Immunoglobulin Genes and Immunity to Herpes Simplex Virus Type 1

To the Editor—In their excellent commentary on the identification of the first common cold sore susceptibility gene, Cunningham and Booth [1] state, “There is little doubt that many more host cell genes controlling HSV [herpes simplex virus] infection… will be discovered as the techniques for discovery of rare gene variants improve.” I would like to suggest some very common variants of immunoglobulin γ genes [2] as candidates, a strong rationale for their involvement in HSV type 1 (HSV-1) disease, and why they have not been detected by the genomewide association studies (GWAS).

Herpes simplex virus type 1 has evolved strategies for decreasing the efficacy of the host immune response and interfering with viral clearance. Herpes simplex virus type 1 glycoproteins gE and gI, expressed as heterodimeric receptor on viral and infected cell surfaces, have functional properties of the Fc gamma receptor (FcγR) that enables the virus to evade immunosurveillance by avoiding the effector consequences of antibody binding, such as antibody-dependent cellular cytotoxicity, complement-dependent neutralization, and phagocytosis. Several studies have shown that HSV-1-encoded FcγR binds anti-HSV-1 antibodies by bipolar bridging: the Fab part of the antibody molecule (paratope) binds to its antigenic target (epitope) on the virus, whereas the Fcγ part of the antibody binds to the FcγR-like binding site on the viral protein, thus offering survival advantage to the virus by sterically hindering the access of FcγR-expressing effector cells (eg, natural killer cells) to the HSV-1–infected cells [3–5]. Interestingly, the HSV-1–encoded FcγR discriminates between 2 immunoglobulin GM alleles/haplotypes: the viral FcγR binds much more strongly to the immunoglobulin G1 (IgG1) molecule carrying the GM 1,17 alleles than the 1 carrying the GM 3 allele, which differs by 3 amino acid residues at positions 214, 356, and 358 of the γ1 chain [6]. Increased affinity of HSV-1 FcγR to the IgG1 molecules expressing the GM 1,17 alleles implies that subjects possessing these alleles are more likely to have their Fc domains scavenged, resulting in decreased immunocompetence to eliminate the virus, and they would consequently be at higher risk of developing HSV-1–induced/spurred diseases.

These genes are unlikely to be detected by GWAS of HSV-1 infection because none of the variants that characterize the 18 testable GM specificities are included in the current genotyping platforms. Furthermore, because these genes were not typed in the HapMap project, they cannot even be tagged (through linkage disequilibrium) by any variants that are included in the genotyping platforms. This underscores the necessity of a candidate gene approach to investigate the role played by the GM gene complex in the immunobiology of HSV-1 infection.

Notes

Financial support. This work was supported in part by the National Institutes of Health (grant AI068618) and the Department of Defense (grants W81XWH-08-1-0373 and W81XWH-10-1-0479).

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to
the content of the manuscript have been disclosed.

Janardan P. Pandey
Department of Microbiology and Immunology,
Medical University of South Carolina, Charleston

References


Received 28 October 2011; accepted 21 February 2012; electronically published 25 April 2012. Correspondence: Janardan P. Pandey, PhD, Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, SC 29425 (pandeyj@musc.edu).

The Journal of Infectious Diseases 2012;206:143–4
© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/infdis/jis317