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

HIV elite controllers (EC) are a scarce population of people living with HIV (<1%) who are able to maintain undetectable levels of viremia in the absence of antiretroviral therapy (cART). Thanks to the implementation of large cohorts of these individuals, it is nowadays known that EC are a heterogeneous phenotype. Approximately, 25% of these subjects can loss virological control and 40% suffer a CD4+ T-cell drop (*León et al., AIDS 2016*). These findings, together with others that show higher hospitalization rates in HIV-controllers compared with non HIV-controllers (*Crowell et al., J Infect Dis 2015*), have made to reconsider HIV-controllers as a model of persistent virological remission in the absence of cART or "functional cure". Nevertheless, these results are controversial. The same authors did not observe these differences in a different cohort (*Crowell et al., J Int AIDS Soc 2016*). In addition, in other large HIV-controller cohorts, neither higher rates of cardiovascular disease nor other non-AIDS events in HIV-controllers compared to non HIV-controllers have been found (*Dominguez-Molina B et al., J Infect Dis 2016*).

The key of this controversy is due to the heterogeneity of the EC phenotype. EC can be classified in "transient controllers" (TC), those that eventually lose viral load control and in "persistent controllers" (PC), those that maintain viral load control indefinitely overtime (*Pernas et al., J Virol 2018, and Chereau et al., PLoS One 2017*). It is important the search of biomarkers that enable the differentiation between these phenotypes for two reasons: 1) it may be possible to design therapeutic strategies for TC before these subjects show HIV-disease progression, 2) it may allow to recognize PC as the true model of functional cure. In fact, several studies have shown that PC have high HIV-specific T-cell response levels (*Pernas et al., J Virol 2018*), associated with low viral diversity and variability together with low viral reservoir levels (*Pernas et al., J Virol 2018, Canouï et al., Open Forum Infect Dis 2017*) compared to TC. Likewise, PC show low levels of inflammation (5). Additionally, these two phenotypes also differ in a peculiar proteomic profile associated with lower levels of inflammation in PC compared to TC (*Rodríguez-Gallego et al., J Infect Dis 2019*). In the same way, the metabolomic and lipidomic profiles are clearly different between these two groups (*Tarancon-Diaz et al., EBioMedicine 2019*). These results on one hand segregate PC as the true model of persistent virological remission and on the other hand, differentiate them from subjects that will lose the spontaneous virological control and may be offered personalized treatment.

These discoveries shed light on the current controversy of whether HIV-controllers may be treated with cART. In recent studies, cART in HIV-controllers has been associated with the decrease in immune activation and inflammation levels (*Li et al., Clin Infect Dis 2019*). However, most of the individuals included in these studies were HIV-controllers with detectable viral load, also known as viremic controllers. In agreement with the results commented above, in the case of a subject infected since 30 years with persistent undetectable viral load and CD4+ T-cell levels above 500 cells/mm^3, the benefit of cART in this scenario might be more than doubtful. Nevertheless, in the case of TC the use of cART and/or complementary immune therapeutic strategies may allow to reduce inflammation levels in these individuals.

Therefore, all these data support PC as the right model of functional cure. This model can be used for the development of immunotherapeutic strategies. It is important to note, that in recent studies in 50% of PC the virus could not be detected in the periphery and in those subjects that the virus was detected, HIV variability and diversity was extremely low (*Pernas et al., J Virol 2018*). Viral dating estimations suggested that viral evolution was stopped very close to the time of infection (*Pernas et al., J Virol 2018*). These findings suggest that may be some of these individuals were able to control the virus since the beginning of the infection and to some extent were able to persistently control viral replication and they can be considered as functionally cured. It is also possible, the provocative hypothesis the some of these subjects were able to achieve a “sterilizing cure”, that is, they were able to eradicate the virus. Independently, that this was the case; this limited group of individuals with a persistent long-term non progressor EC profile is the true model of functional cure. The comprehensive analysis of viral, genetic and immunologic factors in this model will be key for the development of strategies to reduce HIV reservoir for the achievement of the persistent virological remission in the absence of cART in the general population of people living with HIV.

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