HIV vaccine failure probably caused by virus used, says new research

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The recent failure of an HIV vaccine was probably caused by the immune system reacting to the virus 'shell' used to transmit the therapy around the body, according to research published today in the *Proceedings of the National Academy of Sciences*.

The trial, called 'STEP', was halted in September 2007 because preliminary results suggested that people who had been given the vaccine were more likely to be infected with HIV than people who had been given a placebo.

The researchers behind today's study, from Imperial College London, King's College London and Royal Holloway, University of London, say their findings mean scientists may have to rethink other vaccines they are developing for diseases like HIV, tuberculosis and malaria, which are delivered in the same way, using the same virus 'shell'.

The vaccine used an adenovirus, which normally causes the common cold, to enable the vaccine therapy to travel around the body. Harmless HIV genes were then inserted into the virus. It was thought that this would help the immune system to learn to recognise and fight off HIV.

Today's study suggests that after receiving the trial vaccination, people who had previously built up immunity to the adenovirus had an influx of immune cells called CD4 T-cells homing in on their mucous membranes, as these cells prepared to fight off a new adenovirus infection. Mucous membranes are found in areas including the nose, mouth, vagina and gut.

HIV naturally infects CD4 T-cells, so this inadvertently provided HIV with an abundance of potential new homes at the sites where the virus would naturally enter the body during sexual intercourse, thereby increasing people's risk of infection.

The researchers say their findings are a warning for scientists developing adenovirus vaccines against other diseases, as the same effect occurs with other, perhaps all, adenovirus subtypes.

Adenovirus infection is common and there are 51 known human strains. Around half of all adults in the developed world and about 90 percent of individuals in sub-Saharan Africa, where HIV is most prevalent, have built up immunity to the subtype of adenovirus used in STEP.

Preliminary results of the vaccine trial showed that people who had previously been infected with the adenovirus used in the trial had a significantly higher risk of being infected with HIV following the vaccine compared to people who were given a placebo.

Dr Steven Patterson, who is the corresponding author of the study from the Division of Investigative Science at Imperial College London, said: "HIV is a huge threat to global health, with 2.7 million people becoming infected every year. We were all hopeful that the STEP trial would be a success, so when the researchers published their results and the trial was halted, we were all very surprised and disappointed. Scientists use adenoviruses in all sorts of vaccines and we did not expect this result. It was vital to discover what caused this increase in HIV infection risk so we could avoid the same problem in future trials.

"Our research suggests that the adenovirus-based HIV vaccine effectively instructs the cells that HIV infects to gather round exactly where HIV is likely to be introduced. This is clearly worrying for this kind of vaccine. Scientists are currently developing adenovirus-based

vaccines to protect people against TB and malaria as well as HIV, but they may have to rethink these vaccines if the effect we describe in our new paper is a problem for all of them," added Dr Patterson.

The researchers measured antibodies against adenovirus type 5 (Ad-5) and adenovirus type 11 (Ad-11) in 20 healthy volunteers to determine who had been infected. They then took samples of the volunteers' immune cells and grew them in the laboratory to see whether their CD4 cells would recognise Ad-5 and Ad-11. When the researchers added adenoviruses to the tissue cultures, they found that the viruses activated the CD4 cells and caused them to grow and replicate. They found that the newly generated CD4 cells had particular kinds of molecules on their surface that enabled them to migrate to mucosal membranes.

The results also showed that CD4 cells can recognise and react to another distinct subtype of adenovirus, regardless of which subtype the person was infected with initially. The authors say this means all subtypes of adenovirus are likely to be unsuitable in HIV vaccines.

Source: Imperial College London (news : web)