The Role of Race and Gender in T Cell Responses in Children Perinatally Infected with HIV-1

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(See the article by Sharp et al., on pages 1772–80.)

Understanding the immunologic mechanisms that can control the progression of HIV disease is paramount for the development of vaccines or of new strategies for immunotherapy. Whether infection occurs perinatally, sexually, or parenterally, disease ultimately develops in all but a very few individuals, although the time to disease is quite variable. This tremendous variability in disease progression may be influenced by age at the time of infection, viral load, race, and host genetic factors, most notably HLA class and CCR5 [1–8]; however, the influence of gender is more controversial. Additionally, there is evidence that these same factors may also protect against infection in some individuals and in certain settings.

Few studies have assessed the role of race, gender, and host genetic factors in children or adolescents, especially those infected perinatally. However, this population can offer unique clues for our understanding of the interrelationships between host genetic factors and changes in the immune and endocrine systems that occur from the time of transmission through puberty. This is especially important at present, because, worldwide, adolescent girls are becoming infected at an alarming rate and are having babies who are themselves infected. In this issue of the Journal of Infectious Diseases, Sharp et al. [9] have evaluated the influence of race and gender on HIV-1–specific immune responses in a small case-control study of 41 perinatally infected African American and Hispanic children. Patients who were chosen for the study received their care at the same HIV center and were from the same community. They were matched for race, gender, HIV-1 RNA load, age, and CD4+ cell count. HIV-1–specific T cell responses of cryopreserved cells were measured by use of an interleukin (IL)–7 and IL-15–amplified enzyme-linked immunospot (ELISPOT) assay with synthetic peptides of the clade B Gag, Nef, and Tat consensus sequences; HLA typing was also performed.

Sharp et al. [9] made a number of intriguing observations. First, of the 18 matched pairs, total HIV-1–specific responses (the sum of the number of spot-forming cells for Gag, Nef, and Tat peptides) were higher in African American than in Hispanic children. This was driven primarily by the Gag response. Second, African American girls at or near puberty showed the highest HIV-1–specific T cell responses. Finally, there was a trend toward higher Gag responses in children with A*66 and B*58 haplotypes. Trends were also noted for responses related to CD4+ cell count, viral load, and age, although these did not persist in multivariate analyses. Importantly, although African American girls at or near puberty had the highest T cell responses, these responses were not correlated with viral load. In fact, some high responses were even noted when the viral load was >100,000 copies/mL. These findings suggest that race, as well as HLA polymorphisms, may play an important role in HIV-1–specific T cell responses and that sex hormones related to gender may modulate these effects.

However, despite these intriguing findings, there are several limitations in Sharp et al.’s study [9]. First, the sample size was small and highly selected, with a potential bias toward healthier children, given that the majority had high CD4+ cell counts. For instance, 17 of 41 children were <10 years old, and only 1 had a CD4+ count <200 cells/mm³. Second, clinical information for these children was missing, including timing of infection, treatment during the first year of life, and other parameters, such as nadir CD4+ cell count or the development of opportunistic infections. Although children were matched by age, CD4+ cell count, gender, and viral load, few children had low CD4+ cell counts, including those who
were adolescents, which suggests that they may have been receiving some form of antiretroviral therapy or highly active antiretroviral therapy (HAART). However, no HIV-1–specific treatment information is given, and children were not matched by treatment history. This would be especially important if an untreated child was matched with one who had received prolonged HAART or if a long-term nonprogressor was matched with a child who had a low nadir CD4+ cell count, but who, after HAART, had higher cell counts. HAART is recommended for all children <1 year old but not for all children >1 year old [7]. HAART has a significant impact on immune response and function. Children who are partial viral load responders with at least a 0.75-log10 reduction in HIV-1 RNA may have as good an immune response as those who have complete viral suppression [10]. Nevertheless, despite these limitations, this study still highlights a possible impact of race and gender on immune responses in children.

T cell responses are critically important for control of many viral infections. The secretion of interferon gamma (IFN-γ)—a cytokine with potent antiviral effects and a broad range of immunomodulatory functions—is frequently used to evaluate T cell function in HIV infection [11, 12]. The ELISPOT methodology used in Sharp et al.’s study [9] provides the frequency of T cells that recognize HIV-1–specific peptides. The analysis is greatly simplified by stimulating lymphocytes with peptide libraries, which theoretically allows for the detection of all possible T cell responses for a given antigen, irrespective of HLA restriction. Because viral antigens are provided in peptide format, the system is minimally subject to antigen processing for a broad detection of T cells that carry a cognate T cell receptor.

One of the most intriguing observations is that African American girls at or near puberty had the highest responses, even with high viral loads, which suggests that race-associated differences may be modulated by hormonal changes. To date, there have been no studies that have addressed this issue, although a number of studies have indicated that CD4+ and CD8+ cell counts are influenced by gender [3, 13], with females having higher CD4+ cell counts. Also, CD4+ and CD8+ cells have hormonal receptors that may modulate immune responses [14]. A less extensively studied factor is the racial background of infected individuals [3, 15]. Some reports have indicated different progression rates to AIDS among African Americans and Hispanics than in other races [3]. In addition, certain types—such as B*58 and HLA B*57—have been associated with protection against disease progression [4, 5, 16–18]. A noticeable percentage of African American girls in Sharp et al.’s study [9] carried the B*58 type and displayed potent IFN-γ responses to HIV-1 peptides, despite relatively high viral loads.

So, what do IFN-γ numbers of spot-forming cells mean? Studies have shown that there is an association between cytotoxic T cell activity, age, viral load, CD4+ cell count, treatment, and age at the time of treatment, although results have varied [19–25]. Low frequencies (<100 sfc/10^6 peripheral blood mononuclear cells [PBMCs]) have been observed in neonates treated early in life with HAART who maintain an undetectable HIV-1 load (<50 copies/mL) and in individuals with very high viral loads and low CD4+ cell counts [22, 23]. In Sharp et al.’s study [9], there were several children with very low T cell responses who had either high CD4+ cell counts and undetectable virus or low CD4+ cell counts and high viral loads. However, high T cell responses (>1000 sfc/10^6 PBMCs) were noted in 40% of children >5 years old. These results are especially intriguing in light of the fact that the 17 children >10 years old were born before the availability of HAART. Although we do not have any information about the total cohort of patients at the site of enrollment and their outcomes, these data suggest a potential survival advantage of the studied children in view of their relatively high CD4+ cell counts and intact immune systems. Additionally, 10 of 17 children >10 years old carried the HLA B*58 or B*57 allele, although several had high viral loads; both types are known to be associated with delayed progression. Because HLA B*58 is only found in ~10%–20% of the population, the high prevalence in Sharp et al.’s study [9] supports a survival advantage for these children [4, 5]. In contrast, those children who were <10 years old may have received HAART during the first year of life; thus, the survival advantage that may be related to HLA type would have been abrogated. This supposition is supported by the fact that only 2 of 24 children <10 years old carried this HLA type. These findings suggest that age, race, and/or associated HLA type may be important factors in immune responsiveness. However, such gender effects need further study.

Several important questions remain. What is the clinical implication of the number of spot-forming cells (IFN-γ–secreting cells), given that those with both high and low viral loads had >1000 sfc/10^6 PBMCs? What is the relative contribution of various T cells, including CD4+ and CD8+, NK, and Treg cells, in modulating these responses? Finally, how do race, gender, age, and age-related hormonal changes affect these responses? Future studies will need to address these issues.

There are multiple potential implications of the impact of age, gender, and race for vaccine development and public health planning. First, the results suggest that studies of both therapeutic and preventive vaccines should be evaluated in all ages from birth through adolescence. Adolescents may be a particularly important age group to evaluate, given that African American girls at or near puberty had such high IFN-γ responses. Longitudinal evaluations of children as they enter and pass through puberty can assist our understanding. Hormonal effects, including age-related effects—such as adolescence and menopause—and the impact of hormonal
contraception on immune responses are also important to evaluate. Furthermore, vaccine studies need to consider the effects of race, gender, and HLA types on the observed immunologic responses. Similarly, if there were differences in innate and/or adaptive immunity by race or gender, would this affect protective immunity against HIV by vaccination? Thus, the further study of these potential modulating factors will be essential. In summary, emerging evidence, including the results from Sharp et al.’s study [9], suggest that race, gender, and genetic factors should be routinely considered in any analysis of the host factors influencing HIV infections in humans.

References