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Commentary

A Role for Fc-Mediated Humoral Immunity in Reducing HIV Transmission Rates between HIV Serodiscordant Heterosexual Couples☆

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HIV serodiscordant couples are an extremely useful tool for examining immune responses that may contribute to reduced transmission or protection from HIV infection. A homozygous 32-base pair deletion in the gene encoding the Chemokine receptor 5 protein (CCR5) is strongly associated with protection from HIV infection (Huang et al., 1996). In contrast, the contribution of humoral, cellular and innate immunity in individuals who have been repeatedly exposed to HIV-1 but remain seronegative (ESN) protection has been more controversial, with several studies suggesting roles for T cells, neutralizing antibodies and innate immunity, including monocytes and NK cells (Lederman et al., 2010). Analysis of the moderately protective RV144 'Thai' Phase III HIV vaccine trial suggests a role for Fc-mediated humoral immunity in protection and control of HIV infection (Chung et al., 2015; Haynes et al., 2012). However, few studies have examined ESN or serodiscordant couples for Fc-mediated effector responses.

In this issue of EBioMedicine, Ruiz et al. (Ruiz et al., 2017) examined nine heterosexual serodiscordant couples to determine differences in cellular or humoral immune responses. ESN individuals did not induce any significant HIV-specific humoral immune responses, very weak HIV-specific cellular responses were observed in only two ESN, and modestly elevated levels of macrophage-derived chemokine levels were detected in plasma, although this difference lost statistical significance after correction for multiple comparisons. However, the authors report that the magnitude of antibody-dependent cellular cytotoxicity (ADCC) responses and gp120-specific IgG/IgA ratios were elevated within chronically infected HIV individuals who did not transmit HIV to their heterosexual ESN partners. This preliminary work suggests that ADCC magnitude may contribute to reduced viral transmission. Interestingly both ADCC responses and IgG/IgA ratios correlated with increased CD4 + T cell counts, but not viral loads, in HIV individuals that did not transmit to their respective partners, while these associations were absent within chronically infected HIV transmitters. Whether these ADCC responses and IgG/IgA ratios are also elevated at genitorectal mucosal sites of chronical HIV infected non transmitters, the most relevant sites for heterosexual HIV transmission, warrants future investigation. Previous studies have observed HIV-specific ADCC activity in both cervical vaginal (Nag et al., 2004) and seminal plasma samples (Parsons et al., 2016). Furthermore, studies investigating the contribution of specific biophysical properties of these ADCC antibodies, such as epitope specificities, epitope avidity and IgG subclass distribution will be of interest, as they have been previously associated with enhanced HIV disease control and protection from infection in the context of HIV vaccination (Chung et al., 2015; Haynes et al., 2012). In addition, whether other Fc-mediated effector responses including antibody-dependent cellular phagocytosis, antibody-dependent complement activation or polyfunctional Fc-effector responses in general (Ackerman et al., 2016; Chung et al., 2015) contribute to reduced viral transmission deserves consideration.

Ruiz et al. also present preliminary evidence to suggest that IgA may interfere with ADCC responses within HIV-positive individuals. IgG/IgA ratios correlated with ADCC activity within chronically infected HIV non-transmitters, while elevated levels of IgA, and the lowest IgG/IgA ratios were observed within chronic HIV transmitters. These results are of particular interest due to the RV144 'Thai' vaccine trial immune correlates analysis that identified high levels of IgA reduced the efficacy of the vaccine (Haynes et al., 2012). An immunomodulatory role of IgA may not only influence vaccine efficacy but also modulate HIV Fc-mediated immunity (Tomaras et al., 2013) and potentially may have a negative impact on HIV virus transmission.

Ruiz et al. acknowledge that their small cohorts were underpowered to address the differences between HIV chronic transmitters from non-transmitters. Furthermore, they also acknowledge that their HIV-positive non-transmitters cohort included subjects (four of nine) that could be considered 'viremic controllers' (viral loads < 2000 RNA copies/ml). Since viral load is a major determinant of reduced virus transmission (Quinn et al., 2000), this needs to be kept in mind while interpreting their data. Viremic controllers are also known to induce elevated Fc-mediated effector functions compared to chronic HIV progressor subjects (Ackerman et al., 2016). Future studies consisting of larger cohorts of serodiscordant couples, excluding viremic controllers, would be useful to validate these findings. Nonetheless, these results provide preliminary evidence to suggest a role for Fc-mediated

☆ Commentary to: Ruiz et al. "Evaluation of different parameters of humoral and cellular immune responses in HIV serodiscordant heterosexual couples: humoral response potentially implicated in modulating transmission rates."

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humoral immunity in reducing HIV heterosexual transmission rates. Their work also highlights the need to understand the role of IgA and its potential immunomodulatory role of Fc-mediated effector responses, virus control and transmission rates.

Competing interests

The authors have no competing interests.

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References

Ackerman, M.E., Mikhailova, A., Brown, E.P., Dowell, K.G., Walker, B.D., Bailey-Kellogg, C., Suscovich, T.J., Alter, G., 2016. Polyfunctional HIV-specific antibody responses are associated with spontaneous HIV control. PLoS Pathog. 12, e1005315.

Chung, A.W., Kumar, M.P., Arnold, K.B., Yu, W.H., Schoen, M.K., Dunphy, L.J., Suscovich, T.J., Frahm, N., Linde, C., Mahan, A.E., et al., 2015. Dissecting polyclonal vaccine-induced humoral immunity against HIV using systems serology. Cell 163, 988–998.

Haynes, B.F., Gilbert, P.B., McElrath, M.J., Zolla-Pazner, S., Tomaras, G.D., Alam, S.M., Evans, D.T., Montefiori, D.C., Karnasuta, C., Sutthent, R., et al., 2012. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N. Engl. J. Med. 366, 1275–1286.

Huang, Y., Paxton, W.A., Wolinsky, S.M., Neumann, A.U., Zhang, L., He, T., Kang, S., Ceradini, D., Jin, Z., Yazdanbakhsh, K., et al., 1996. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. Nat. Med. 2, 1240–1243.

Lederman, M.M., Alter, G., Daskalakis, D.C., Rodriguez, B., Sieg, S.F., Hardy, G., Cho, M., Anthony, D., Harding, C., Weinberg, A., et al., 2010. Determinants of protection among HIV-exposed seronegative persons: an overview. J. Infect. Dis. 202 (Suppl. 3), S333–338.

Nag, P., Kim, J., Sapiega, V., Landay, A.L., Bremer, J.W., Mestecky, J., Reichelderfer, P., Kovacs, A., Cohn, J., Weiser, B., et al., 2004. Women with cervicovaginal antibody-dependent cell-mediated cytotoxicity have lower genital HIV-1 RNA loads. J. Infect. Dis. 190, 1970–1978.

Parsons, M.S., Madhavi, V., Ana-Sosa-Batiz, F., Center, R.J., Wilson, K.M., Bunupuradah, T., Ruxrungtham, K., Kent, S.J., 2016. Brief report: seminal plasma anti-HIV antibodies trigger antibody-dependent cellular cytotoxicity: implications for HIV transmission. J. Acquir. Immune Defic. Syndr. 71, 17–23.

Quinn, T.C., Wawer, M.J., Sewankambo, N., Serwadda, D., Li, C., Wabwire-Mangen, F., Meehan, M.O., Lutalo, T., Gray, R.H., 2000. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai project study group. N. Engl. J. Med. 342, 921–929.

Ruiz, M.J., Salido, J., Abusamra, L., Ghiglione, Y., Cevallos, C., Damilano, G., Rodriguez, A.M., Trifone, C., Laufer, N., Giavedoni, L.D., et al., 2017. Evaluation of different parameters of humoral and cellular immune responses in HIV serodiscordant heterosexual couples: humoral response potentially implicated in modulating transmission rates. EBioMedicine. https://doi.org/10.1016/j.ebiom.2017.11.001.

Tomaras, G.D., Ferrari, G., Shen, X., Alam, S.M., Liao, H.X., Pollara, J., Bonsignori, M., Moody, M.A., Fong, Y., Chen, X., et al., 2013. Vaccine-induced plasma IgA specific for the C1 region of the HIV-1 envelope blocks binding and effector function of IgG. Proceedings of the National Academy of Sciences of the United States of America.