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CHAPTER

3

Viral Emerging Pathogen Evolution

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INTRODUCTION

Science has tried to explain the origin and evolution of living beings; this has not been an easy task, because science has raised different theories that have generated controversy. The appearance of infectious diseases is related to the evolution and molecular organization of living beings, and to explain their appearance, we must acknowledge the geological and paleontological history of the earth. The history of the earth is composed of four eons (geochronological units) called Hade, Archaic, Proterozoic and Fanerozoic. The eons are divided into eras, which in turn are divided into periods, epochs, and ages.

Different studies suggest that the first life forms appeared about 4100 million years ago, at the end of the Hadean eon and during the Archean eon. These primitive life forms apparently possessed well-organized molecular structures called LACA (last archaeal common ancestor) and could have been given in an environment in the absence of oxygen,

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hyperthermophilic and later thermophilic, which is compatible with the conditions of the planet during that time. There is not a well-defined moment for the appearance of LACA, it is even suggested that it could have been the same LUCA (last universal common ancestor), or it could have originated from eukaryotic cells (Boussau et al., 2008; Glansdorff et al., 2009; Vesteg and Krajcovic, 2008).

Approximately 2400 million years ago, during the Proterozoic eon, there was an increase in oxygen levels in the oceans and in the atmosphere, in an event known as Great Oxygenation Event. This change favored the appearance of the first eukaryotes; oxygen levels were increasing, and about 750 million years ago during the eon Phanero, there was a new event known as Neoproterozoic Oxygenation Event that led to the appearance of the first organisms multicellular (Knoll and Nowak, 2017). On the other hand, it has been suggested that infections have been present at the same timescales through evolution. But it has been difficult to demonstrate conclusively, since no fossil elements have been found, which allow establishing the exact moment of evolution in which infectious diseases appeared throughout the evolutionary process. However, the etiological agents that produce diseases can be the result of a complex coevolutionary process. Interactions between host, infectious agents, and immunity have determined the epidemiological dynamics, which has played an important role at the evolutionary level. The coevolution of viruses and the host defense system may have been a determining factor in the evolution of both viruses and their hosts (Mideo et al., 2011). The emergence of emerging and reemerging infectious diseases, with a high impact on morbidity and mortality throughout history, has been the result of the interaction of multiple environmental factors and the genetic pressure exerted by microorganisms and their hosts in both pathways.

EONS, ERAS, AND GEOLOGICAL PERIODS

The eons correspond to the periods of time in which the history of the earth is divided, from its detailed study, the events that have occurred can be ordered in respect to the history of the planet. The determination of the beginning and end of an aeon is carried out, thanks to the eonotemas (set of rock strata or sediments that have been formed during this period of geological time and which reflect the geological and biological events that have taken place). The divisions of the time of highest rank are the eons (Hadean, Archaic, Proterozoic, and Phanerozoic), of lower rank are the periods, and even of lower rank, the epochs. All these divisions make up the stratigraphic table or scale of

the geological time that divides the 4500 million years of history of the planet (Knoll and Nowak, 2017).

Eón Hadeico, started about 4.567 million years ago, when the earth was formed and collided with another celestial object protoplaneta called Tea, giving rise to the Moon. An important fraction of material must has been vaporized in this impact, creating an atmosphere of vaporized rocks around the earth. The condensation of the vaporized rocks took approximately 2000 years, leaving a heavy atmosphere of carbon dioxide with hydrogen and water vapor, which gave rise to oceans of liquid water. This eon ended about 4 billion years ago.

Aeon Archaic, beginning 3.8 billion years ago and ending 2.5 billion years ago. Here there was an evolution of the earth's crust, the solidification of the inner core of the earth, and the generation of the magnetic field, an intense bombardment of meteorites occurred. In this eon the first molecules of ribonucleic acids and the first forms of molecular life arose.

Eon Proterozoic, began 2500 million years ago and ended 541 million years ago. The atmosphere became increasingly rich in oxygen, unicellular life forms capable of metabolizing oxygen appeared, and at the end of this eon is the Ediacaran era, during which emerged the macroscopic animals and bilaterian animals. Different volcanic and sedimentary deposits were formed and a supercontinent was generated, known as Pannotia. At the end of this eon, glaciation took place on a global scale. The Proterozoic era comprises the period.

Eon Fanerozoico, started 542 million years ago and continues up to present day. During this period, living organisms took complex forms, evolved, and diversified widely. The aeon is divided into three eras: Proterozoic, Paleozoic, Mesozoic, and Cenozoic. The Paleozoic era comprises six periods: Cambrian, Ordovician, Silurian, Devonian, Carboniferous, and Permian; during which there is a diversification of animals, tetrapods and arthropods; plants colonize the earth; and plants with seeds and amniotic egg emerge. The Mesozoic era comprises three periods: Triassic, Jurassic, and Cretaceous, during which appear dinosaurs, the oldest mammal forms, and flowering plants. The Cenozoic era includes two periods: Paleogene and Neogene, during which appear primates, hominins, and finally *Homo sapiens* (Knoll and Nowak, 2017) (Fig. 3.1 and Table 3.1).

VIRUSES AND EVOLUTION

Viruses are generally defined as noncellular entities consisting of nucleic acids, either DNA or RNA, surrounded by a protein coating called a capsid and, in some cases, by a lipid envelope or membrane.

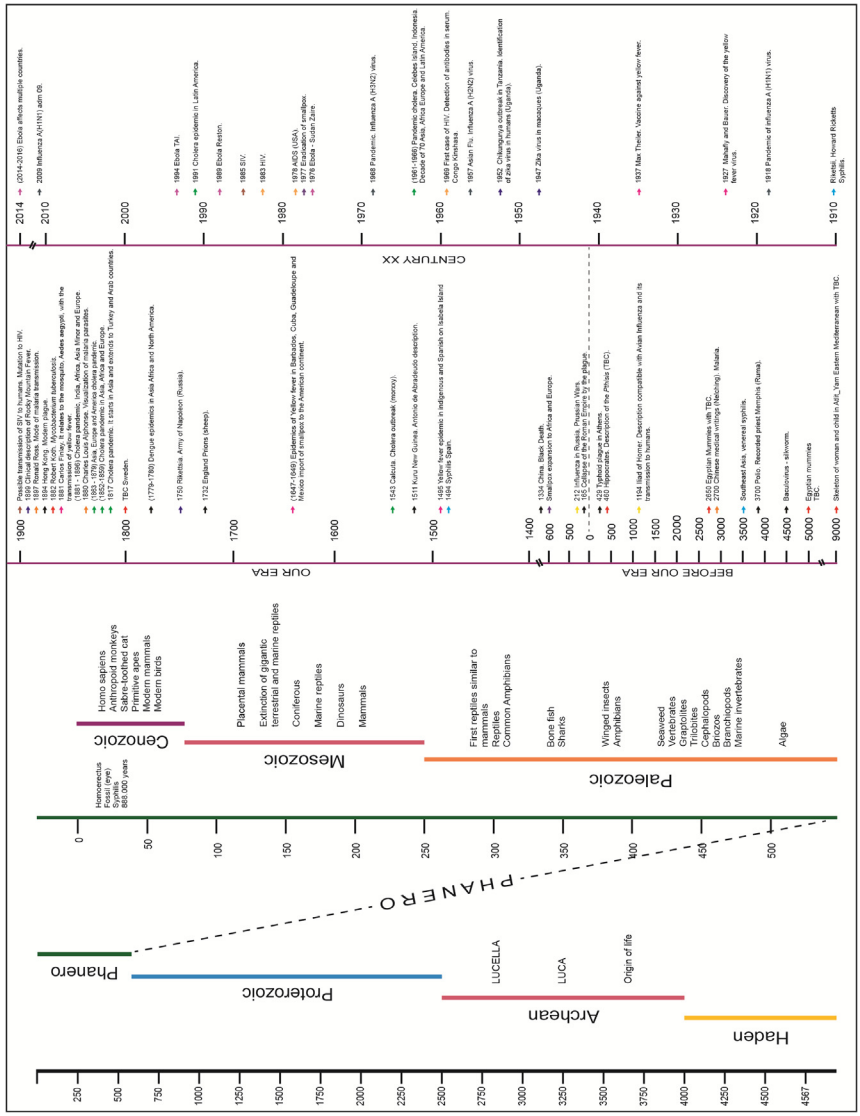

FIGURE 3.1 Time line on the origin of life and records of the appearance of some infectious diseases in man. *Source: Quintal, D., 1996. Historical aspects of the rickettsiosis. Clin. Dermatol. 14, 237–242; Gonzálex, V.L.M., Casanova, M.M.C., Pérez, L.J., 2011. Cólera: Historia y actualidad. Rev. Cienc. Méd. 15 (4), 280–294; Hershkovitz, I., Donoghue, H.D., Minnikin, D.E., Besra, G.S., Lee, O.Y., Gernaey, A.M., et al., 2008. Detection and molecular characterization of 9000-year-old* Mycobacterium tuberculosis *from a Neolithic settlement in the Eastern Mediterranean. PLoS One 3 (10), e3426; CDC (a). History of smallpox. Tomado de: <https://www.cdc.gov/smallpox/history/history.html>; CDC (b). History of smallpox. Tomado de: <https://www.cdc.gov/plague/history/index.html>; CDC (c). The history of malaria, an ancient disease. Tomado de: <https://www.cdc.gov/malaria/about/history>.*

TABLE 3.1 Eons, Eras, and Geological Periods

Super eon	Eon	Era	Period	Date (million years ago)	Event
Precambrico	Hadean			4567–4000	• Moon • Atmosphere of CO_2 with H_2 and water vapor
	Archean			4000–2500	• Beginning of life • RNA • LUCA • LUCELLA • Biological carbon and sulfur cycles
	Proterozoic	Ediacaran		2500–541635–541	• Atmosphere rich in oxygen • Unicellular forms of life • Simple multicellular eukaryotes • Macroscopic animals • Bilaterian animals
	Phanero	Paleozoic	Cambrian	541–252	• Animal life appears in the seas
			Ordovician		• Domination of invertebrates
			Silurian		• First air breathing animal
			Devonian		• Fish with hard scales and amphibians appear
			Carboniferous		• Appear large forests of ferns, first reptiles and flying insects
			Permian		• Extinction
		Mesozoic	Triassic	252–66	• Older forms of mammals
			Jurassic		• Dinosaurs

(*Continued*)

TABLE 3.1 (Continued)

Super eon	Eon	Era	Period	Date (million years ago)	Event
			Cretaceous		• Plants with flowers
		Cenozoic	Paleogene	66–0	• Primates
			Neogene		• Hominis • *Homo sapiens*

Viruses are also often described as obligate intracellular parasites, because they need living cells for replication (Kostyrka, 2016).

They were discovered at the end of the 19th century as pathogens of plants and animals. They are the most abundant organisms in nature, infect all known forms of cell life and are present in all the environments explored, and the repertoire of viral genes is greater than that of some eukaryotic cells (Koonin and Dolja, 2013). Viruses have played an important role in the understanding of cell evolution, even for a long time, they have not been part of conventional biology, nor are they included in the tree of life. This has been supported, among other aspects, by their small size, intracellular nature, absence of functional translation mechanisms, lack of metabolic activity, and scarce presence of fossil records compared to cells (Nasir et al., 2012).

Viruses are not primitive life forms, because viruses are parasites of cells. They need cells to replicate and evolve, while primitive life forms must have predetermined cells: they must have been able to replicate autonomously and produce organic material from inorganic matter. However, viruses could represent relatively modified descendants of primitive life forms (phylogenetic role) (Kostyrka, 2016; D'Hérelle, 1928).

The main roles of viruses in the first scenarios of the origin of life were identified. In the first place, the virus could be the image of primitive life, a way of imagining what primitive life forms could have been, could be interpreted by one part as living and another as nonmetabolizing (Podolsky, 1996); for Forterre (2010), viruses could not exist without cells because of their definition as obligate intracellular parasites. However, this does not mean that the viruses did not exist before the DNA cells (Kostyrka, 2016).

The origin of the viral ancestors is still controversial; the debate remains whether the viruses evolved from their own structures or if they evolved from the cells that infected or housed them as hosts. Three general hypotheses are proposed to explain the origin of viruses: (1) as the precursors of life, (2) reduced forms of parasitic organisms, and (3) fugitives from modern genomes (Nasir et al., 2012).

The ubiquitous existence of viruses that infect members of the three cell domains is a suggestion that the cell lineage of the Last Universal Common Ancestor, or the Last Universal Cellular Ancestor (LUCA), and of the other cell lineages that lived in the Archean eon (3.5 billion years ago) were already victims of viral attacks. In fact, it is feasible that the viruses originated before LUCA, when the cells still had genomes made up of RNA and not DNA (Forterre, 2010). Viruses could have mediated the transition from RNA to DNA; ribozymes and RNA molecules capable of self-duplication and biological catalysis would be the ideal models for these primitive life forms (Kostyrka, 2016).

If viruses were already present in the biosphere when LUCA was existent, it would be expected to find some common features among the viruses that now infect the members of the different domains. This is the case for some archaeal viruses, bacterioviruses, and eukaryotes that share homologous proteins of the capsid or ATPases, or both, which suggests that they all evolved from a common virus that existed at the time of LUCA or even earlier. Therefore the viruses are very old, and the ancestral virosphere was probably already diverse and abundant in the times of LUCA (Forterre, 2010).

To explain why modern viruses are clearly different from one domain to another, it has been suggested that the three ancestral populations of cellular organisms at the origin of modern domains randomly selected three different parts of the ancestral virosphere. The presence of viruses that have a common origin in the three chosen virospheres would explain the presence of homologies between some viruses that infect different domains (Forterre, 2010).

The discovery of mimivirus and megavirus mimic many parasitic cell organisms, they have a partial translation apparatus, including several aminoacyl-tRNA synthetases, which is apparently functional. Phylogenetic studies to determine the origin of giant viruses show how viruses appear together with cells on a comparable evolutionary timescale and form a basal group of the tree of life, suggesting an ancient origin of these giant viruses (Nasir et al., 2012; Forterre, 2010).

In a recent genome-wide structural phylogenomic analysis, we have shown that large-to-medium-sized viruses coevolved with cellular ancestors and have chosen the evolutionary reductive route. Phylogenetic analyses based on structural genomics and evolutionary bioinformatics have shown that viruses sized large to medium have coevolved with cellular ancestors and have chosen the evolutionary reducing pathway. The results suggest important phases in the evolution of viruses: (1) origin of the primordial cells and coexistence with cellular ancestors (Kostyrka, 2016), (2) prolonged pressure of genome reduction, (3) relatively late adaptation to the parasitic lifestyle of virions (Koonin and Dolja, 2013), and (4) establishment of the diverse cellular life on the planet (Nasir et al., 2012).

The use of protein structural domains and particularly the families of fold domains has proven to be useful and reliable in global phylogenetic studies. These protein folding structures are more conserved than the genetic sequences, which are highly variable and usually cannot contain deep historical evidence. The analysis of 304 families of structural fold domains of viral proteomes that included 229 of Archaea, Bacteria, and Eukarya showed that the majority ($>50\%$) of these "universal" fold superfamilies were of ancient origin when they were plotted in an evolutionary time line obtained from phylogenies of protein domains.

Older structures were important for metabolism and translation, suggesting a primitive cellular origin of the viruses. From this perspective, it is proposed that LUCA originated at least two descendants, LUCELLA (last universal cellular ancestor) the last universal ancestor of cells that developed ribosomes and advanced protein biosynthesis (ribocells) and virocell the ancestor of a cell lineage that never deployed the ribosomal machinery and finally transformed into viral parasites and modern virocells (Nasir et al., 2012).

The virocell possibly coexisted with the evolution of cell lineages. This ancient lineage was unable to retain most of the translation machinery and never developed the biosynthesis of ribosomal proteins, since ribosomal proteins and rRNA are absent in viruses. This genome was probably an integral component that was compartmentalized. The phylogenomic data also indicate that the major proteins of the capsid and other proteins necessary for viral pathogenicity were acquired late, after the appearance of LUCA and LUCELLA at least 1.3 billion years ago. This is an alternative view in which the appearance of the capsid coincides with the appearance of modern cells and viral adaptations to parasitism. From this moment, the archaic virocell began to acquire additional structures necessary to infect the descendants of LUCELLA (Nasir et al., 2012).

The comparison between the genomes of mimivirus and megavirus allowed one to demonstrate a set of common genes most likely derived from a common ancestor; this set of ancestral genes included some associated with the translation of proteins; under this scenario the Megaviridae of today is mainly derived from a series of reduction events in the genome of the ancestor of these viruses (Arslan et al., 2011).

The nature of the virus allows us to propose a hypothetical evolutionary model based on the way they parasitize cells and the way they fuse with their host cells. By losing their membrane and cellular structure within the host cell, the viruses are living beings that sequester the host and make available to them precursors for the synthesis of their specific molecules and to the host's genetic information processing machines. In the translation, this created unique parasitic and evolutionary opportunities. This fusion model proposes that viruses originated from parasitic cellular organisms that fused with their host cell. Among modern viruses the life cycle of poxviruses and other complex viruses provides convincing evidence for the fusion model. Some of these viruses have indisputable cellular remnants that are better explained by an evolutionary origin of cell ancestors (Bandea, 2009).

However, up to now, there are no identifiable "universal" viral genes that are common to similar viruses, ubiquitous cellular genes. In other words, there are no examples of common viral components that are analogous to ribosomal RNA genes and ribosomal protein genes, which

are common to cellular genomes. This is a convincing reason that the phylogenetic tests of the "common viral ancestry" hypothesis seem to be inconclusive (Harish et al., 2016).

Another hypothesis proposes the transitional evolution of viruses that they possibly originated from primitive plasmids, due to the similar form of endogenous or vertical and self-replicating transmission as modern conjugative plasmids. The viruses can also be localized in evolutionary time, as molecular structures that adapted to intracellular development (Bandea, 2009).

VIRUS EVOLUTION AND THE IMMUNE SYSTEM

The coevolution of viruses and host defense systems plays a key role in the evolution of both viruses and host cells. Where sometimes viral genes are often recruited to fulfill cellular functions, there are many evidences that reveal a central role of viruses in the evolution of life (Koonin and Dolja, 2013).

The innate immune response exerts a significant selective pressure during the process of virus entry into the cell, since it acts from the early stages of the interaction between the virus and the host, developing effective evasion mechanisms to achieve a successful infection (Sumner et al., 2017). Mechanisms that seek to explain coevolutionary processes have been proposed. An initial kind of arms race between viruses and hosts is proposed, followed by a kind of deescalation of that war in order to explain the coexistence of virus and host (Weissman et al., 2018).

The CRISPR (clustered regularly interspaced short palindromic repeats) system has been proposed as an adaptive immune system of prokaryotes, which incorporates a specific immunological memory in the form of short DNA sequences; acquired from foreign genetic elements (spacers) and uses this memory to direct them to their corresponding target sequences (protospacers) during the next infection. CRISPR can lead to a rapid increase in the arms race (ARMS RACES) between bacteria and phages, in which evolutionary and population dynamics occur on the same timescale (Childs et al., 2012; Paez-Espino et al., 2015).

Theoretical and experimental studies of the CRISPR–Cas bacterial immune system, where the behavior of well mixed compensation mechanisms and losses are counteracted, suggest that there is a regular loss of immunity on the part of the host bacteria, which can thus produce phage–host. Although both mechanisms can have a stable coexistence, only the immune loss does so robustly within realistic parameter ranges (Weissman et al., 2018; Weinberger et al., 2012).

The recombination processes allow the viruses to evade the CRISPR system more effectively than point mutations. The CRISPR immune system imposes selective pressure on the phages and, in the same way, they also exert a selective pressure on the bacteria. The effectiveness of the CRISPR system has a direct impact on the fitness of the bacteria, taking into account that this is surrounded by multiple strains of phages and their survival depends on the ability to recognize them by the CRISPR system, and these will have a greater chance of survival. On the other hand, phages may present mutations that allow them to evade recognition by the CRISPR system, but studies suggest that recombination events could be more effective in this evasion, contributing to a greater degree to the evolutionary process to avoid the CRISPR system (Han et al., 2013).

The major histocompatibility complex (MHC) is crucial for the adaptive immune response of vertebrates and is among the most polymorphic gene families known. Its high diversity is usually attributed to the selection imposed by rapidly evolving pathogens. The new MHC alleles, introduced through mutation, recombination, or gene flow, are predicted to give the host superior resistance (Phillips et al., 2018). Using targeted crosses of the Trinidadian guppy model, a tractable parasite, and exposure-controlled infection trials, showed that new variants of MHC are associated with less severe infections (Phillips et al., 2018).

RELATIONS BETWEEN VIRUSES AND INSECTS

Insects have a special role in our understanding of viral evolution and how they became pathogens. Insects are taxonomically a diverse group of organisms and are common eukaryotic hosts for viruses. Paleontology has helped to explain the host–virus relationship of insects, on the basis of the possible or particular singularity of the obligatory symbiotic viruses of some braconid parasitic wasps. These circular dsDNA viruses, related to insects, are the nudivirus, the genus *Bracovirus* and the families Baculoviridae and Hytrosaviridae. All of them are exclusively pathogenic for arthropods, which harbor nucleocapsids wrapped in rod form and replicate in the nucleus. Phylogenetic studies clearly show that nudivirus and baculovirus are very close groups (Thézé et al., 2011).

The bracoviruses were maintained only in the chromosomes of their associated wasp. Each bracovirus and its wasps act together as a single genomic entity that shares the same evolutionary history. So that their speciation events are contemporary, therefore, to build the phylogenetic tree of DNA insect virus, age was used, based on the age of the amber fossil of the wasps belonging to the bracovirus carrying the

microgastroid complex. Using this information, it was possible to establish that the ancient baculovirus, nudivirus, and bracovirus insect viruses appeared possibly 350 million years ago in the Paleozoic era in the Carboniferous period, when insects and crustaceans were already believed to have appeared 400 million years ago. It is important to note that in the carboniferous period the holometabolic insects with larval stages and complete metamorphosis appeared (Thézé et al., 2011).

By relating the large-scale evolutionary history of the large DNA viruses of insects with their hosts, it is possible to observe that the ancestors of the baculovirus and nudivirus lineages infected the evolved ancestors of their existing hosts, suggesting a coevolutionary scenario of colonization in which the insect viruses had as survival resources the same insects but without destroying them. When the insects evolved into new species, they provided an evolutionarily modified form of the ecological niche required for the cycle of replication of the virus, which adapted and colonized the new host. This mechanism of ecological speciation eventually produced new species of virus. In the evolutionary timescale, with the extinction of many phylogenetic lineages of the host insects and the viruses, the genes of the viruses were maintained, so a very large cophylogenetic divergence should not be expected (Thézé et al., 2011). Findings on the evolution of foamy retroviruses, which have evolved with values above 100 Ma (Katzourakis et al., 2009), suggest that common macroevolutionary scenarios affected viruses regardless of their modes of replication or origin.

The appearance of pathogenic RNA viruses is often associated with their genomic plasticity and alterations in the environment that lead to new contacts with the host. Nearly 50 new human pathogens have been identified, with a predominance of RNA viruses, many as a result of introductions in human populations transferred mostly from other species (Domingo and Holland, 1997). Transferences between species usually mediate the appearance of pathogens through the stochastic generation of virus variants capable of replicating in a new host, in the appropriate ecological environment. Several RNA viruses, including HIV (Gao et al., 1999), SARS coronavirus (Guan et al., 2003; Marra et al., 2003) and dengue virus (DENV) (Wang et al., 2000) have caused recent epidemics by changing their host ranges to increase infections in humans.

For most RNA viruses, it is not clear whether the expansion of the host range involves adaptation to new hosts or preexisting infections. For example, phylogenetic analysis indicates that DENV arose through a transfer of nonhuman primates to human hosts (Wang et al., 2000; Holmes and Twiddy, 2003). Given similar selection pressures and rates of evolution shared by other RNA arboviruses, evidence from the DENV studies suggests that the emergence of other arboviral pathogens through adaptation for urban transmission is also possible.

The majority of arboviruses are RNA viruses that lack polymerases with correction activity and, therefore, exhibit error frequencies of $\approx 10-4$ (Steinhauer et al., 1992). Its high mutation frequencies, rapid replication and large population sizes allow these viruses to adapt rapidly to fluctuating environments. However, comparisons of RNA arbovirus sequences reveal that they are relatively stable in nature, and genetic studies suggest that strong purifying selection dominates their evolution (Holmes and Twiddy, 2003; Jerzak et al., 2005). This stability may result from the requirement of replication in two different hosts, which presents contradictory demands for replication and adaptation and which may restrict adaptation to any of the hosts only by imposing a cost of physical conditioning where the adaptations are antagonistic (Woolhouse et al., 2001).

Viruses transmitted by arthropods (arboviruses) and other human microbial pathogens have been emerging (not reemerging) for centuries. Arthropod vectors and their feeding preferences (anthropophilic or ornithophilic) play an important role in the geographical expansion of these diseases (Gould et al., 2003; Gould and Solomon, 2008). Recent evidence based on the sequencing of DNA and nucleotide polymorphisms (SNPs) of *Aedes aegypti* supports the evidence that shows that mosquito populations in the New World are derived directly from African populations. *A. aegypti* originated in Africa and then colonized the Americas, Oceania and the Asian tropics through trade during the 17th–19th centuries (Powell and Tabachnick, 2013; Brown et al., 2011; Brown et al., 2014; Bennett et al., 2016; Crawford et al., 2017). This redistribution of *A. aegypti* coincided with the appearance of yellow fever and dengue fever in the Americas and dengue fever in Asia (Gould et al., 2003; Tabachnick, 1991; Urdaneta-Marquez and Failloux, 2011).

Molecular epidemiological studies have shown that the ancestral lineage of yellow fever virus (YFV) originated in Africa between 2000 and 4000 years ago. On the other hand the South American YFV separated from the African YFV approximately 200–400 years ago. These data support the original concept that indicates that the YFV arrived in the Americas during the period of slave trade (Gould et al., 2003; Bryant et al., 2007; Moureau et al., 2015).

The adaptation of *A. aegypti* to breed in peridomestic and domestic environments where they tend to enter homes, attracted by the human smell (Weaver and Forrester, 2015), feeding mainly on humans (Harrington et al., 2001) and laying eggs that survive on water poor in nutrients, has been primordial in the emergence of arboviruses associated with *A. aegypti* and has played an important role in the emergence of the global pandemic caused by CHIKV and ZIKV (Weaver and Lecuit, 2015; Musso and Gubler, 2016).

Although CHIKV is an alphavirus, it shares epidemiological, ecological and biogeographic characteristics with flavivirus YFV, DENV and ZIKV associated with transmission by *A. aegypti*, including the dependence of jungle Aedes in the forest cycle and domestic Aedes in the cycle of transmission of human epidemics (Gould and Higgs, 2009; Chen et al., 2016). It is likely that during the 17th and 19th centuries, dengue and chikungunya fever were misdiagnosed; as a result, some of the epidemics that were clinically diagnosed as dengue in the Americas and in Africa during the 17th–19th centuries were probably caused by CHIKV. Chikungunya fever, native to East Africa and Zanzibar, had crossed the Indian Ocean at intervals of approximately 40–50 years from 1770 to 2005–14 (Gould et al., 2017).

Unlike flaviviruses, alphavirus transmission is mainly associated with ornithophilous mosquitoes of the Culex species, which also feed on other animals, including humans, this makes their geographical dispersion strongly influenced by the birds they infect.

CONCLUSIONS

The debate about the origin of viruses has not yet been finalized. Two great possibilities are stated, their existence before their host cells or their evolution from these. The viruses play an important role in the understanding of cell evolution, and their right to be included in the tree of life must be restored.

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