A Comparison of Two Studies

Pigtail macaques and HIV/AIDS research

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The following two studies are a sample of research produced in the quest for a cure of human immunodeficiency virus (HIV). Researchers in both cases have been determining which cells become infected and how the progression of disease leads to the development of acquired immunodeficiency disorder or AIDS. Both state that results obtained from in-vitro, or literally 'in glass', studies have not been consistent with in-vivo results. In-vivo means that it happens within a live body. It does not necessarily mean that it is a human body and in HIV research pig-tail macaques (PTM) are frequently used as a model for the disease.

Comparing the two studies, nineteen years apart, allows us to see how little progress has been made in research since the early days when HIV was first discovered. The more recent of these two reports was published in 2012. In this study seventeen macaque monkeys were used to follow the progression of simian immunodeficiency virus (SIV). SIV occurs in nonhuman primates and is said to have a similar pathway to HIV in humans, even though humans do not contract it.

The earlier study was published in 1993 drawing on literature from the mid-eighties (shortly after AIDS was discovered). Researchers used genetic material which was isolated from tissue taken from human patients who were infected with HIV.

Both studies described the presence and action of Nef. This is the negative regulatory factor and it is one of many proteins present in primate lentiviruses (those responsible for HIV-1, HIV-2 and SIV).

Nef affects lymphocytes (a type of white blood cell responsible for fighting infection) by destroying or down-regulating the molecules CD3 and CD4 on the cell surface. This process damages the host's immune response to infection and ensures the success of the disease.

Researchers of the 2012 report state that there have been few studies to address CD3 and CD4 down-regulation in vivo. Two to be exact, both of which were conducted in 2010, although they state that there is "a body of evidence… that HIV preferentially infects particular subsets of T cells in vitro and in vivo." they have omitted to mention the 1993 research.

Title (1):

Characterisation of simian immunodeficiency virus-infected cells in pigtail macaques

Wendy R. Winnall, Amy Sexton, Sheilajen Alcantara, Sarah Roath, Robert De Rose, Stephen J. Kent 2012

Dept of Microbiology and Immunology, University of Melbourne, Royal Parade, Parkville 3010 VIC, Australia.

It was postulated that, "Defining which cells become infected with SIV in-vivo should assist in unravelling the pathogenesis of HIV/SIV infection" (p 11).

Method

This study used seventeen pigtail macaques who were infected with an SIVmac virus. Intracellular SIV was studied by flow cytometry in serial blood samples and lymph node samples during acute infection. After two weeks a high proportion of lymphocytes were negative for surface CD3 and CD4.

Discussion

The high proportion of SIV-infected lymphocytes that are $CD3^-$ and $CD4^-$ has important implications for the in vivo study of pathogenesis of SIV/HIV infections

"The apparent loss of surface CD3 and CD4 from SIV-infected cells indicates that infection has led to down regulation of these proteins from the cell surface, however we have not formally demonstrated down regulation in vivo."

Title (2):

CD4 down-regulation by nef alleles isolated from human immunodeficiency virus type 1-infected individuals.

Roberto Mariani, Jacek Skowronski

Proc. Natl. Acad. Sci. USA, Vol 90 pp5549-5553 June 1993 Medical Sciences

Method

In this research the HIV-1 virus Nef gene was isolated. It was taken from the peripheral blood leucocytes of HIV-1 infected humans.

"We show that CD4 down regulation is a frequent property of primary HIV-1 Nef alleles…Our observations strongly suggest that CD4 down regulation reflects a conserved function of Nef, which is selected in-vivo in HIV-1 infection. Methodology here provides quantitative assays to establish whether alterations in Nef correlate with the dynamics of disease progression in human AIDS."(p5549)

Discussion:

"It is well established that disease progression can vary greatly among HIV infected people. Results in in-vivo experiments in rhesus monkeys indicated that nef is essential for SIV pathogenesis and a deficiency of Nef can protect infected animals…CD4 down-regulation reflects a conserved, selected, in vivo function of Nef". (p5553)

Comments

- The 2012 study is repetitive and does not acknowledge previous research. Nineteen years after the 1993 report which researched HIV in humans by using the blood and lymph tissue of infected patients, researchers from Melbourne University conducted a similar study. They used a different virus to HIV and a different species to humans and unsurprisingly, they failed to demonstrate down-regulation of CD3 and CD4 in vivo.

- Researchers of the 2012 study stated that only two publications described in vivo down-regulation of CD4 and CD3, although the 1993 publication described this process in humans.
- Researchers in the recent study say that using macaques infected with SIV "Permits knowledge of the timing of infection and the pigtail macaque exhibits uniform and rapid progression to disease…**allows a more detailed analysis of the in-vivo infection than study of HIV infected individuals"**. Follow up of the reference cited for this statement showed that yes, PTMs get sick quicker than Rhesus monkeys but there was no comparison to the study of HIV infected humans and monkeys.
- The 2012 report is written in technical jargon and it is unlikely that an animal ethics committee would be able to evaluate whether it is in keeping with the original proposal, if the final report was even evaluated.

Humans and monkeys are unique living systems. They still share some genes and processes conserved through evolutionary pathways, hence the sameness. Their differences, however, are created by changed genes and processes and alternate combinations and regulation of those which were conserved. If researchers study conserved functions at a cellular level they will see only the sameness and not notice that the context has changed, nor will they gain information on the complex interaction within the whole organism.

HIV researchers have turned from studying an illness in humans to studying a different illness in monkeys. They say it 'should ultimately lead to more refined strategies to treat or prevent infection' and 'should assist in unravelling the pathogenesis of human immunodeficiency virus infection'. After nineteen years they are no further ahead and since the discovery of HIV, approximately 100 vaccines have been shown to be effective in animal models, but not one has worked in humans. That's hardly surprising, given that they're studying a different disease in a different animal. And with a population of over thirty four million HIV/AIDS sufferers it begets the question: Why are we not studying HIV in humans instead of SIV in monkeys?

On a positive note, advances in the control and treatment of HIV/AIDS have arisen from population studies and preventative programmes.

References:

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