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Transient immunosuppression during short interruption of HAART: Another key to HIV cure in the "Berlin patient"?

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ABSTRACT

Transient immunosuppression in lentiviral infections leads to an auto-vaccination followed by the rise of serum neutralizing activity and a significant decrease in a set-point viral load, which becomes undetectable in some cases. Arguably, in the "Berlin patient" (Hütter G, et al., N Engl J Med, 2009) an induction chemotherapy-mediated transient immunosuppression episode during short interruption of HAART might have led to at least a "functional cure" before allogeneic stem cell transplantation. Neutralization-enhancing RF antibodies (NeRFa) induced as a part of secondary immune response after transient immunosuppression may have played a key role in neutralization of infectious HIV-IgG complexes in extracellular reservoirs. Transient immunosuppression during short non-structured treatment interruption (TI-SNSTI/HAART) regimen would be promising for the achievement of HIV cure on a large scale.

Introduction

Human immunodeficiency virus (HIV) in patients can form both extracellular [1–3] and intracellular reservoirs [4,5]. Nowadays significant efforts are being made towards a "sterilizing cure" by targeting latent virus in intracellular reservoirs [4–7]. It automatically implies that extracellular HIV has already been eliminated. In the reality, follicular dendritic cells (FDCs) in HIV-infected patients represent another obstacle to HIV cure [8,9] by forming the largest extracellular viral reservoir, which is not eradicated by highly active antiretroviral therapy (HAART) [3,10,11]. By the beginning of the asymptomatic period more than 98% of HIV particles are located on the surface of FDCs [12].

Follicular dendritic cells retain the long-term infectiousness of HIV particles covered by antibodies [3,13] and effectively support an infection of CD4+ T cells migrating through the secondary lymphoid organs [1,3]. An autopsy data showed that FDCs on their surface contain a monophyletic group of HIV variants with highly progressing diversity at the *env* gene by comparison with other compartments such as T cells [2]. This fact along with *in vitro* data [14] further support the hypothesis that at the end of asymptomatic period HIV *env* gene mutates via AID-mediated somatic hypermutation mechanism [15] like immunoglobulin genes encoding antibodies. Such mutations not only allow the virus to be ahead of the adaptive immune response but also may lead to uncontrolled R5-X4 HIV-1 switching towards acquired immunodeficiency syndrome (AIDS) [15].

IgM NeRFa for neutralization of infectious HIV-IgG complexes

Eradication of the extracellular HIV reservoirs always represented a problem probably due to the absence of the methodologies how to neutralize infectious HIV-IgG complexes especially in the light of the role of antibody-dependent enhancement of infection (ADE) in progression to AIDS [16,17]. At present rheumatoid factor-mediated neutralization of the virus in the presence of complement [18] is the only known way to neutralize extracellular viral particles covered by infection-enhancing antibodies. The fundamental defensive role of IgM rheumatoid factor (RF) in the protection of mother and the offspring from infection [19,20] is further supported by the ability of such antibodies to enhance neutralization of different pathogens [21], including HIV [22]. Physiological IgM RFs appearing during secondary immune response [23,24] should be discerned from pathological self-associating IgG RFs in rheumatoid arthritis [25].

Neutralization-enhancing RF antibodies (NeRFa) [26–28] might potentially prevent ADE and neutralize HIV in the presence of complement. Induction of NeRFa is promising for an elimination of infectious HIV-IgG complexes covered by complement molecules from the FDCs reservoir [27,29]. Transient immunosuppression with dexamethasone in ponies infected with equine infectious anemia virus with deleted principal neutralizing domain ($EIAV_{\Delta PND}$) led to a 100-fold drop in a set-point viral load with a highly specific rise of the neutralizing activity in the serum [30]. This is consistent with the induction of NeRFa against $EIAV_{\Delta PND}$ [28]. In other cases of EIAV infection such an

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immunosuppressive treatment led even to undetectable values of set-point viral load [31]. Similar auto-vaccination effect leading to the rise of neutralizing activity coinciding with a sharp drop in viral load has been observed in HIV-infected patient after treatment with rituximab during HAART interruption [32].

A Key from the "Berlin patient"

The "Berlin patient" [33] up to date is the only patient in which a "sterilizing cure" for HIV has presumably been achieved [34]. Despite multiple thorough investigations of the case the following two questions arise:

(i) Why the success of the "Berlin patient" still cannot be reproduced?
(ii) Could the "functional" or even a "sterilizing" cure states in the "Berlin patient" have occurred before allogeneic stem cell transplantation (alloSCT)?

Indeed, several attempts to achieve HIV cure by means of homozygous CCR5delta32 (CC chemokine receptor 5 gene with a deletion of 32 base pairs) alloSCT have failed [4,35,36]. Also the viral load has been undetectable for the whole period starting from several days before alloSCT onwards indefinitely [33,34,37]. Therefore it is not excluded that even without alloSCT the result would be same.

In the article [37] authors compared one unique case, i.e. the "Berlin patient", with other settings where HIV rebounded after HAART discontinuation following alloSCT. But this comparison cannot be the "evidence" that homozygous CCR5delta32 alloSCT has cured the "Berlin patient". Indeed, one of the induction chemotherapy courses before alloSCT in the "Berlin patient" took place during a short interruption of HAART thus leading to a viral rebound up to $6.9*10^6$ (HIV RNA/ml) [33]. This is a key aspect that distinguished the "Berlin patient" from other patients. Induction chemotherapy course for acute myeloid leukemia is inevitably immunosuppressive [33]. Unfortunately, for unknown reasons the authors avoided mentioning this key episode of the short interruption of HAART both in the article with an "evidence" for a cure [37] and even in the figure depicting timeline of clinical events in the "Berlin patient" [34].

It can be hypothesized that at least a "functional cure" in the "Berlin patient" has been achieved before alloSCT due to immunosuppressive episode on the induction chemotherapy course during short interruption of HAART by taking into account the following facts:

(i) Post-transplantation therapy is severely immunosuppressive [33]. Therefore after transplantation while being on the regimen off HAART the rapid viral rebound within 3–4 weeks is expected like in similar post-transplantation settings [36,38,39]. This time is almost twice as little as the time (61 day after alloSCT) [33] of achievement of complete chimerism in the "Berlin patient".
(ii) Extracellular viral reservoirs are not affected by alloSCT. Viral load after alloSCT was undetectable despite the fact that intestinal macrophages expressed CCR5 receptor even 159 days after alloSCT [33].
(iii) Preexisting X4/R5X4 HIV-1 variants (2,9% of the total viral population) "disappeared" after alloSCT [33]. This is in contrast to the quick rebound of X4 variants in a similar setting of homozygous CCR5delta32 alloSCT [36].
(iv) Antibodies against HIV gp120 and gp41 envelope proteins, in contrast to other viral proteins, remain in significant amounts 625 days after alloSCT [33]. The same trend continues to be at 40 months [37] and even 60 months [34] after alloSCT despite constantly undetectable viral load.

All these facts are consistent with a model according to which NeRFa might have been induced after the short immunosuppressive episode off HAART at the second course of induction chemotherapy before alloSCT. Neutralization-enhancing RF antibodies may neutralize the extracellular virus via complement-dependent mechanism [18,22,40] with subsequent clearance of immune complexes [41]. It is not excluded that cells expressing HIV antigens, like cancer cells expressing viral antigens on their surfaces, might be recognized by NeRFa with subsequent destruction by complement-mediated cytotoxicity [27,42]. Latently infected cells either have a limited life span or might be destructed anyway after spontaneous HIV reactivation by the mechanism mentioned above. Continuous NeRFa-mediated neutralization of all extracellular viral particles even on its own might be able to eliminate all HIV from the organism due to the limited life span of infected cells. To sum up, the successful induction of NeRFa in the "Berlin patient" might have led to the gradual eradication of both extracellular and intracellular HIV reservoirs thus approaching the "sterilizing cure" state in the long term.

The last "feast" for HIV

Transient immunosuppression (TI) regimen may lead to a significant decrease of the set-point viral load (SPVL) [30]. On the contrary, HAART does not change SPVL [32,43]. It seems that the decrease of SPVL might prolong the length of the asymptomatic period in HIV-1 infection [44]. Both short non-structured treatment interruption (≤ 4 weeks) [45] and transient immunosuppression off HAART [32,33,38] regimens seem to be safe for patients. Combination of two regimens into one would lead to the transient immunosuppression during short non-structured treatment interruption (TI-SNSTI/HAART) setting, in which HAART plays a very important role to control the maximal viral load during immunosuppressive episode.

Transient immunosuppression off HAART regimen is characterized by at least 10 to 100-fold rises in viral load [32,38] during immune suppression in comparison to the initial SPVL. It seems that maximal value of viral load and the speed with which it rises during immunosuppression episode might be critical for the successful induction of NeRFa at secondary immune response upon "burst" of viral replication. Maximal viral load upon TI-SNSTI/HAART regimen in the "Berlin patient" before alloSCT [33] and in the "Frankfurt patient" after alloSCT [38] reach almost the same value. Therefore future analytical treatment interruption in the "Frankfurt patient" might say whether the "feast" for HIV upon its replication just after alloSCT was the last one. Also analytical treatment interruption in the "Oxford patient" [32] may be informative.

A view outlined above points to the new possibilities to be investigated. Reproduction of TI-SNSTI/HAART regimen in HIV-infected individuals exactly as in the "Berlin patient" might be particularly promising. Will it lead to the absence of viral rebound after analytical treatment interruption or even to a "sterilizing cure"? By that time the beautiful molecular mechanisms behind such a success will probably require even more attention from many physicians working urgently to reproduce HIV eradication on a massive scale.

Conflict of interest statement

None

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