human cytomegalovirus: Silent killer

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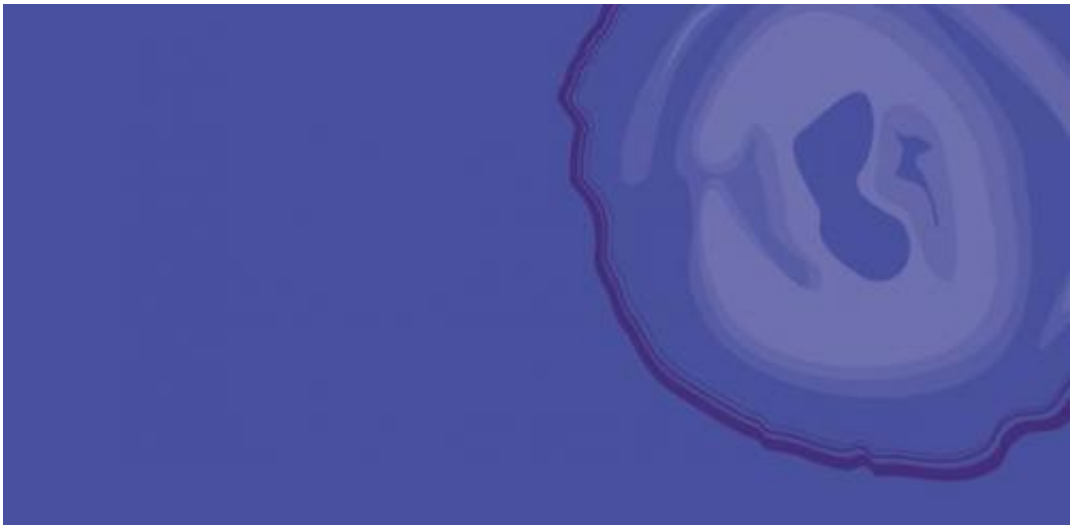

HCMV. Credit: The District

Many of us are infected with a virus we'll never clear. While we're healthy, it's nothing to worry about, but when our immune system is suppressed it could kill. To catch the herpes virus human cytomegalovirus (HCMV) you must be exposed to someone who has it. This isn't difficult: it is carried by around 65% of the population. Once in the body, HCMV persists for life owing to its clever ability to avoid our immune system and to go into hiding inside our cells in a latent state. Now, research is identifying changes in these cells that could lead to a new route to eradicating the virus.

"HCMV can be acquired very early in childhood, and the number of

people infected gradually rises throughout life," said Professor John Sinclair, a molecular virologist in the Department of Medicine. "The active virus can not only be passed from an infected mother to her child in breast milk but can easily be transferred from child to child in saliva – one child puts a toy in their mouth, then it's passed to another child who does the same, and the virus is passed on. It's also a sexually transmitted disease, so there's another increase in infections when people become sexually mature."

Once acquired, the virus goes into a latent state in the body. If it reactivates in healthy people, their immune responses prevent it from causing disease. But when the immune system is suppressed, active HCMV becomes dangerous. It is a major cause of illness and death in organ and bone marrow transplant patients, who are given drugs to deliberately suppress their immune system and prevent their body rejecting the transplant. With an increasing demand for transplants in the UK, HCMV is set to become a growing problem.

"If it's not treated well, or it develops resistance to antiviral drugs, HCMV can lead to pneumonitis – inflammation of the lung tissue – and, in the most extreme case, it replicates all over the body and the patient ends up with multiple organ failure," said Dr Mark Wills, a viral immunologist working alongside Sinclair in the Department of Medicine.

"Tissue from donors carrying the virus often has to be used for transplants because there are so few donors and so many people carrying the virus," said Sinclair. "By transplanting bone marrow, or an organ from someone with the infection, you're giving the patient the virus and you're immune-suppressing them. That's the worst of both worlds."

And HCMV is not a worry just for transplant patients. "HCMV is now the leading cause of infectious congenital disease – that is, disease

present at birth," said Sinclair. Women in early pregnancy who are newly infected with HCMV or whose HCMV reactivates are at real risk, and this can lead to disease in their unborn baby. HCMV also targets HIV-AIDS patients, where a progressive failure of the immune system allows this opportunistic infection to thrive.

There is no vaccine to prevent HCMV infection, and the antiviral drugs available to treat it have significant toxicity and only limited effectiveness. In addition to the problem of viral resistance, drugs can only target HCMV in its active state, which means the virus can never be fully eradicated. "You can suppress the virus down to a very low level, but you can never get rid of the latent reservoir with the currently available antiviral drugs," said Wills.

Sinclair and Wills, who have just received their fifth consecutive five-year grant from the Medical Research Council (MRC), have focused on understanding how the virus maintains this latent infection in specialised cells of the immune system and how the immune system is prevented from eliminating the virus from the body.

"The belief has always been that, in its latent state, HCMV was just sitting there doing nothing, waiting to reactivate," said Sinclair. "But we've started to identify major changes in latently infected cells, and we think these are targetable with novel drugs and immunotherapies.

"One change is in a transporter protein normally used by the cell to pump out things it needs to get rid of," he added. "If you put the chemotherapy drug vincristine on a healthy cell, the cell will pump it out and survive. Working with Paul Lehner at the Cambridge Institute for Medical Research we found that, during latent infection, this transporter protein is less effective, making the cell more prone to killing by vincristine." Their results were published in *Science* in April 2013.

"In addition to treatment with drugs, we're looking into immunotherapies – treatments based on using the patient's immune system," said Wills. "Clearly, the difficulty is that all healthy people have very good immune responses to the virus, yet we all still carry it and can never get rid of it. There must be a problem here – the virus is deliberately trying to evade the immune system by manipulating it."

Sinclair and Wills are trying to understand how the virus does this while in its latent state. Their findings show that HCMV disrupts the proper activation of the immune system by manipulating small signalling molecules called cytokines and chemokines, which normally help to kick-start the process of removing a foreign invader. "Now we know this, we can start to think about intervening," said Wills.

"We've also found that latently infected cells are producing a number of viral proteins," added Wills. "That's a dangerous strategy for the virus, because these proteins could be presented on the surface of the cells they're hiding in, which would attract immune cells like T cells to kill them. Our initial research showed that there are T-cell responses – so why aren't the viral cells being eliminated? It's paradoxical." In further investigations, they uncovered another mechanism in which the virus was promoting a certain subtype of T cell that suppresses the immune system. "So now we're working to remove the immunosuppressive component of that immune response by either removing or neutralising the function of the immunosuppressive T-cell subtype, to enable the other components of the body's immune response to target the infected cells," added Wills.

By targeting latent infection, this work holds great promise for developing better methods of treatment for HCMV and for the design of a vaccine. "If you intervene just before a transplant, and use this immunotherapeutic technique to target the latently infected cells, in combination with the drugs, you can purge the infected cells," said

Sinclair. "This massively reduces the potential that HCMV will reactivate in the person receiving the transplant, because effectively you're not giving them the virus," he added.

They have proved this concept in the laboratory and their new MRC grant will enable them to trial its effectiveness in a model system as a stepping stone to human clinical trials. "A decade ago we couldn't have even contemplated doing this type of work," said Sinclair, "but now we have worked out what's going on during latent infection, we can try to target these changes. Being able to clear the latent infection is key to eradicating much of the disease caused by HCMV that we see in the clinic."

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