EBioMedicine 13 (2016) 27–28

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Why Are Some HIV-1 Subtypes More "Wimpy" at Causing Disease?

William A. Paxton

Clinical Infection, Microbiology and Immunology, Institute of Infection and Global Health, University of Liverpool, Liverpool, L69 7BE, UK

ARTICLE INFO

Article history:
Received 18 October 2016
Accepted 18 October 2016
Available online 18 October 2016

In this issue of *EBioMedicine*, Venner and co-authors [1] expand the observation that variant subtypes of HIV-1 are highly divergent in terms of biological phenotypes. This study goes further to link this diversity to disease course and outcome. Through studying a natural history cohort of HIV-1 infected Ugandan and Zimbabwean women from time of infection and in some cases through to 9 years of follow up the authors conclude that those infected with subtype C viruses have lower rates of CD4 T-cell decline and progress slower in disease than those infected with either subtype A or D viruses. Through comparing viral isolates for cell-entry, PBMC replication and cell-to-cell transmission they demonstrate that subtype C viruses are generally less fit than other subtypes. The strength to this report is the finding that these differences in viral phenotype match natural clinical progression.

The observation that HIV-1 subtype C viruses are in general less fit for viral fitness, both in vitro and in vivo, than other subtypes raises interesting questions regarding the basic virology of HIV-1 and constraints on viral evolution. It has been well documented that HIV-1 subtype C is the most prevalent subtype within certain regions of Africa, namely Ethiopia and South Africa, even when other subtypes reside within the population, indicating a transmission fitness that is not associated with replication capacity. This can be down to numerous genetic differences within the host population and which have all been linked to control of viral replication, including HLA types, chemokine and/or chemokine receptor haplotypes as well as cytokine genes which relate to enhancement or control of viral replication [2]. The present study, although comparing individuals from two different countries (Uganda and Zimbabwe), goes some way to highlight that these populations do not differ in relation to such genes. The findings demonstrate major differences in the biological properties between the HIV-1 subtype isolates which are preserved over time. Why should subtypes maintain strictly delineated phenotypes, especially given the high evolution capabilities of the virus? Why do subtypes not converge towards being the fittest in terms of transmission as well as maintaining high viral loads during disease? Is selection down to differences in which cell-types are initially infected or which cell-types are targeted and eliminated leading to differences in maintenance of immunity and better viral control? If so, this would be via a phenotype restricted by the Env (gp120/gp41) properties of the virus influencing which cell-types are preferentially infected. There must be some strong biological barrier that maintains this block to subtype convergence; currently unknown but essential to decipher.

Subtype C viruses rarely switch co-receptor phenotype and generally maintain solo CCR5 usage, whereas other subtypes and especially D, frequently switch co-receptor to using CXCR4 [3]. There seems to be an inherent molecular component to the HIV-1 Env protein that maintains a configuration that associates with entry efficiency and replication fitness that can manifest in maintenance of properties such as co-receptor usage. The major regions of the gp120 protein directing co-receptor usage are the variable loops and where molecular pressure maintaining a specific phenotype resides [4]. The gp120 amino acid profile of viruses that undergo transmission and those emerging following infection and later in disease have been well characterised [5,6]. It has recently been identified that the amino acid length of the V1V2 and V4V5 regions are inversely correlated at time of infection and lost following seroconversion [7]. Env-induced antibody responses likely contribute to the maintenance or selection of these properties in vivo but why these should be different amongst individuals infected with variant subtypes is not known. It is established that gp120 sequences can be linked to antibody selection, mainly in terms of V1V2 and V3 diversity, especially relating to N-linked glycosylation profiles [8]. Antibody selection is typically absent at time of transmission thereby allowing for potential selection or reversion of transmitted viruses. Structural constraints within the gp120 protein likely associate with Env function, which may differ between subtypes and can be influenced through antibody selection. It has been proposed that a smaller V1V2 region with less glycosylation can enhance HIV-1 fusion for subtype C viruses on both CD4 T-cells and macrophage [9]. A more recent study has indicated that genetic variations within the subtype C gp41 molecule can impede HIV-1 entry and replication within CD4 T-cells and modulate cell-to-cell transmission but not in macrophages [10]. The results are interpreted that subtype specific Env incorporation within viral membranes can be subtype specific. Therefore, does a complex specific interaction exist not just between the regions of the gp120 protein but also between the gp120 and gp41 molecules?

Collectively, there are major restrictions within Env biological properties between the HIV-1 subtypes which lead to variation in HIV-1

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.10.014.
E-mail address: w.a.paxton@liverpool.ac.uk.

http://dx.doi.org/10.1016/j.ebiom.2016.10.023

transmission rates and which can influence disease. The maintenance of such properties indicates that the molecular constraints are preserved and provide some promise that not all Env targeted therapies or vaccines can be readily escaped. Understanding these constraints will likely pinpoint where therapy and vaccine strategies need to be directed, albeit in a subtype as well as regional specific manner. Similarly, antiretroviral treatment requirements may differ regionally dependent on the circulatory types.

Disclosure

I declare no competing interest.

References

Venner, C.M., Nankya, I., Kyeyune, F., et al., 2016. Infecting HIV-1 subtype predicts disease progression in women of sub-Saharan Africa. EBioMedicine 13, 305–314.

M[c]Claren, P.J., Carrington, M., 2015. The impact of host genetic variation on infection with HIV-1. Nat. Immunol. 16, 577–583.

Abebe, A., Demissie, D., Goudsmit, J., et al., 1999. HIV-1 subtype C syncytium- and nonsyncytium-inducing phenotypes and coreceptor usage among Ethiopian patients with AIDS. AIDS 13, 1305–1311.

Pollakis, G., Kang, S., Kliphuis, A., et al., 2001. N-linked glycosylation of the HIV type-1 gp120 envelope glycoprotein as a major determinant of CCR5 and CXCR4 coreceptor utilization. J. Biol. Chem. 276, 13433–13441.

Derdeyn, C.A., Hunter, E., 2008. Viral characteristics of transmitted HIV. Curr. Opin. HIV AIDS 3, 16–21.

Mosier, D.E., 2009. How HIV changes its tropism: evolution and adaptation? Curr. Opin. HIV AIDS 4, 125–130.

Pollakis, G., Baan, E., van Werkhoven, M.B., et al., 2015. Association between gp120 envelope V1V2 and V4V5 variable loop profiles in a defined HIV-1 transmission cluster. AIDS 29, 1161–1171.

Derdeyn, C.A., Decker, J.M., Bibollet-Ruche, F., et al., 2004. Envelope-constrained neutralization sensitive HIV-1 after heterosexual transmission. Science 303, 2019–2022.

Cavrois, M., Neidleman, J., Santiago, M.L., et al., 2014. Enhanced fusion and virion incorporation for HIV-1 subtype C envelope glycoproteins with compact V1/V2 domains. J. Virol. 88, 2083–2094.

Santos da, S.E., Mulinge, M., Lemaire, M., et al., 2016. The envelope cytoplasmic tail of HIV-1 subtype C contributes to poor replication capacity through low viral infectivity and cell-to-cell transmission. PLoS One 11 (9), e0161596.