Animal model replicates human immune response against HIV, could revolutionize HIV vaccine research

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One of the challenges to HIV vaccine development has been the lack of an animal model that accurately reflects the human immune response to the virus and how the virus evolves to evade that response. In the July 18 issue of *Science Translational Medicine*, researchers from the Ragon Institute of Massachusetts General Hospital (MGH), MIT and Harvard report that a model created by transplanting elements of the human immune system into an immunodeficient mouse addresses these key issues and has the potential to reduce significantly the time and costs required to test candidate vaccines.

"Our study showed not only that these humanized mice mount human immune responses against HIV but also that the ability of HIV to evade these responses by mutating viral proteins targeted by CD8 'killer' T cells is accurately reflected in these mice," says Todd Allen, PhD, senior author of the report. "For the first time we have an animal model that accurately reproduces critical host-pathogen interactions, a model that will help facilitate the development an effective vaccine for HIV." Recent studies by Allen's team and others have revealed that immune control of HIV is significantly limited by the ability of the virus to evade immune responses by rapidly mutating.

The traditional animal model for HIV research is the rhesus monkey, which can be infected with the related simian immunodeficiency virus (SIV). But differences in viral sequences between SIV and HIV, along

with differences between the human and monkey immune systems, limit the ability of the SIV model to replicate directly key interactions between HIV and the human immune system. Development of an effective HIV vaccine will require a greater understanding of how human immune responses succeed or fail to control HIV.

The current study was designed to test the humanized BLT mouse, a model created by transplanting human bone marrow stem cells, along with other human tissue, into mice lacking a functioning immune system. Andrew Tager, MD, a co-author of the report and director of the MGH Humanized Mouse Program, explains, "Multiple researchers have contributed to dramatic improvements in the ability of humanized mice to model human diseases. Earlier studies with BLT mice performed at the University of Texas Southwestern Medical Center, the MGH and elsewhere have demonstrated that this particular humanized mouse model reproduces many aspects of the human immune response."

Timothy Dudek, PhD, of the Ragon Institute, lead author of the current study, adds, "Unlike normal mice, these humanized mice can be infected with HIV. But there has been little evidence regarding whether they reproduce the interaction between HIV and the human immune system, particularly the development of specific immune responses that exert control over HIV by targeting critical regions of the virus."

Tager's team at the MGH Center for Immunology and Inflammatory Diseases created groups of humanized BLT mice using cells and tissues from human donors with different alleles, or versions, of the immune system's HLA molecules, which flag infected cells for destruction by CD8 T cells. Particular HLA alleles, such as HLA-B57, are more common in individuals naturally able to control HIV, and some of the mice generated by Tager's group expressed this important protective allele.

Six weeks after the mice had been infected with HIV, the researchers found that the virus was rapidly evolving in regions known to be targeted by CD8 T cells. Their observation indicated that not only were the humanized mouse immune systems responding to HIV but also that the virus was mutating to avoid those responses in a manner similar to what is seen in humans. In mice expressing the protective HLA-B57 allele, just as in human patients who control viral levels, CD8 responses were directed against an essential region of the virus, preventing viral mutation and allowing the animals to more effectively contain HIV.

"We now know that these mice appear to replicate the specificity of the human cellular response to HIV and that the virus is attempting to evade these responses just as it does in humans," says Allen, an associate professor of Medicine at Harvard Medical School. "We are currently studying whether we can induce human HIV-specific immune responses in these animals by vaccination, which would provide a rapid, cost-effective model to test the ability of different vaccine approaches to control or even block HIV infection. If we can do this, we'll have a very powerful new tool to accelerate HIV vaccine development, one that also may be useful against other pathogens."

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