Purging a virus from organ transplants

April 7 2015

Human cytomegalovirus (HCMV) is an extremely common virus, which as other members of the herpes virus family causes life-long infections in humans. Most individuals are exposed to HCMV during childhood, yet symptoms can be easily fought off by a healthy immune system. However, infections can be life-threatening for individuals with defective immunity, for instance newborn babies, people with AIDS, or those taking immunosuppressive drugs following organ transplantation. Scientists at Ecole Polytechnique Federale de Lausanne (EPFL) have discovered the molecular switch that allows HCMV to either lie dormant or reactivate its infection. The switch can be manipulated with simple drugs to force the virus out of dormancy, making it easy to target with antivirals. Published in eLife, the study shows how HCMV could be fought in high-risk patients and purged from organs before transplantation.

HCMV infects 60% of the population in industrialized countries, and almost everybody in less affluent places. This virus persists for life by hiding in blood-making ("hematopoietic") stem cells, where it lies dormant and goes completely unrecognized. It occasionally reactivates in the descendence of these hematopoietic stem cells, but these bouts are rapidly tamed by the immune system. However, in people whose immune system has been compromised, e.g. by AIDS, and organ transplant recipients who have to take immunosuppressive drugs, HCMV reactivation can cause devastating symptoms.

Throwing the switch

The lab of Didier Trono at EPFL discovered a protein that switches HCMV between dormancy and reactivation. They found this protein to be bound to the HCMV genome in latently infected hematopoietic stem cells and, upon a variety of external stimuli, to undergo a modification that allows for viral activation.

Furthermore, the researchers were able to control this switch with a drug called chloroquine, usually used against malaria. When they treated hematopoietic stem cells containing dormant HCMV with chloroquine, the virus reactivated and became exposed, opening the door to maneuvers aimed at eliminating virus-infected cells.

The simplicity of the study's design underlies its enormous significance. On one hand, it sheds light on the molecular mechanism by which HCMV becomes dormant in hematopoietic stem cells, possibly offering insights into similar infections by other herpes viruses. On the other hand, the study provides a straightforward method for forcing HCMV out of dormancy in infected tissue. Coupled with a simultaneous dose of an antiviral, this could become a standard regimen for eradicating HCMV from high-risk patients and purging it from tissue before transplantation.

Trono's team is now testing the method's efficiency in purging HCMV from cells to be used for bone marrow transplantation. Following that step, the group will be developing the first trials in humans.

More information: Rauwel B, Jang SM, Cassano M, Kapopoulou A, Barde I, Trono D. Release of Human Cytomegalovirus from latency by KAP1/TRIM28 phosphorylation switch. *eLife* dx.doi.org/10.7554/eLife.06068

Provided by Ecole Polytechnique Federale de Lausanne