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From 'purging' to 'endogenization' of the HIV genome: a new approach to HIV eradication?

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The development of antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection represents one of the greatest achievements of modern medicine. ART has significantly changed the clinical outcome of HIV-infected individuals, the rates of HIV-related mortality/morbidity and the nature/transmission of HIV-1 infection in countries with access to antiretroviral drugs [1].

It is now evident, however, that this approach cannot rapidly lead to a cure for HIV infection. Indeed, the virus may still persist in specific reservoirs even in treated patients in whom viraemia is well controlled [2,3]. More intriguingly, the fact that treated patients may present a residual immune dysregulation associated with chronic immune activation [4] makes HIV eradication an aspirational goal. In addition to causing uncertainty, this has led us to consider the topic of HIV eradication with some scepticism.

All these considerations, alongside issues of compliance, drug access and toxicity linked to chronic therapy, highlight the need to implement different and innovative strategies in the field of HIV eradication. In other words, together with an extensive approach to the issue from a traditional scheme-driven point of view, we need to continue to investigate HIV eradication from a completely new and ground-breaking standpoint. One possibility is to extrapolate and apply to the HIV field findings and knowledge from areas only potentially related to the HIV issue.

In this context, the paper by Didier Raoult's group published in this issue of CMI [5] represents an interesting and challenging approach to the topic. It is a radical change resulting from the use of advanced molecular techniques. The authors speculate that the persistence of HIV-DNA in the host genome should no longer be considered an obstacle to HIV eradication but, rather, the beginning of a process of HIV endogenization that may ultimately lead to eradication of HIV infection from the human species.

Editorial Commentary on:
Colson P, Ravaux I, Tamalet C *et al.* HIV infection en route to endogenization: two cases. *Clin Microbiol Infect* 2014; 20: 1280–1288.

Starting from the fact that the characterization of 'HIV elite controller' status (i.e. subjects achieving long-term control of viraemia without highly active antiretroviral therapy [6,7]) has not yet been elucidated, the study monitored two HIV-infected patients (one subject for more than 10 years) with no HIV-related disease and no detection of plasma HIV RNA or cell-associated HIV DNA with routine tests. Both subjects were infected at different times and in different ways and are immunologically reactive against HIV proteins (indicating that they were actually infected). However, their PBMCs harbour very few copies of integrated HIV-DNA (detected only when new molecular techniques are used) that are not replication-competent, probably due to the high content of transcription stop signals. The authors assumed that APOBEC3G, a well-known cytosine deaminase that can be encapsidated and may subsequently hypermutate the neosynthetized cDNA inside the virion during reverse transcription, might be functionally involved in inducing such high defectivity in the HIV genome.

The literature on the acquisition of retroviruses in the human genome is plentiful but, so far, few attempts have been made to frame this knowledge in the field of HIV. Indeed, we know that human chromosomes contain a huge number of retroviral sequences (they account for about 8% of our genome) [8,9]. Once inserted into the human genome none of these retroviral sequences remain static as they have suffered from post-insertion mutations (including insertion of transcription stop signals), deletions and recombinations that have stopped them being infectious. At least some of the above modifications are known to be driven by the action of now well-known cellular restriction antiretroviral factors, of which the APOBEC-superfamily is one of the most prominent [10]. It is assumed that the origin of such retroviral sequences and the related process of endogenization (the process entailing a germline integration that ultimately allows vertical transfer and functional attenuation of the provirus) are derived from exogenous retroviruses that circulated millions of years ago. However, although we do not have any demonstration in humans, it is no longer true that this phenomenon occurred

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only millions of years ago. In 2006 two papers demonstrated an endogenization process in Koala retrovirus (KoRV) introduced into koala bears only a century ago [11,12]. Functional assessment of specific sequences contributing to KoRV's attenuation from KoRV's closest genomic relative, the highly infectious exogenous gibbon ape leukaemia virus (GALV)-like progenitor virus, has allowed the identification of specific modifications in the KoRV genome that correlate with its endogenization [13]. This phenomenon is still under scrutiny to find the evolutionary advantage of the virus undergoing such a process. The model may hopefully provide interesting findings to support the fascinating speculation provided in the paper by Raoult's group paper on the role, if any, of viral endogenization in the eradication of HIV infection.

Several caveats must be taken into account when reading the study of Raoult's group [5].

First, the study examined only two subjects. Therefore, before fully considering the data we have to wait for studies involving substantially larger numbers of subjects (that include for instance 'elite controller' cohorts).

Second, in this paper the association between APOBEC3G and induction of defectivity in the HIV genome in the two subjects is only speculative and, before reaching any conclusion on the issue, other cellular restriction factors, acting in different ways and causing other types of inactivation, should be considered. Moreover, the presence of defective HIV proviral genomes in cellular DNA from patients in various clinical conditions has been described, due to a number of mechanisms, including deletions and APOBEC3-induced editing [14].

Third, the clinical relevance, if any, of the current observations needs to be further elucidated, given that the endogenization process does not necessarily mean inactivation of the HIV genome. Studies are in progress to exploit the potential pathogenetic role of human endogenous retrovirus (HERV) sequences and their possible association with disease, particularly tumorigenesis [15,16].

Nevertheless, new avenues of research are being explored in our understanding of HIV-host interactions and pathogenesis. These new findings, together with the related speculations, may be further exploited in the search for new HIV-1 cure strategies.

Transparency Declaration

The author has declared no conflict of interest.

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