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Commentary

Long-term Persistent Elite HIV-controllers: The Right Model of Functional Cure

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The understanding of the mechanisms associated to the natural control of HIV-infection is essential to achieve HIV-long-term remission or new insights in HIV cure strategies. Despite the enormous advances in the last 15 years showing that the presence of protective genetic factors, as protective HLA alleles and the associated cytotoxic T-lymphocytes (CTL) response, are capital for the spontaneous control of HIV-infection (Pereyra et al., 2010), the detailed nature of the mechanisms associated with this phenomenon are not completely clear. In the study by Bendenoun et al. (2018) in EBioMedicine, the authors describe the case report of the spontaneous control of HIV-1 for ten years in a homosexual man after transmission by his unique couple, who was not able to naturally control the virus. Similar reports had been previously published (Bailey et al., 2008; Buckheit III et al., 2012) but in this case, in contrast to previous works, both individuals had no protective HLA-alleles.

How this individual was able to persistently control de virus is not well understood. The clues to answer this question come from the fact that in a comprehensive analysis the authors found incomplete western blot against HIV-1 during 10 years of follow up, extremely low HIV-1 reservoir in peripheral blood and tissues, no blips of viral load, high polyfunctional CTL response and enhance capacity of antibody-dependent cell cytotoxicity (ADCC) in NK cells compared to his couple. These features associated to persistent control of HIV-infection are very similar to those found in the extreme phenotypes of elite HIV-controllers found in a French cohort (Canouï et al., 2017) with the exception that these individuals had weak HIV-specific CD8 + T-cell response measured by the ability to suppress HIV-1 infection of autologous CD4 + T cells ex vivo. The results by Bendenoun et al. (2018) are also in accordance with the low reservoir and high polyfunctional HIV-specific T-cell response measured by intracellular cytokine staining recently found in a similar phenotype of individuals that persistently controlled the virus compared to patients that transiently controlled HIV-1 (Pernas et al., 2017). As discussed by the authors the individual of the case report may be one of these examples of extreme phenotype with persistent long-term elite control of HIV-infection. This is important, because it is everyday clearer that the HIV-controllers scenario is quite heterogeneous in terms of definitions and immunologic and virological characteristics related to disease progression (Leon et al., 2016). The delineation of the right model of "persistent" elite HIV-controller phenotype is essential for two main reasons. First, it is unclear in the current treatment guidelines whether elite HIV-controllers must be treated with antiretrovirals. Elite HIV-controllers who lose their capability at the mid-short term might be benefited of combined antiretroviral treatment thanks to the identification of predictive biomarkers (Pernas et al., 2017). Second, individuals who persistently control the virus for even more than 25 years since infection with no viral "blips", high CD4 + T-cell counts, extremely low reservoir and low levels of activation comparable to non-HIV infected subjects, might be considered as a right model of functional cure that will undoubtedly help for the development of future HIV-cure strategies. An indiscriminate treatment of these patients will eliminate this model.

The implementation of large cohorts of elite HIV-controllers will help for the identification of this extreme phenotype with the aim to refine the immune correlates of persistent natural HIV-control. In this sense, protective HLA-alleles are for sure to go on playing a major role, as it has been recently shown in a cohort of long term non progressor HIV-controllers enriched in this persistent elite HIV-controller phenotype (Dominguez-Molina et al., 2017). However, like in the case report presented herein and other works, no association was found between spontaneous control and protective HLA alleles (Tsai et al., 2016). Interestingly, other factors like certain KIR ligands, ADCC-mediated response, dendritic cell mechanisms (Machmach et al., 2012) and others yet undefined are likely to be associated with persistent control of HIV-1 infection.

Despite that the host factors seem to be essential in the persistent control of the virus in this case report (Bendenoun et al., 2018), the fact that both individuals were heterozygous for CCR5Δ32, does not clarify if this "bottleneck" could render a lower virus fitness that enabled the spontaneous virus control. It remains also unknown at what date during the follow up occurred the transmission. This is important because there was a period of time where the input of virus was potentially small due to the low viral load levels.

In any case, persistent elite HIV-controllers must be considered as a model of functional cure. Studies like the one presented by Bendenoun et al. (2018) show that spontaneous long-term control of HIV-infection is possible even in the absence of protective HLA-alleles. Future efforts are necessary to identify this very scarce proportion of individuals that are able to persistently control the virus and use them as the right model of functional cure to redefine immune correlates of long-term remission that will help to new designs of HIV-cure strategies.

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Disclosure

The authors declared no conflicts of interest.

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