Scientists disarm HIV in step towards vaccine

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Researchers have found a way to prevent HIV from damaging the immune system, in a new lab-based study published in the journal Blood. The research, led by scientists at Imperial College London and Johns Hopkins University, could have important implications for the development of HIV vaccines.

HIV/AIDS is the third biggest cause of death in low income countries, killing around 1.8 million people a year worldwide. An estimated 2.6 million people became infected with HIV in 2009.

The research shows that HIV is unable to damage the immune system if cholesterol is removed from the virus's membrane. Usually, when a person becomes infected, the body's innate immune response provides an immediate defence. However, some researchers believe that HIV causes the innate immune system to overreact and that this weakens the immune system's next line of defence, known as the adaptive immune response.

In the new study, the researchers removed cholesterol from the membrane surrounding the virus and found that this stopped HIV from triggering the innate immune response. This led to a stronger adaptive response, orchestrated by immune cells called T cells. These results support the idea that HIV overstimulates the innate response and that this weakens the immune system.

Dr Adriano Boasso, first author of the study, from Imperial College

London, said: "HIV is very sneaky. It evades the host's defences by triggering overblown responses that damage the immune system. It's like revving your car in first gear for too long. Eventually the engine blows out.

"This may be one reason why developing a vaccine has proven so difficult. Most vaccines prime the adaptive response to recognise the invader, but it's hard for this to work if the virus triggers other mechanisms that weaken the adaptive response."

HIV takes its membrane from the cell that it infects. This membrane contains cholesterol, which helps to keep it fluid. The fluidity of the membrane enables the virus to interact with particular types of cell. Cholesterol in the cell membrane is not connected to cholesterol in the blood, which is a risk factor for heart disease but is not linked to HIV.

Normally, a subset of immune cells called plasmacytoid dendritic cells (pDCs) recognise HIV quickly and react by producing signalling molecules called interferons. These signals activate various processes which are initially helpful, but which damage the immune system if switched on for too long.

In collaboration with researchers at Johns Hopkins University, the University of Milan and Innsbruck University, Dr Boasso's group at Imperial have discovered that if cholesterol is removed from HIV's envelope, it can no longer activate pDCs. As a consequence, T cells, which orchestrate the adaptive response, can fight the virus more effectively.

The researchers removed cholesterol using varying concentrations of beta-cyclodextrin (bCD), a derivative of starch that binds cholesterol. Using high levels of bCD they produced a virus with a large hole in its envelope. This permeabilised virus was not infectious and could not

activate pDCs, but was still recognised by T cells. Dr Boasso and his colleagues are now looking to investigate whether this inactivated virus could be developed into a vaccine.

"It's like an army that has lost its weapons but still has flags, so another army can recognise it and attack it," he said.

More information: A. Boasso et al. 'Over-activation of plasmacytoid dendritic cell inhibits anti-viral T cell responses: a model for HIV immunopathogenesis.' *Blood*, 19 September 2011.

Provided by Imperial College London