

Beyond Neutralization: Antibody-Mediated Cytotoxicity In HIV Control

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As HIV continues to spread despite improved prevention strategies, the only possibility to end the loss of lives caused by the epidemic is a vaccine that either prevents the infection or controls the progressive loss of immune cells that leads eventually to AIDS. The design of either of those vaccines requires a better knowledge of the natural mechanisms that block the virus at the entry site or its replication. Non-human primate studies have demonstrated the importance of neutralizing antibodies—that is antibodies that can recognize and bind to the virus and inhibit its function—in HIV prevention. Aside from neutralization, an important role is covered by antibody-dependent cellular cytotoxicity (ADCC), an immune mechanism through which an effector cell actively lyses an infected target cell whose membrane-surface antigens have been recognized by the antibody.

In an article published in April on *Cell Host & Microbe*, Caitlin Milligan and coworkers from Julie Overbaugh's group in the Division of Human Biology at Fred Hutch addressed the question of whether ADCC is involved in reducing transmission or mortality rate in a cohort of neonates born from HIV+ mothers. Antibodies are passively transferred from mothers to their infants during pregnancy and thus infants born to HIV-positive mothers have HIV-specific antibodies at birth. This setting mimics that of a vaccine whereby HIV-specific antibodies are present at the time of virus exposure. The researchers compared the ADCC activity in a group of neonates that acquired the disease to one that did not. "We did observe that infants who remained uninfected had higher ADCC than those who became infected, however the relationship was not significant. This result does hint at a protective effect of ADCC antibodies in infection, but we may have lacked the power to detect a significant difference between the groups because of the small number of infected infants. Thus, larger studies will have to be conducted to determine whether or not pre-existing ADCC activity protects from infection", explains Ms. Milligan.

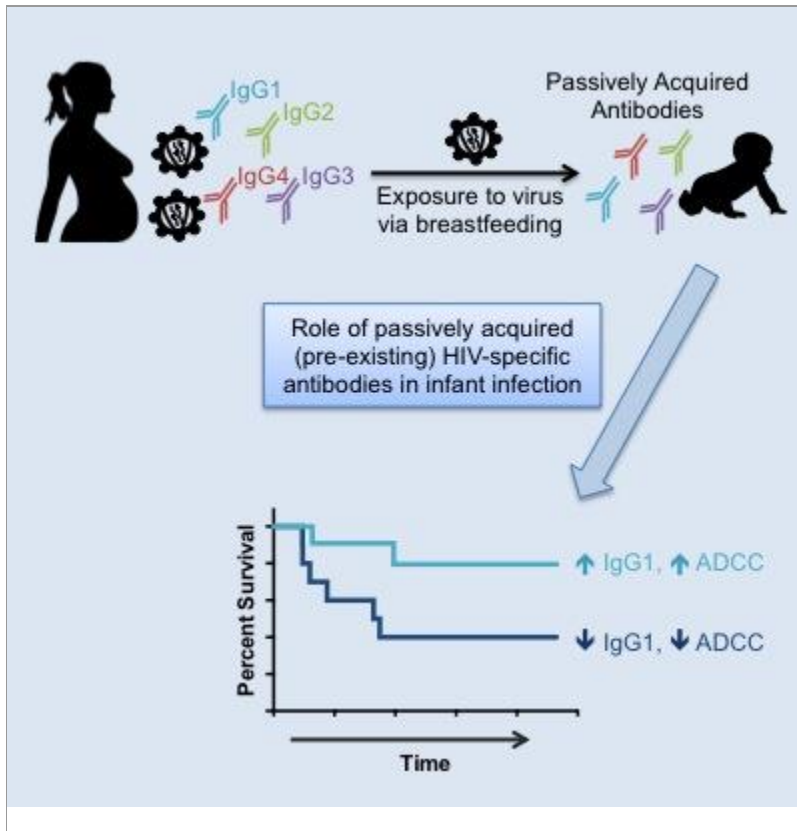
When the researchers looked more closely at infected infants, they saw a higher survival rate in those with higher ADCC. Thus, passively acquired ADCC is important in controlling disease progression. Surprisingly, they did not observe the same pattern in maternal ADCC. "It was definitely surprising that we observed an association between infected infant passively acquired ADCC activity

and survival, but the same association was not seen with maternal antibodies. Given that the infant ADCC activity was passively acquired from the mother we were expecting to see the same result with maternal samples. We have not yet clarified why the results were different but the difference may be due to timing of maternal antibody sampling or a difference in passive transfer of antibodies to the infant", continues Ms. Milligan, and then emphasizes another aspect of the finding: "This result also has larger implications for the mother-to-child transmission field as maternal antibodies are often used as a surrogate for the infant passively-acquired antibodies in studies - our result suggests that maternal antibodies may not always be an appropriate surrogate measure for infant passively acquired responses for some antibody functions such as ADCC."

Furthermore, based on results from previous neutralizing antibody studies in macaques, the researchers hypothesized that a higher passive ADCC activity would mirror the de novo activity developed by infants after infection. Instead, their results showed no correlation between ADCC from transferred maternal antibodies and the de novo ADCC. The level of ADCC immediately after birth cannot be considered as an indication of de novo responses.

In summary, said Ms. Milligan, "Overall, the results from our study suggest that pre-existing ADCC antibody activity may provide a therapeutic effect in individuals who become infected. And thus, eliciting ADCC-mediating antibodies by a therapeutic vaccine could be a desirable goal."

[Milligan C, Richardson BA, John-Stewart G, Nduati R, Overbaugh J.](#) 2015. Passively Acquired Antibody-Dependent Cellular Cytotoxicity (ADCC) Activity in HIV-Infected Infants Is Associated with Reduced Mortality. *Cell Host Microbe*, 17(4), 500-6.



"Image provided by Caitlin Milligan"

Schematic representation of the role of maternal antibody ADCC in infant born from HIV+ mothers that acquired the infection.