Preview

HIV-1 protection: Antibodies move in for the kill

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Identifying the immune responses needed for protection against HIV is critical to finding an effective vaccine. In this issue of *Cell Reports Medicine*, Thomas and colleagues[1] show that antibodies that kill infected cells correlate with infant HIV infection outcomes more so than antibodies that block viral entry.

Defining the basis for protective immunity to HIV-1 has remained elusive, despite decades of intensive study. During that time, the pendulum has shifted multiple times, from betting on T cell responses for protection to, in recent years, focusing more heavily on neutralizing antibodies (nAbs). The rationale for the latter rests on the fact that nAbs effectively block virus entry in cell culture systems, and some of the most potent nAbs do so at very low concentrations. Moreover, hundreds, perhaps thousands, of studies have shown that nAbs also very effectively prevent infection in animal models. However, disappointingly, this protection has not extended to humans passively infused with an HIV-specific broadly neutralizing antibody, largely reflecting the considerable variation in susceptibility of naturally occurring HIV variants to a given neutralizing antibody, something that is not tested in animal studies.[2] The study by Thomas et al.[1] in this issue of *Cell Reports Medicine* provides some insights bearing directly on protection in exposed humans, as they show that antibodies that mediate antibody-dependent cellular cytotoxicity (ADCC) have more of an impact on HIV acquisition risk than neutralizing activity in infants exposed to HIV during breastfeeding. Passively transferred, ADCC-mediating antibodies were also associated with a decrease in morbidity in infants who acquire HIV, whereas neutralizing responses were not.

Non-neutralizing antibodies, specifically antibodies that function by eliminating infected cells through ADCC have often been dismissed in the HIV vaccine research world. Yet, there is increasing evidence that these types of antibodies could contribute to both protection from HIV infection and improved outcomes when infection occurs.[3,4] The setting of mother-to-child HIV transmission (MTCT) lends itself to studies of protective antibody immunity because infants of mothers with HIV are exposed to virus in the presence of passively transferred, HIV-specific antibodies. Thomas et al.[1] used this setting to examine both the contribution of neutralization and ADCC mediated by passively transferred antibodies to infant infection risk. The cohort studied included 16 transmitting and 26 non-transmitting mother-infant pairs from the Breastfeeding, Antiretroviral, and Nutrition (BAN) study. The study by Thomas et al.[1] was unique in that it examined both ADCC and neutralization of autologous virus, the virus present in the individual mother of each infant—a notable difference from previous studies, which typically evaluated neutralization against heterologous HIV strains or antigens. They also used an infected cell target to measure ADCC, which provides a more relevant measure of activity. Thomas et al.[1] show that HIV-exposed, uninfected (HEU) infants mediated higher ADCC against maternal Env variants than HIV-exposed, infected (HEI) infants. This result aligns with another recent study in which there was a trend observed between passively acquired ADCC and reduced MTCT risk, together supporting a protective role of ADCC-mediating antibodies present at the time of exposure.[4]

While the ideal outcome of antibody-based protection is preventing infection, antibodies can also be beneficial if they blunt infection and/or limit disease if infection does occur. Thomas et al.[1] also demonstrated that ADCC, but not the combined measure of ADCC and neutralization, was inversely correlated with time to serious adverse events during 1 year of follow-up after birth in HEI infants. This is consistent with prior studies of passive antibodies in two cohort studies of infants exposed through breastfeeding, both of which demonstrated that ADCC mediated by passive HIV antibodies at the time of birth correlated with improved clinical outcome in infants who acquire HIV near the time of or after birth.[5,6] Similarly, neutralization was not associated with infant clinical outcome.[5] The finding of very similar results across multiple cohorts with different features provides compelling evidence for a role of ADCC antibodies present at the time of acquisition in limiting disease. These findings suggest a need for studies to understand the basis for this effect. Given that ADCC antibodies kill infected cells, one hypothesis is that their presence very early in infection leads to a reduction in the viral reservoir. This would also affect viral levels, and one prior study demonstrated an association between passive ADCC and viral load, but the sample size was small, and thus, more work is needed.[5] The challenge with testing this hypothesis will be identifying cohorts and samples from before the very successful implementation of prevention of mother-to-child transmission (PMTCT) efforts, which would confound such studies.

The findings of Thomas et al.[1] are important because they give insight into the basis of HIV antibody protection in humans, which remains challenging to study absent an effective vaccine. With this report, there are now multiple studies that reach nearly identical results, supporting a role for passively acquired ADCC in protecting infants from infection and disease. Importantly, they do so with four different assay methods in three different cohorts infected

with diverse HIV subtypes, measuring the response against maternal autologous virus as done in this study and measuring the response against heterologous variants in prior studies. In addition, the present study's findings align with results from one investigating the one partially protective vaccine, where ADCC antibody responses were implicated in the observed protection.[7] Thus, human studies continue to point to ADCC antibodies as the most likely path to protection, suggesting that vaccine concepts should place more emphasis on these types of antibodies, which Thomas et al.[1] report are not directly correlated with neutralizing antibody responses. Indeed, the same framework appears to be emerging with SARS-CoV-2, with early emphasis on nAb responses in vaccines but a greater and greater appreciation of the lack of breadth of these antibodies against a mutating virus.[8] For SARS-CoV-2, the data are also increasingly pointing to a role for ADCC antibodies, supporting the need to develop approaches based on ADCC antibodies to combat two of the most globally important pathogens.[9,10]

DECLARATION OF INTERESTS

The authors declare no competing interests.

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