One world, one health, one virology of the mysterious labyrinth of coronaviruses: the canine coronavirus affair

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Human coronaviruses (HCoVs) often have animal origins and then adapt to humans by jumping directly or via an intermediate host. The emergence of SARS-CoV in 2003, MERS-CoV in 2012, and SARS-CoV-2 in late-2019, confirms that coronaviruses can cause severe-to-fatal disease and that bats are probably the source of these viruses, highlighting the role of animals as reservoirs.[1]

In 2017–18, a closely related, but distinct, canine coronavirus (CCoV) was identified for the first time in the nasopharyngeal swabs of children with pneumonia in Malaysia.[1] The virus, CCoV-HuPn-2018, cultivated in the canine A72 cell line, was characterised as a novel canine-feline-like recombinant virus with a very unique deletion in the nucleoprotein. This feature was similar to the deletion found in SARS-CoV and SARS-CoV-2 that occurred very soon after introduction in humans, suggesting the zoonotic origin of CCoV-HuPn-2018. Analysis of the virus's genes highlights that CCoV-HuPn-2018 could have infected cats and pigs at one point, but it probably jumped directly from dogs into people, as the majority of the genome was the same as the CCoV strains, TN-449 and HLJ-073.[1]

This discovery focuses attention on CCoVs and to what these viruses have taught. Since the first report of CCoV in 1971, no great attention was given to this pathogen as it was commonly associated with mild gastroenteritis in dogs. But in the past few decades, the history of CCoV was characterised by the emergence of new viruses, some with pronounced pathogenic potential, which brought questions about their ability to undergo mutations and recombination.[2]

The fascinating evolutionary history of CCoVs is closely intermingled with the history of porcine transmissible gastroenteritis virus (TGEV) and the two feline coronavirus genotypes, feline coronavirus-1 (FCoV-1) and feline coronavirus-2 (FCoV-2). CCoV gave rise to FCoV-2 through homologous RNA recombination with FCoV-1 between the *S* and *M* genes.[3] Furthermore, the analysis of the accessory protein gene, *ORF3*, highlighted that TGEV originated from CCoV through cross-species transmission.[4]

Data have also suggested that two genotypes of CCoVs exist (CCoV-1 and CCoV-2). Phylogenetic analyses have shown that these viruses share up to 96% of nucleotide identity in the genome but have highly divergent *S* genes, and that CCoV-1 is more closely related to FCoV-1 than it is to CCoV-2;[5] CCoV-2 has been well known since 1971 and is closely related to FCoV-2.

In 2005, a highly virulent pantropic CCoV-2 strain, CB/05, was detected in dogs with a systemic fatal disease.[6] Sequence analysis of the 3′ end of the CB/05 genome showed that it had a high amino acid identity to CCoV-2, although the S protein had the highest identity to FCoV-2, strain 79-1683. The virus induces severe clinical signs, lymphopenia, and infection of the lymphoid tissue, strongly suggesting that CCoVs can change their tropism, acquiring the ability to spread from the enteric tract to the internal organs.[7]

Additional data arose when CCoVs that had potential double recombinant origins, through partial *S* gene exchange with TGEV, were identified in dogs with gastroenteritis.[8] The analysis of a region of the genome (3′-end) of four recombinant viruses, and the analysis of the nearly full-lengh genome of two of those four strains, revealed the existence of the recombinant TGEV-like CCoVs. These events represent a kind of sliding door, in which the original CCoV gave rise to TGEV and, subsequently, TGEV gave rise to a TGEV-like CCoV onset. Considering the genetic and antigenic differences between the original and recombinant viruses, CCoV-2 was additionally divided into two different subtypes, CCoV-2a and CCoV-2b, which include reference and TGEV-like CCoV-2 isolates.[8]

To assess the distribution of TGEV-like CCoVs, an epidemiological survey was done in European canine populations. About 20% of the CCoV-positive samples were characterised as TGEV-like CCoVs, confirming that the new virus effectively circulates in European countries.[7]

These findings underline the ability of CoVs to undergo recombination and genetic evolution, and to easily cross interspecies barriers. This high potential for genetic recombination ensures the proliferation of new strains that might have selective advantages over their parental genomes.[9] The newly identified CCoV-Hupn-2018 should lead researchers to pay special attention to the

mechanisms of recombination among coronaviruses, in addition to the onset of variants as a result of mutations. The recombination observed in CCoVs could be a warning sign for the evolution of SARS-CoV-2 and continuous monitoring of these viruses is required.

We declare no competing interests.

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