Genomics and zoonotic infections: Middle East respiratory syndrome

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Summary
The emergence of Middle East respiratory syndrome (MERS) and the discovery of MERS coronavirus (MERS-CoV) in 2012 suggests that another SARS-like epidemic is occurring. Unlike the severe acute respiratory syndrome (SARS) epidemic, which rapidly disappeared in less than one year, MERS has persisted for over three years. More than 1,600 cases of MERS have been reported worldwide, and the disease carries a worryingly high fatality rate of >30%. A total of 182 MERS-CoV genomes have been sequenced, including 94 from humans and 88 from dromedary camels. The 182 genomes all share >99% identity, indicating minimal variation among MERS-CoV genomes. MERS-CoV is a lineage C *Betacoronavirus* (βCoV). MERS-CoV genomes can be roughly divided into two clades: clade A, which contains only a few strains, and clade B, to which most strains belong. In contrast to ORF1ab and structural proteins, the putative proteins encoded by ORF3, ORF4a, ORF4b, ORF5 and ORF8b in the MERS-CoV genome do not share homology with any known host or virus protein, other than those of its closely related lineage C βCoVs. Human and dromedary viral genomes have intermingled, indicating that multiple camel-to-human transmission events have occurred. The multiple origins of MERS-CoV suggest that the virus has been resident in dromedaries for many years. This is consistent with the detection of anti-MERS-CoV antibodies in dromedary camels as early as the 1980s.

Keywords
Coronavirus – Evolution – Genome – Infection – Middle East – Middle East respiratory syndrome.

Introduction

Global health threats due to emerging infectious agents are exemplified by human immunodeficiency virus (HIV), influenza virus and severe acute respiratory syndrome coronavirus (SARS-CoV). Compared with HIV and influenza virus, CoVs are relatively understudied: in PubMed there are more than 290,000 publications on HIV and 80,000 publications on the influenza virus, as compared with fewer than 12,000 papers on CoVs. More than 60% of publications on CoVs were published in the last 12 years, either during or after the SARS epidemic of 2002–2004, which generated great interest in various aspects of CoV research.

The emergence of the Middle East respiratory syndrome (MERS) and the discovery of the MERS coronavirus (MERS-CoV) in 2012 have caused concern to both the public and the World Health Organization (WHO), which considers MERS-CoV 'a threat to the entire world' (1). SARS disappeared rapidly after its intermediate amplification animal hosts (primarily palm civets) were identified and segregated from humans by the closure of wild animal markets in provinces in Southern China. In contrast, MERS has persisted for more than three years. At the time of writing, more than 1,600 cases of MERS have been reported worldwide and the disease carries a worryingly high fatality rate of >30% (2). This high mortality rate is associated with acute renal failure, which occurs in half of all MERS patients, compared to around only 7% of SARS patients.

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Coronaviruses: the cause of large epidemics

In the 12 years since the end of the SARS epidemic, there has been an explosion in the number of novel CoVs discovered (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13). CoVs are currently classified into four genera by the Coronavirus Study Group of the International Committee for Taxonomy of Viruses: *Alphacoronavirus* (αCoV) (formerly group 1), *Betacoronavirus* (βCoV) (formerly group 2), *Gammacoronavirus* (γCoV) (formerly group 3) and *Deltacoronavirus* (δCoV) (14). The latter is a novel CoV genus that was discovered in 2009 (15). There are four lineages within the βCoV genus: A, B, C and D. Lineages B, C and D were added during and after the SARS epidemic. There are three major reasons for the high diversity of CoVs. Firstly, CoV genomes are very plastic because the low fidelity of their RNA-dependent RNA polymerases leads to high mutation rates of 1 per 1,000–10,000 nucleotides replicated (16, 17). Secondly, CoVs have high rates of homologous RNA recombination due to their unique mechanism of random template switching during RNA replication (18, 19). Thirdly, CoVs have a greater capacity to incorporate new genes compared with other RNA viruses because of their relatively large genomes (about 26–32 kilobases). These three factors enable diverse strains and genotypes to be generated within a single CoV species. In addition, the new variants or species can adapt to new hosts and ecological niches, sometimes causing major zoonotic outbreaks that can have disastrous consequences.

Of the four CoV genera, βCoV is the most 'dangerous' to humans: at least three relatively recent animal-to-human interspecies jumping events have resulted in large epidemics. The first event occurred among lineage A βCoVs and involved at least nine animal species: cattle, antelope, giraffe, deer, waterbuck, alpaca, dromedary camels, rabbits and humans. The virus jumped from animals (bovine CoV-like viruses) to humans (human CoV OC43) about 120 years ago; it is now well adapted to humans and still in circulation (20). The second jumping event occurred in lineage B βCoVs (human SARS-CoV and related animal viruses). It involved horseshoe bats, civets and humans (at least), with the virus jumping from civets to humans about ten years ago (3). The latest event occurred in lineage C βCoVs, resulting in the current, ongoing MERS epidemic (21, 22). Although there is evidence that bats are the main reservoir for the ancestral βCoVs and dromedaries are the immediate reservoir for MERS-CoVs, a significant number of cases were unrelated to exposure to bats or dromedaries (23). Therefore, the range of animal sources and paths of interspecies transmission remain uncertain.

MERS-CoV is an emerging infectious disease agent

A cluster of 13 patients and ten healthcare workers presented with severe pneumonia to an intensive care unit in Jordan in March/April 2012, but no causative microbe was definitively identified (24). After two months, this outbreak was found to be linked to another patient who died from pneumonia and renal failure in Saudi Arabia (22). During the same period, another patient, who was from Qatar but was treated in the United Kingdom, also suffered a similar illness (25). By 31 December 2015, WHO had announced a total of >1,600 confirmed human cases of MERS, with >600 deaths, representing a fatality rate of >30%. These MERS patients were all linked to the Middle East, with the largest number of cases reported in Saudi Arabia (2). All MERS patients, whether in North America, Europe, North Africa or other parts of Asia, have been directly or indirectly linked to an affected individual from the Middle East (26, 27, 28, 29, 30, 31, 32, 33, 34, 35). In addition to severe pneumonia, acute renal insufficiency has been found in a significant proportion of MERS patients (23, 36). Owing to the lack of resources and expertise in the Middle East, most studies on MERS-CoV are currently performed through collaborations with researchers in countries with no or very few imported cases of MERS. A recent outbreak of MERS in South Korea had a total of 186 cases and a fatality rate of 19% (37, 38). The relatively higher mortality rate in the Middle East compared with the Korean outbreak could be due to the higher proportion of patients with underlying diseases such as diabetes mellitus in some Middle East countries (e.g. Saudi Arabia).

Genomics of MERS-CoV

Genome organisation and encoded proteins

MERS-CoV has a 30,119-nucleotide genome with a G + C content of 41%. Its genome contains ten open reading frames (ORFs) that encode ORF1ab, spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins and five putative non-structural accessory proteins (ORF3, ORF4a, ORF4b, ORF5 and ORF8b; Fig. 1). ORF1ab, S, E, M and N are conserved among all CoVs. ORF1ab occupies two-thirds of the genome and is cleaved into 16 non-structural proteins (nsps), nsp1 to nsp16, by the two viral proteases: papain-like protease (nsp3) and chymotrypsin-like protease (nsp5). Expression of the S protein on the viral surface, protruding outward, gives it a 'corona' or crown appearance. The S protein mediates attachment of the virus to its receptor, dipeptidyl peptidase 4 (DPP4), an evolutionary conserved protein that is abundantly expressed in the lower respiratory tract of humans (39, 40). Notably, like

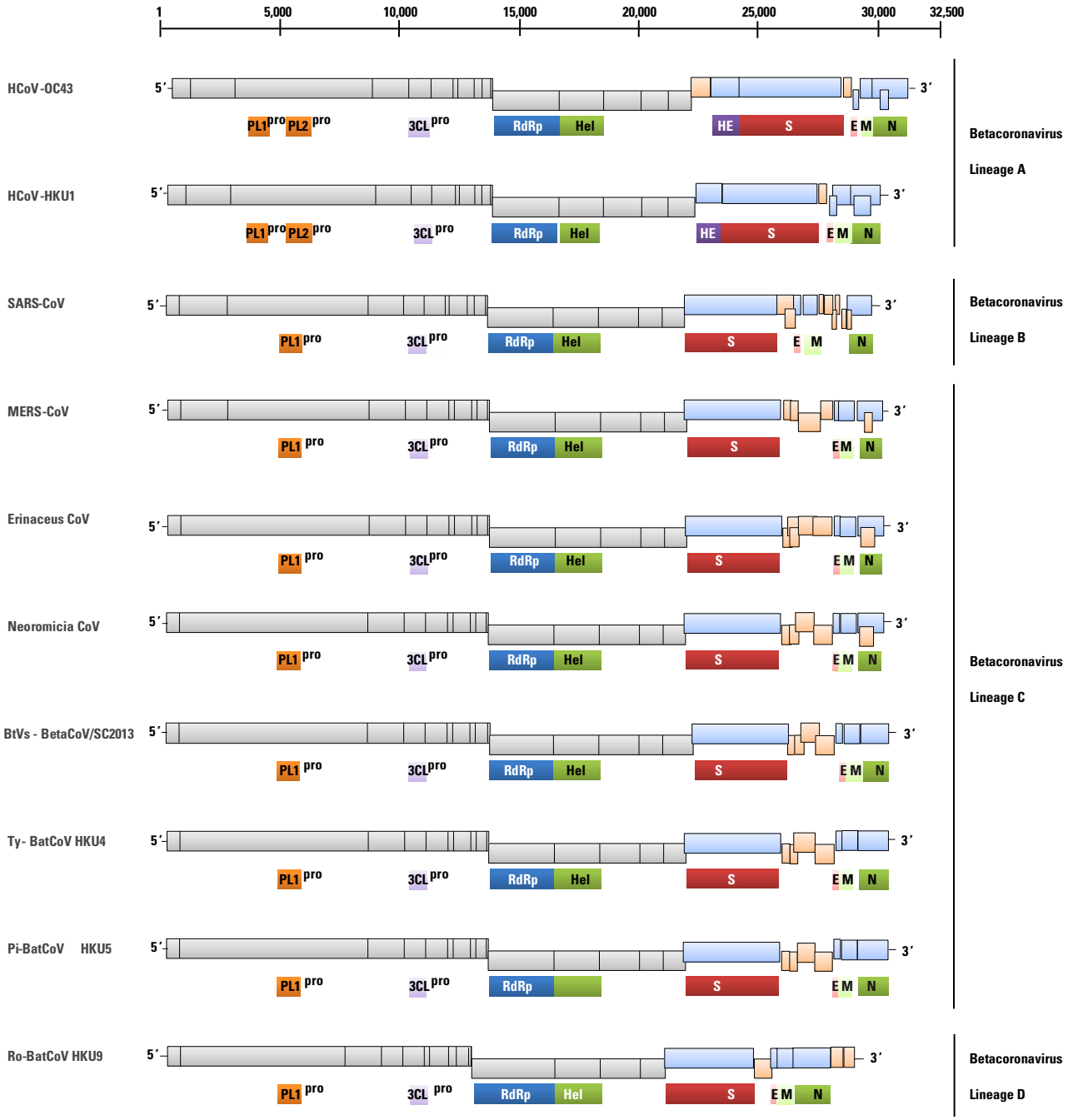

Fig. 1
Genome organisation of coronaviruses in βCoV lineage C and representative coronaviruses in βCoV lineages A, B and D

Tylonycteris bat CoV HKU4, MERS-CoV binds to DPP4 (41, 42). The E and M proteins are also expressed on the virus surface, while the N protein is associated with the viral RNA genome. These three proteins are important for virion assembly. It is notable that the regions encoding ORF1a, ORF1b and upE have been used as molecular diagnostic targets for MERS-CoV RNA detection (43, 44).

In contrast to ORF1ab and the structural proteins, the putative proteins ORF3, ORF4a, ORF4b, ORF5 and ORF8b share homology with no known host or virus proteins, other than those of the closely related lineage C βCoVs (45, 46). The ORF4a protein was recently shown to be a novel immunosuppressive factor that inhibits type I interferon production (47). Bioinformatics analysis showed

that this protein has a double-stranded RNA-binding domain that can interact with poly(I·C). Interestingly, the corresponding protein of *Pipistrellus* bat CoV HKU5 (but not that of *Tylonycteris* bat CoV HKU4) is an interferon antagonist. The ORF4 protein was shown to interact with interferon-inducible double-stranded RNA-dependent protein kinase activator A (known as PACT) in an RNA-dependent manner, but not with retinoic acid-inducible gene 1 protein (RIG-I) or interferon-induced helicase C domain-containing protein 1 (MDA5). It also inhibits PACT-induced activation of RIG-I and MDA5 without affecting the activities of downstream effectors (48). This may represent a new mechanism through which MERS-CoV employs a viral double-stranded RNA-binding protein to evade the host innate immunity. Similarly, the putative ORF4b and ORF5 proteins were also found to be interferon antagonists (49, 50), suggesting that MERS-CoV possesses multiple mechanisms for evading the host innate antiviral immune response.

Phylogenetic analysis

When it was discovered in 2012, MERS-CoV was shown to belong to βCoV lineage C. It is most closely related to *Tylonycteris* bat CoV HKU4 and *Pipistrellus* bat CoV HKU5, which were discovered in 2006 in the lesser bamboo bat (*Tylonycteris pachypus*) and the Japanese pipistrelle (*Pipistrellus abramus*), respectively (7). However, the significant sequence divergence between MERS-CoV and both *Tylonycteris* bat CoV HKU4 and *Pipistrellus* bat CoV HKU5 suggests an evolutionary gap (Fig. 2). In the last three years, other MERS-CoV-related viruses or partial sequences have also been identified in bats from the Middle East, Africa, Europe, Asia and Central America; however, they also show considerable sequence divergence from MERS-CoV (Fig. 2) (51, 52, 53, 54). To date, the closest bat counterpart to MERS-CoV, *Neoromicia capensis* bat CoV, was detected in a bat in Africa (55). Although this virus showed high sequence similarity to MERS-CoV in most regions of its genome, the spike gene, especially the S1 subunit, is genetically diverse. This suggests that recombination events are involved in the emergence of MERS-CoV. Interestingly, a lineage C βCoV, named *Erinaceus* CoV, was also recently identified in the European hedgehog (*Erinaceus europaeus*), which has a close phylogenetic relationship to bats (56). All of the existing evidence indicates that bats are the most likely reservoir for the original ancestor of MERS-CoV.

Analysis of human and camel MERS-CoV genomes

By 31 December 2015, a total of 182 MERS-CoV complete genomes had been sequenced: 94 from humans and 88 from dromedary camels (57, 58, 59, 60, 61, 62, 63). Comparative analysis of these genomes resulted in a number of conclusions. Firstly, all 182 genomes share >99% identity,

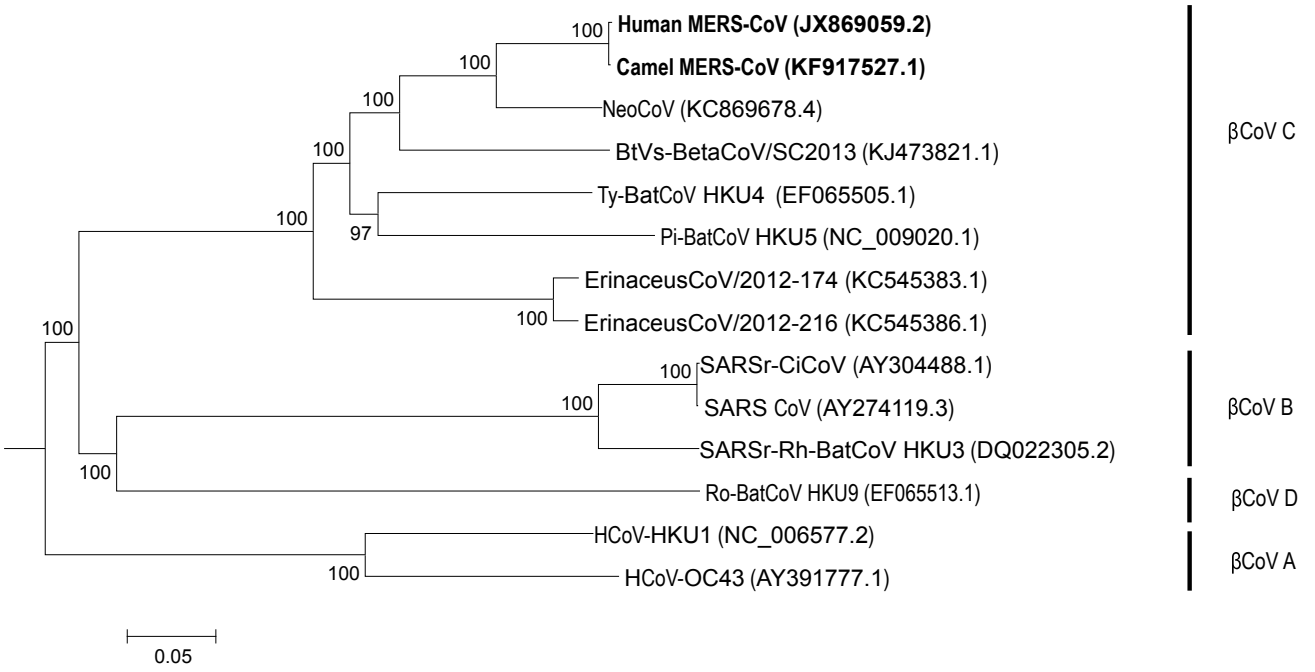

Fig. 2
Phylogenetic relationships of coronaviruses in βCoV lineage C and representative coronaviruses in βCoV lineages A, B and D analysed using whole genome sequences
Accession numbers are indicated in parenthesis

indicating that minimal variation exists among MERS-CoV genomes. Secondly, MERS-CoV genomes can be roughly divided into two clades, A and B. Most strains belong to clade B, with clade A containing only a few strains (58, 60, 62, 64, 65). Thirdly, the genomes of human and dromedary viral strains have intermingled, indicating that multiple camel-to-human viral transmissions have occurred. The multiple origins of MERS-CoV suggest that the virus has been resident in dromedaries for many years. This is consistent with sero-epidemiological studies that identified anti-MERS-CoV antibodies in dromedary camels as early as the 1980s (66, 67, 68, 69). The situation in SARS is different: the ancestral SARS-CoV only recently jumped from bats to civets (70). Fourthly, although recombination events might have occurred among MERS-CoV genomes, it is difficult to be certain that this is the case because of the high sequence similarity among genomes: a few chance mutations in specific bases may resemble recombination events.

Zoonotic potential of MERS-CoV

MERS is a zoonotic viral disease that is rarely transmitted from dromedary camels to humans. However, it is not known whether the virus can be passed from other members of the Camelidae family to humans. Several sero-epidemiological investigations have been performed in different camel species in different countries and continents. So far, no antibodies against MERS-CoV have been detected in South American camelids or Bactrian camels (71, 72). Therefore, MERS-CoV infection of dromedaries seems to be limited to Africa and the Middle East (66, 67, 68, 69, 73, 74). Over 90% of all dromedaries investigated from this region possess antibodies against the virus; some of these animals have been serologically positive for anti-MERS-CoV antibodies for more than 30 years (69). MERS is not a new infection in dromedaries, and although a few young animals (<1%) develop nasal discharge, the infection produces no other clinical signs of disease. Very close contact with these young dromedaries may result in a human MERS-CoV infection, sometimes with fatal consequences. Although the mode of human-to-human MERS-CoV transmission is not fully understood, the virus has caused frequent healthcare-associated outbreaks in hospitals in Saudi Arabia (75, 76) and an outbreak in South Korea in 2015 (77). Recent investigations in South Korea have shown serious environmental contamination, including the presence of viral particles in patients' rooms, medical devices and air ventilation units, leading to the closure of some hospitals (78).

Over the last three years, several hundred samples from necropsied serologically positive MERS-CoV adult dromedaries more than four years old have been tested for MERS-CoV. Most dromedaries came from farms where the virus had been isolated from the nasal cavities of young animals. The samples included nasal swabs, tonsil and lung tissue, intestinal lymph nodes, udder lymph nodes, and milk. No virus was isolated from any of these samples, although the virus could be isolated from nasal swabs of younger dromedaries (79, 80). Intensive serological follow-up investigations in dromedary dams and their calves showed a pattern of infection typically seen in infected children. After maternal antibodies against MERS-CoV disappear in dromedary calves (generally between four and eight months of age), infection takes place and affected young dromedaries develop antibodies against the field strains. These antibodies can persist into adulthood. During the short sero-negative period, the virus can be isolated from nasal swabs (79). So far, despite extensive testing of other animal species (including rodents, ticks, horses and small ruminants), the source of infection in young dromedaries has not been identified.

Although transmission from dromedaries to humans has been documented, it is rare. There are several reasons for this. Only young dromedaries with no or low titres of maternal antibodies against MERS-CoV are susceptible to infection and the virus is only excreted for eight days. This was confirmed by studies in the United States that involved the experimental infection of young dromedaries (65). The young animals were reared with their mothers for a year and had no or very little contact with their human keepers. Under these conditions, <1% of the infected calves had nasal discharge.

Other coronaviruses in dromedaries

A bovine CoV-like CoV known as dromedary camel CoV UAE-HKU23 (DcCoV UAE-HKU23) is present in dromedaries (81). In 2014, the authors of the present paper sequenced the complete genome of this virus directly from dromedary faecal samples and characterised its phylogenetic relationship with other CoVs (82). It was found to be closely related to the *Betacoronavirus 1* species of βCoV lineage A, which includes bovine CoV (11). Recently, another αCoV found in alpacas was also discovered in nasal samples from dromedaries. This virus is reported to be co-circulating with MERS-CoV and DcCoV UAE-HKU23 in camels in Saudi Arabia (62).

Conclusion

The available epidemiological and genomic data suggest that MERS-CoV might have been circulating for a long time in Africa before spreading to the Middle East by camel trade through the Horn of Africa. It will continue to be a threat to

both animal and human health in this region and worldwide for the foreseeable future. Co-circulation of MERS-CoV, DcCoV UAE-HKU23 and alpaca CoV in dromedaries may lead to recombination among the different camel CoVs within the same host. The high CoV recombination rate is likely to generate novel CoVs that may cross species barriers and occasionally cause severe disease episodes and outbreaks. Before the SARS epidemic, only ten CoVs with complete genome sequences were available. After 12 years of work worldwide by various groups, we now have a much better understanding of the diversity, classification and phylogeny of CoVs. Continuous surveillance in various mammals and birds and the discovery of novel CoVs are crucial for generating a more complete phylogenetic map of CoVs and responding to the next epidemic.

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La génomique et les infections zoonotiques : le syndrome respiratoire du Moyen-Orient

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Résumé

L'émergence du syndrome respiratoire du Moyen-Orient (SRMO, ou MERS d'après son sigle anglais) et l'identification en 2012 du coronavirus responsable de cette maladie (MERS-CoV) indiquent que nous sommes en présence d'une épidémie semblable à celle du syndrome respiratoire aigu sévère (SRAS). Toutefois, contrairement à l'épidémie du SRAS qui avait rapidement disparu en moins d'un an, le MERS persiste depuis plus de trois ans. Plus de 1 600 cas de MERS ont été notifiés dans le monde ; la maladie présente un taux de létalité particulièrement préoccupant, s'élevant à plus de 30 %. Au total, 182 génomes du MERS-CoV ont été séquencés jusqu'à présent, dont 94 provenaient de virus isolés chez l'homme et 88 chez des dromadaires. Ces 182 génomes ont en commun un pourcentage d'identité de 99 %, dénotant une très faible variabilité des génomes viraux. Le MERS-CoV appartient à la lignée C du genre *Betacoronavirus* (βCoV). Les génomes du MERS-CoV se répartissent, dans leurs grandes lignes, en deux clades : le clade A, qui ne contient que quelques souches, et le clade B regroupant l'immense majorité des souches. Contrairement à ce qui se produit avec la protéine ORF1ab et les protéines structurales, les protéines potentiellement codées par les gènes ORF3, ORF4a, ORF4b, ORF5 et ORF8b du génome du MERS-CoV ne présentent aucune homologie avec des protéines virales ou de l'hôte autres que celles d'autres bêta-coronavirus de la lignée C, qui lui sont étroitement apparentés. Les génomes des virus affectant l'homme et le dromadaire se sont entremêlés, ce qui montre que le virus a connu de multiples épisodes de transmission des camélidés à l'homme. Les origines multiples du MERS-CoV témoignent d'une présence prolongée du virus (plusieurs années) chez les dromadaires. Ce constat est corroboré par le fait que des anticorps anti-MERS-CoV ont été détectés chez des dromadaires dès le début des années 80.

Mots-clés

Coronavirus – Évolution – Génome – Infection – Moyen-Orient – Syndrome respiratoire du Moyen-Orient.

Genómica e infecciones zoonóticas: el síndrome respiratorio de Oriente Medio

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Resumen

La aparición del síndrome respiratorio de Oriente Medio (MERS, por sus siglas en inglés) y el descubrimiento del coronavirus que lo causa (MERS-CoV) en 2012 parecen apuntar al advenimiento de una nueva epidemia análoga a la del síndrome respiratorio agudo severo (SRAS). Pero a diferencia de lo ocurrido con la epidemia de SRAS, que en menos de un año había desaparecido, el MERS lleva más de tres años presente. En el mundo se han notificado más de 1.600 casos de MERS, y la enfermedad presenta una tasa de letalidad muy alta y preocupante, superior al 30%. Hasta ahora se han secuenciado un total de 182 genomas del MERS-CoV, 94 de ellos obtenidos a partir de personas y 88 a partir de dromedarios. Estos 182 genomas comparten identidad en más de un 99%, lo que pone de manifiesto un nivel mínimo de variación entre los genomas coronavíricos. El coronavirus del MERS pertenece al linaje C del género *Betacoronavirus* (βCoV). Los genomas de este virus pueden ser divididos, a grandes rasgos, en dos clados: el clado A, que agrupa unas pocas cepas; y el clado B, al que pertenecen la gran mayoría de las cepas. A diferencia de lo que ocurre con la proteína ORF1ab y las proteínas estructurales, las proteínas que supuestamente codifican los genes ORF3, ORF4a, ORF4b, ORF5 y ORF8b del genoma del MERS-CoV no comparten homología con ninguna proteína conocida de otros virus o anfitriones, salvo con proteínas de otros betacoronavirus del linaje C estrechamente emparentados con él. Los genomas de los virus que afectan a personas y dromedarios se han entremezclado, lo que indica que se han producido numerosos episodios de transmisión de camélidos a humanos. De los múltiples orígenes del MERS-CoV se deduce que el virus lleva muchos años siendo residente en dromedarios, lo que concuerda con el hecho de que ya en los años ochenta se detectaran anticuerpos anti-MERS-CoV en dromedarios.

Palabras clave

Coronavirus – Evolución – Genoma – Infección – Oriente Medio – Síndrome respiratorio de Oriente Medio.

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