New genetic lineage of Ebola virus discovered in great apes

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Since its discovery 30 years ago, Ebolavirus has struck repeatedly in several epidemics breaking out mainly in Central Africa. Gorillas and chimpanzees are also victims of the violent haemorrhagic fever attacks the virus triggers. With the aim of understanding more of Ebola's action mechanisms, scientists collect viral RNA samples from infected individuals at each outbreak. Hitherto it was only possible to analyse genetic sequences isolated from humans.

Research scientists from the IRD and the International Medical Research Centre of Franceville in Gabon recently succeeded in mapping virus sequences from samples taken from anthropoid apes. Analysis of this genetic material and that collected during human epidemics that have broken out since 2001 demonstrated the existence of a new lineage genetic of the Zaire species (ZEBOV).

It also revealed that genetic recombination events, processes extremely rare for this type of virus, would have taken place between 1996 and 2001. They would have given rise to recombinant viruses responsible for the epidemics that occurred between 2001 and 2003. This set of data now obtained should allow reassessment of the models of Ebola epidemics that occurred over the past few years

The Zaire species of Ebolavirus (ZEBOV) remains the most virulent of the various known species. It alone is responsible for 88% of human deaths from haemorrhagic fever recorded since Ebola's discovery in 1976. It was moreover the species involved in the two-month long

epidemic which raged in the Democratic Republic of Congo (DRC). In spite of the mass of scientific data collected during previous epidemics, the international scientific community has still not succeeded in determining the evolutionary development of the Ebolavirus and more particularly that of ZEBOV.

Investigations were restricted by the scarcity of available data. Only 12 gene sequences coding for the glycoprotein (GP), a molecular structure that enables the virus to penetrate a cell before infecting it, have currently been identified. Furthermore, these sequences, isolated from infected humans between 1976 and 2001, appear to belong to a single genetic lineage originating from the first epidemic documented in the DRC in 1976. This apparent genetic uniformity therefore suggested that epidemics that broke out after 1976 all stemmed from the very first one. However, recent discoveries by a joint IRD-CIRMF team have called this hypothesis into question.

Between 2001 and 2006, these scientists discovered 47 animal carcasses in Gabon and the Republic of Congo. Among them were the remains of 18 gorillas and 5 chimpanzees. The rapid tissue decomposition of the carcasses meant that the search for RNA sequences coding for GP was conclusive for only 6 gorillas and one chimpanzee. Nevertheless, phylogenetic analysis of these was able to show that the virus which had contaminated the seven primates belonged to a new genetic lineage of ZEBOV. This lineage, named B, showed 2 to 3% genetic divergence from lineage A, the one in which scientists had hitherto classified all the viruses gathered from infected humans.

For the purposes of this study, the GP sequences of the viral strains responsible for human epidemics documented since 2001 were also put through phylogenetic analysis. Up to 2003 this confirmed that the viral strains indeed belonged to lineage A. However, the characterization and subsequent phylogenetic analysis of the viral strains involved in the latest

two human outbreaks in the Republic of Congo (Mandza in November 2003 and Etoumbi in May 2005) proved that these strains belonged to lineage B.

These findings prompted the scientific team to push the investigations further. A similar phylogenetic analysis performed on another sequence of the viral genome, coding this time for nucleoprotein (NP 1), showed that the viral strains responsible for human epidemics that occurred between 2001 and 2003 all fall into lineage B. The IRD researchers consider that these seemingly contradictory results in fact provide proof that the wild strains of Ebolavirus are capable of exchanging genetic material by recombination processes.

This process is currently well known for positive RNA viruses (1) such as HIV, but it is much more rare for negative RNA viruses to which the Filoviridae family viruses (Ebola, Marburg) belong. The involvement of this genetic recombination, never described in this family of viruses, carries new clues as to the processes of emergence of Ebolavirus in humans and the great apes. It also suggests that some still unknown, much less pathogenic, strains circulate in the wild.

Estimates derived from this research put the time of the recombination events at between 1996 and 2001. The events would in particular have given rise to viruses responsible for epidemics that struck Gabon and the Republic of Congo between 2001 and 2003.

Now if genetic recombination mechanisms are indeed part of the arsenal of the Ebolavirus, this element must be taken into account for prospects of developing live attenuated vaccines for prevention strategies against the virus-induced haemorrhagic fever epidemics. In such a context this type of vaccine, whose basic principle lies in the triggering of a strong immune reaction in a patient by inoculation with a virus with strongly attenuated pathogenicity, would carry the risk of generating undesirable

effects.

Attenuated virus could for example hybridize with one of the wild strains of the Ebolavirus and hence give rise to a new pathogenic virus. With the aim of characterizing better the processes involved, the next step is to identify the exact genome location on the where this genetic material exchange between viral lineages takes place. In order to do that, the complete genetic mapping of the different viral strains remains to be accomplished.

Note: (1) The genome of RNA viruses can be coded in two different directions. The genes are either stored in the direction 5'->3' (positive polarity or +), as is the case in the messenger RNA contained in our human cells, or in the opposite direction (negative polarity or -).

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