Press release concerning the publication …

Title

Integration of the HIV-1 DNA in the genome of the cell: groups M and O do it alike, only differently!

Summary

The AIDS pandemic is caused, essentially, by HIV-1 subtype M which originated from a virus that infects chimpanzees. In a study published by the journal PLoS Pathogens, the team of Matteo Negroni, at the IBMC in Strasbourg, reports that, during the adaptation of the virus to humans, the integrase of HIV-1 M acquired a new function. This function was, instead, already present in the integrase of the minor variant of HIV-1, subtype O when the ancestor of this virus (a virus that infects gorillas) was transmitted to humans. Surprisingly, though, to develop this function HIV-1 M used parts of the integrase that are different from those used by the gorilla viruses and therefore by HIV-1 O. These observations document the diversity of the evolution pathways that viruses can follow to adapt to a new host after a zoonotic transmission. Unravelling the underlying mechanisms allowing this diversity is important to evaluate the threats that these transmissions constitute for the human health.

Main text

The circulating strains of HIV are subdivided, based on their genetic diversity, in two types, further subdivided in groups. The pandemic is essentially due to type 1 and, more specifically to group M and, to a lesser extent, group O. HIV-1 M descends from a virus that infects chimpanzees, while HIV-1 O from a virus infecting gorillas. Despite these markedly different origins, the two viruses seem to have followed convergent evolutionary paths in humans, leading to two variants of HIV-1 almost indistinguishable between them. It is thus commonly accepted that infection by these two viruses is ensured by homologous proteins with closely similar functions.

The integrase is the viral enzyme responsible for inserting the genome of the virus into that of the cell (integration). In group M viruses, we have identified a new functional motif essential for integration: the CLA motif (“C terminal” region). All HIV-1 M have the same amino acid sequence in this motif, indicating that it confers a strong advantage. On the other hand, this motif is not found in group O integrases where its function is ensured by another motif (NOG), located in another region of the protein. In the NOG motif, all isolates O have a sequence that is strictly conserved and absent in isolates M. Although this functional dichotomy between homologous proteins is surprising, it can be partly explained by the different origins of these two groups of HIV-1. The NOG motif, that is already present in the virus of gorillas that originated HIV-1 O, was most likely inherited by HIV-1 O from its ancestor. The CLA motif, instead, cannot have been inherited by HIV-1 M from its ancestor, since in the corresponding region of viruses infecting chimpanzees, even if similar amino acids are found, there is no sequence conservation. This suggests that , in chimpanzees the motif is not required, while it is in humans. This requirement would be at the origin of the selection of the CLA motif in HIV-1 M.

In viruses, the need for genome compaction often leads to the emergence of multifunctional proteins or, at least, proteins highly optimized in their functions, thanks to the contribution of various functional motifs. Integrase is one such protein. The presence of the NOG motif in HIV-1 O already at the moment of its first infection of humans suggests that the region of the protein where the CLA motif will emerge in HIV-1 M had likely not been subjected to this selection pressure in HIV-1 O, where it could have evolved to ensure another function. We cannot say whether this process was undertaken or not, but it appears that, in the background

of the snapshot taken to trace the evolution of a protein in the context of zoonotic transmission, we might have captured an intermediate step in the acquisition of additional functionality of this protein.

When infecting a new species, a virus faces a drastic change in environment. Adapting to this new condition requires an acceleration of its evolution. A thorough understanding of the evolutionary mechanisms used by the virus in this case is therefore important to understand the threat to our health constituted by the transmission of animal viruses to humans.

Figure legend:
On the left, the results obtained in cell culture show that the infectivity (schematized by the number of viruses drawn) of HIV-1 M is completely abolished (grey virion) if the functional motif CLA is removed (green sword) but it is restored by the insertion of the NOG motif (blue sword) of the HIV-1 O isolates. On the right, the analysis of the sequences of the circulating CLA and NOG motifs shows that the NOG motif was inherited by HIV-1 O from its ancestor (a virus infecting gorillas) while the CLA motif (in HIV-1 M) was selected after infection of humans of the virus infecting chimpanzees.