Title of the Article*: HIV neutralization in extracellular reservoirs

A recent *Perspective* article[1] about HIV cure focuses mainly on eradication of latently infected cells. Paradoxically enough, existence of follicular dendritic cells (FDCs) in germinal centers of secondary lymphoid organs as the biggest extracellular viral reservoir in HIV-infected individuals[2, 3] may significantly devalue all the approaches to eliminate an intracellular virus.

Follicular dendritic cells preserve long-term infectivity of extracellular HIV particles even covered by neutralizing antibodies and up-regulate receptor CXCR4 on the neighbour $CD4^+$ T cells to promote infection[2]. Follicular dendritic cells carry a monophyletic group of viral variants with an ever increasing diversity in the *env* gene[3] that is consistent with the somatic hypermutation mechanism for R5-X4 HIV-1 switching[4].

Absence of viral particles on FDCs is characteristic to natural hosts of SIV such as african green monkeys (AGMs) which do not progress to AIDS (ref.5). African green monkeys also do not transmit SIV to the offspring during breastfeeding despite high extracellular viral load in the milk[6]. Can efficient neutralization of viral particles be the key for both phenomena mentioned above? Interestingly, autologous neutralization is absent in the milk of non-natural hosts of SIV (ref.6).

In AGMs IgG content in milk is 10-fold lower than in plasma despite both fluids have similar values of autologous neutralization meanwhile fraction of milk with depleted IgG has no neutralization activity[6]. Can IgM rheumatoid factor (IgM RF) in the milk of natural hosts amplify SIV neutralization? Indeed, IgM RF may enhance IgG-mediated neutralization of HIV (ref.7). Similarly, IgM RF strengthens IgG immune response and protects lactating rats and their offspring from infection with a protozoan parasite[8].

Such neutralization-enhancing RF antibodies (NeRFa) (ref.9, 10) of IgM class may have several potential functions against HIV: (i) conversion of infection-enhancing antibodies into neutralizing and prevention of antibody-dependent enhancement (ADE) of infection by means of interaction with Fc-part of the IgG attached to the virus; (ii) inhibition of HIV deposition on the surface of FDCs via competition with complement C3 fragments for binding to IgG-coated viral particles; (iii) enhancement of HIV neutralization by providing highly avid cross-linking interactions with an ability to aggregate viral particles covered by IgG.

Mechanisms of HIV neutralization outlined above await researchers for further experimental support. Clearance of viral particles from FDCs in natural hosts of SIV may potentially exist[5]. Can IgM RF underlie such an effect? Simultaneously, there are predictions on the possible role of IgM RF in preventing accumulation of HIV in lymph nodes[7]. Deeper understanding of virus neutralization with an emphasis on FDCs reservoir may inform future anti-HIV therapeutic and prophylactic strategies based on induction of IgM NeRFa (ref.9, 10).

Elimination of all latently infected cells alone may not lead to a cure, because extracellular virus in the FDCs reservoir retains R5-X4 HIV-1 switching potential with an ability to infect and massively kill $CD4^+$ T lymphocytes on the way to AIDS. To sum up, induction of NeRFa towards neutralization of extracellular HIV might constitute an additional cure strategy for an International AIDS Society.

References

1. Deeks, S.G. *et al*. *Nat. Med.* **22**, 839-850 (2016).
2. Burton, G.F., Keele, B.F., Estes, J.D., Thacker, T.C. & Gartner, S. *Semin. Immunol.* **14**, 275-284 (2002).
3. Keele, B.F. *et al. J. Virol.* **82**, 5548-5561 (2008).
4. Suslov, K.V. *Immunol. Lett.* **91**, 1-2 (2004).
5. Brenchley, J.M. *et al*. *Blood* **120**, 4172-4181 (2012).
6. Wilks, A.B. *et al. J. Virol.* **85**, 9517-9526 (2011).
7. Douvas, A., Takehana, Y., Ehresmann, G., Chernyovskiy, T. & Daar, E.S. *AIDS Res. Hum. Retroviruses* **12**, 1509-1517 (1996).
8. Clarkson, A.B.Jr. & Mellow, G.H. *Science* **214**, 186-188 (1981).
9. Suslov, K.V. in Advances in Medicine and Biology Vol. 87 (ed. Berhardt, L.V.) 81-106 (Nova Science Publishers, New York, NY, 2015).
10. Suslov, K.V. *Curr. Immunol. Rev.* **12**, 118-124 (2016).

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