A reductionist approach to HIV research

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A major obstacle to HIV research is the virus's exquisite specialisation for its human host - meaning that scientists' traditional tools, like the humble lab mouse, can deliver only limited information. Now, a team of researchers writing in BioMed Central's open access *Journal of Biology* have made an ingenious assault on this problem by creating a mouse that has key features of HIV infection without being infected with HIV.

George Kassiotis, from the Division of Immunoregulation at MRC National Institute for Medical Research, worked with a team of researchers to create mice whose CD4+ T cells, the cells eliminated by HIV infection, commit a kind of suicide upon activation. He said, "Although these mice do not fully reproduce every aspect of human HIV-associated immune dysfunction, they do approximate two key immune alterations - CD4+ T cell immune deficiency and generalized immune activation. Further definition of the precise balance between CD4+ T cell killing and immune activation and deficiency will be vital to our understanding of the pathogenesis of immune deficiency virus infection."

The CD4+ T cells in the researchers' mice were engineered to express a toxin, diphtheria toxin A fragment, upon activation. This genetic self-destruct system causes the death of the cell within 48 hours. The resultant loss of activated immune cells caused the mice to exhibit symptoms with some similarities to those of immunodeficiency virus infection. There are clear differences between the mouse and a human infected with HIV, however, such as the fact that the ongoing depletion of nearly all activated CD4+ T cells in the mice does not result in the

progressive erosion of naďve and memory CD4+ T cells seen during HIV infection.

None-the-less, insights gained from this reductionist model can only help our understanding of human disease. In a commentary on the work in the same issue of Journal of Biology, experts on T cells and HIV at the US National Institutes of Health comment that the mouse will be as useful for its differences from human infection as it will for its similarities.

More information: Generalized immune activation as a direct result of activated CD4+ T cell killing, Rute Marques, Adam Williams, Urszula Eksmond, Andy Wullaert, Nigel Killeen, Manolis Pasparakis, Dimitris Kioussis and George Kassioti, *Journal of Biology* 2009, 8:93; doi:10.1186/jbiol194

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