing angelalazar.2008@yahoo.com

Authors' contributions

Angela Madalina Lazar (AML) is the principal investigator of this manuscript (Viewpoint). AML is the responsible author for the study concept, design, writing, reviewing, editing, and approving the manuscript in its final form. AML has read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. However, Viewpoint Articles need no ethics committee approval.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interest.

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Article Info

Received: 13 February 2021
Accepted: 03 April 2020
Published: 15 April 2021

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