

COULD NOVEL CORONA VIRUS (SARS-CoV-2) BE THE EVOLVING FACE OF A NEW GENERATION OF GENETICALLY COMPLEX EPIDEMIOLOGICAL CHALLENGE?

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ABSTRACT

The recent outbreak of the novel Corona virus (SARS-CoV-2), that has taken the world by storm, is a disturbing case of severity posed by a highly dynamic viral strain. Suspected to have originated from bats, a reservoir host of many deadly viral diseases, the COVID-19 pandemic might be an alarming but a substantially preliminary instance of a much complexly evolving future of disease epidemiology, at the interface of rapid and robust genetic recombination, mutation and highly adaptable strains of the *Coronaviridae* family. Keeping these attributes in mind, the idea of host(s) as “mixing pot” is introduced through this review to capture the plausible future of the Corona virus dynamics through a vector-borne transmission.

Keywords: *Coronavirus, Zoonotic, Mixing Pot, Recombination, RNA Virus, Reservoir Host, Host Switching*

INTRODUCTION

The recent COVID-19 pandemic owing to the viral strain SARS-CoV-2 of the *Coronaviridae* family, has wreaked havoc across the globe. Preliminary findings suggest its origin in bats, which thereafter crossed the species barrier from an intermediate host, eventually spreading within humans. However, such instances have been seen in the past, as evident in the SARS epidemic of 2002 or the MERS-CoV outbreak in 2012 (Perlman and Netland, 2009; Afelt *et al.*, 2018). A wide range of infectious diseases are in fact caused by zoonotic pathogens originating in wildlife and then spreading to humans (Klimpel and Mehlhorn, 2014; Kading and Schountz, 2016; Bhattacharya *et al.*, 2019). Bats are an important reservoir of several pathogenic agents, mainly viruses, and many of them have already caused disease outbreaks worldwide (Wang *et al.*, 2009; Anthony *et al.*, 2017; Monchatre *et al.*, 2017). This is hypothesized to be attributed to the fact that bats are the only mammals with the capability of powered flight, which enables them to have a longer range of migration compared to land mammals. They are also the second largest order of mammals, accounting for about a fifth of all mammalian species, and are distributed worldwide (Fan *et al.*, 2019). Moreover, the increase in the rate of viral infections involving bats, is attributed to an expanding overlap between bat and human habitats, a classic example of man-animal conflict.

REVIEW OF LITERATURE

Corona-Viruses: An Insight

Since the early 1960's, Corona-viruses (CoVs) have been defined as a novel virus causing mild to severe respiratory tract infections (Huang *et al.*, 2016). CoVs have the largest RNA viral genomes, ranging from 26 to 32 kilobases in length. Their expanded genome size may be due to increased fidelity of replication, after acquiring genes encoding RNA-processing enzymes (Fan *et al.*, 2019). Expansion of genome can increase the repertoire of genes encoding accessory proteins that are essential for CoVs to adapt to a specific host (de Haan *et al.*, 2005). Thus, among CoVs, genetic recombination events, gene interchange, and gene insertion or deletion are of common occurrence. Next generation sequencing tools have made it possible to detect new strains in the *Coronaviridae* family and as such it is expanding rapidly. As a result, CoV taxonomy is constantly changing (Subissi, *et al.*, 2014). In fact, this large family of viruses are common among many different species of animals, such as camels, cattle, cats, rodents and bats. Rarely, animal CoVs can infect humans and, as a result, may spread among humans during epidemics such as MERS, SARS, and SARS-CoV-2 (COVID-19).

Bats as Reservoir Hosts of CoVs

Advanced virological and genetic studies have shown that bats are reservoir hosts of both SARS-CoV and MERS-CoV and before these viruses spread to humans,

they use other animals as intermediate hosts (Huang *et al.*, 2016). According to studies, the gene source of alpha-CoV and beta-CoVs are mostly from bats, whereas bird CoVs are the gene source of gamma-CoVs and delta-CoVs. In recent studies, it has been observed that the novel virus causing epidemics bears similarities with the CoV isolated in bats. An important and crucial thing to note at this point when countries across the world are grappling with the pandemic situation involving COVID-19, is that most mosquito-borne viral diseases also originate from animal sources (mammals, birds etc). As such the possibility of viral recombination event in cases of coinfection in host arises. Instances of recombination events among two different strains of RNA virus is not unheard of, e.g.: RO-Bat CoV GCCDC1 contained a unique gene integrated into the 3'-end of the genome that did not have homologs in any known Coronavirus, but according to the phylogeny and sequence analyses, most probably originated from the p10 gene of a bat orthoreovirus (Huang *et al.*, 2016). The observations made from sub genomic mRNA and cellular-levels, depicts that the p10 gene is functional and induces the formation of cell syncytia. Therefore, the heterologous inter-family recombination event that has taken place in this case, between a single-stranded, positive-sense RNA virus and a double-stranded segmented RNA virus, provides remarkable insights into the fundamentally robust mechanisms of viral evolution.

'Mixing Pot' – A Possibility?

CoV infected reservoir hosts like bats can transmit pathogens through bodily fluids, faecal matter, blood, saliva and others, but how exactly the transmission cycle through intermediate hosts work, before spilling over to humans is a matter of debate. In this context a quick look at the transmission pattern of other viruses such as those of Dengue and Japanese Encephalitis, also harboured in bats, might be insightful. The transmission of these viruses involves arthropods that belong to the Flavivirus genus (Flaviviridae) including several relevant human pathogens associated with encephalitis and haemorrhagic fevers (Sotomayor *et al.*, 2014). Despite Flaviviridae being the second most frequent viruses found in bats, the role of these animals in the dynamics of viral spreading is not understood adequately. However, there is similarity of Dengue virus with the primitive mosquito-borne encephalitis viruses. Interestingly enough, this virus has significantly evolved to develop a notable biological feature, called "lymphotropism" which has segregated

them from their more primitive neurotropic ancestors. This shift of the dengue virus from neurotropic ancestors towards a lymphatic system, points towards a very crucial depiction of change seen naturally (Monath, 1994; Basu and Bhattacharya, 2016). Moreover, Dengue virus (DENV) is a positive sense single-stranded RNA virus whereas CoVs are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species (Briguglio *et al.*, 2011; Azhar *et al.*, 2015). Keeping these in mind it might be commented that evolution within the Coronaviridae family might lead to future strains of this virus currently limited to the respiratory system, to adapt within the environment of the blood circulatory system of the hosts. As such a possibility arises whereby these animal or human hosts can act as 'Mixing pot' of evolutionarily significant recombination events. Thus, a condition may eventually arise in these said mixing pots that have compatible host range selection within mosquitos thereby raising the possibility of a future CoV variety with insect vectors. In fact, it must be noted that previous studies through Co-phylogenetic reconciliation analysis have shown host switching to be an attribute involved in CoV evolution.

Host Switching

Interestingly, in a study conducted in 2016, it was found that in 2 species of rodents (which is another reservoir host of CoVs), namely *Apodemus* sp. and *Myodes* sp., genetic segregation between Coronaviruses have occurred and also indicate co-evolution with the host family (Monchatre *et al.*, 2017). It is thus alarming to note that host switching might be one of the most significant evolutionary mechanisms for the dynamic Corona viruses, evident in the current global pandemic as well. As mentioned already, bats are important reservoir hosts of a number of deadly viruses such as rabies viruses, Nipah viruses, Ebola, Coronaviruses and Flavivirus such as Japanese encephalitis virus (JEV) and dengue virus (DENV) (Bhattacharya and Basu, 2014; Sohrabi *et al.*, 2019; Sahin, 2020) Among these, DENV and JEV have a vector-borne transmission through mosquitoes, highlighting the potency of bat as a highly dynamic viral reservoir that could be a future candidate of host switching events for other viruses, thereby leading to the scenario of the proposed mixing pot.

DISCUSSION

From an evolutionary perspective, Coronaviruses from bats have the most genetic diversity and are older than

all Coronaviruses recognized from any other animal species. In recent studies, analysing the lineage-specific selection pressure, only SARS Coronaviruses in civets and humans were seen to be under significant positive selection, thereby demonstrating an instance of recent interspecies transmission. This study also highlighted that in bats, Coronavirus has constant population growth, compared to viruses from all other hosts, indicating that Coronaviruses are endemic in different species of bats, with introductions to other animals repeatedly as well as occasional occurrence in other species. Moreover, bats are also likely to be the natural hosts for all presently known Coronavirus lineages and probably all Coronaviruses recognized in other species were derived from viruses residing in bats (Vijaykrishna *et al.*, 2007). In the current scenario, the spill over of a highly infectious zoonotic pathogen to humans, causing COVID-19, has become a global public health security threat. Its high transmissibility is found to be dramatically rapid. This points towards underlying genetic recombination events that accentuates potentially evolving virus strains, to cross the species barrier, as evident from established studies. Moreover, if Ro-Bat CoV GCCDC1 explicitly depicts an interfamily heterologous recombination event, such events may also occur among other viral family. Keeping in mind such dynamic genetic modification, apprehension is raised regarding the adaptability of coronaviruses in new vector/host ranges. Especially, the fact that mosquitoes are vectors of dengue, an RNA virus with a reservoir host in bats, it's not improbable to think that a significant triad of connection exists. The possibility is thus raised whereby CoVs seen to thrive in a vast range of climatic challenge, can evolve into strains compatible with vectors like mosquitoes. Climate change coupled with rampant deforestation and rapid globalisation can act as significant selection pressures, further alleviating mutation probabilities that can lead to transmission cycle of future CoV onsets involving hematophagous arthropods (example: mosquitoes and ticks) as vectors. Apart from genetic modifications, epi-genetics changes may also contribute towards mutable strains. Further possibilities of CRISPR based interference of an already dynamic gene pool of Coronaviruses, is a concerning avenue for future evaluation.

CONCLUSION

CoVs with their genetic variability, rapid adaptability and recombinant tendencies, poses a real and

challenging threat. Possibilities of more advanced evolved CoV strains with new host ranges and transmission cycles involving insect vectors, could further complicate the disease epidemiology with co-infection and other such instances. Thus, a comprehensive evaluation of the disease causing agents of the Coronaviridae family, that encompasses further studies on their crossing of species barrier, genetic modification rates, replicative conditions in hosts, mutation events, cross-family recombination events and adaptive evolution towards a vector-borne disease of the future, is needed for holistic understanding and better combating of imminent viral pandemics.

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