Copycat viruses outwit the immune system

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Herpes virus can make its own version of a human protein that regulates complement activation, enabling it to evade destruction by the host's immune system [1]. Studies of viruses that lack this protein have helped to identify a component of the immune system that is essential in dealing with both acute and latent viral infections. This could pave the way for a novel approach to the study of viral diseases and could lead to the development of novel antivirals.

Herpes virus

Once it enters the body, herpes virus hides in cells, often to re-emerge and cause diseases such as shingles, genital herpes and cancer. It was not known how the virus manages to evade immune attack during this latent period. Recent research from Washington University School of Medicine at St Louis (http://www.medschool.wustl.edu) has shown that, in mice, herpes virus uses molecules similar to the host's natural proteins to thwart an immune-system attack [1].

The investigators focused on the complement system, a set of serum proteins that the host uses to regulate the immune system when invaded by certain infectious organisms. The complement factor C3 is the key player in this system of proteins, which kills viruses or virus-infected cells by punching holes in the cell membrane. To ensure that the system doesn't fire up unnecessarily, healthy cells produce regulators of complement activation (RCA).

The herpes virus strain γHV68 can make its own RCA, thus evading the immune response. The Washington University team engineered a mutant mouse virus that lacks the RCA mimic protein, and compared its effects with those of the normal virus, both in normal mice and in mice lacking C3.

Disguise tactics

The RCA protein is clearly a mask: deleting it decreased virulence during acute infection and mice lacking interferon ($IFN\gamma R^{-/-}$) would not develop persistent infection if it was absent. The study showed that it requires about 100-fold more of the mutant virus than of the normal virus to cause disease in healthy mice. This mutant virus grew 27 times slower, and failed to spread to other organs during acute infection. However, in mice lacking C3, mutant virus was just as virulent as normal virus during acute infection and did not need to disguise itself with RCA to survive.

Previous wisdom held that the complement system kicks in primarily during acute herpes infection, and other immune system components, such as T-and B-cells, fight infection during chronic phases. The Washington University team found that healthy mice infected with γHV68 showed few signs of persistent infection, but C3-deficient mice did develop persistent infection. Thus, complement must also control this phase of infection.

'Our findings explicitly show that complement plays a role during persistent and latent infection, and that was unexpected,' said study leader Herbert W. Virgin, Professor of Pathology, Immunology and Molecular Biology at Washington University. 'They also emphasize that we can't study a viral protein during just one part of a virus's life cycle and assume we understand the function of that protein. It is important to look at it during all phases of infection.'

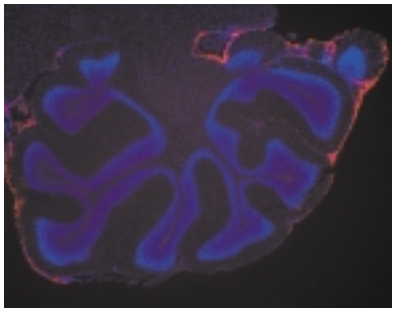

Figure 1. Immunofluorescence staining of the whole brain of mice with meningoencephalitis at low power with anti-γ-herpesvirus 68 (γHV68) antibody. Blue represents cells in the layers of the cerebellum and red represents viral–antigen-positive cells in the meninges of wildtype γHV68-infected mice, five days post-infection. Figure amplification: 1700. Reproduced, with permission, from Ref. [1].

Beyond herpes virus?

Other reports [2–4] have described complement-evasion molecules on viruses that modify the severity of acute infection, according to Harvey Friedman, Chief of the Infectious Disease Division at the University of Pennsylvania (http://www.upenn.edu). 'An unexpected observation in this paper,' he commented, is 'the finding that complement reduces the virus' ability to develop latent infection, which establishes complement as a critical component in host defense against viruses.'

Different stages of infection

Is it possible that some people develop a comparable deficiency in complement, leaving them vulnerable to herpes virus?

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This hasn't been evaluated, said Virgin, but he added: 'It could have been overlooked.'

The complement system has been studied extensively in pox and herpes viruses, according to Peter Lachmann from the UK's Centre for Veterinary Science in Cambridge (http://www.vet.cam.ac.uk). 'What seems to be new… is the biological effect on latency in C3 knockout mice, which looks interesting,' he commented. 'Mostly, complement-deficient humans do not have problems with pox viruses or herpes viruses,' he added. This is probably because the main immune control of such viruses is through T cells, and the effect of complement is, as suggested by its name, complementary.

Other evasionary tactics

Recent research has shown that susceptibility to the pathogen *Borellia bergdorferi*, which causes Lyme disease, also involves complement. According to Klaus Kurtenbach at Imperial College of Science, Technology and Medicine (http://www.ic.ac.uk), the interaction of Lyme disease spirochetes with host complement is 'a new framework that has only recently been recognized.'

Spirochetes in the gut of the tick that transmits Lyme disease interact with complement, he explains. *Borrelia* express proteins that specifically bind the complement-regulator factor H of animals that the ticks feed upon, and spirochetes that coat themselves with host complement regulators are protected against lysis. 'This is not exactly mimicry, rather deflection of innate immunity,' Kurtenbach said.

The next step in herpes virus research is to elucidate the molecular mechanism by which the γHV68 protein mimic regulates complement, said Virgin. He added, 'This viral protein is the only one of its class that regulates complement in both mouse and humans.' This unique characteristic could make it useful for further studies of complement, he says.

References

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Do all paths lead to DARPP-32?

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A central brain chemical involved in signaling pathways that range from the psychostimulant action of caffeine to the biochemical effects of the antidepressant Prozac has now been linked to a psychiatric illness. Patients with schizophrenia were found to have significantly reduced levels of DARPP-32 in the dorsolateral prefrontal cortex, an area of the brain that is compromized in schizophrenia. This is the first time that DARPP-32 has been implicated in a disease, and suggests that this brain processor might be associated with other psychiatric or neurological disorders.

The biochemistry of DARPP-32

Dopamine- and cyclic AMP-regulated phosphoprotein of relative molecular mass 32,000 (DARPP-32) has a key role in many neurotransmitter pathways throughout the brain [1]. It has been shown to be involved in controlling receptors, ion channels and other physiological factors including the brain's response to drugs of abuse, such as cocaine, opiates and nicotine. A recent study has also shown that the stimula tory effect of caffeine on motor activity is reduced in laboratory mice that have been genetically altered to lack the DARPP-32 protein [2].

DARPP-32 is reciprocally regulated by the two neurotransmitters that are most often implicated in schizophrenia – dopamine and glutamate (Fig. 1). Dopamine activates DARPP-32 through the D1 receptor pathway and disables DARPP-32 through the D2 receptor. Glutamate, acting through the *N*-methyl-D-aspartate receptor, renders DARPP-32 inactive.

It was this association that gave William E. Bunney Jr, Professor of Psychiatry at the University of California at Irvine (http://www.uci.edu/), and his colleagues the impetus to look at the levels of this brain chemical in patients with schizophrenia. 'DARPP-32 appeared to be sitting at a really key control spot in this metabolic pathway,' he explains.

Their analysis of 14 deceased schizophrenia patients found a selective decrease of DARPP-32 protein levels in the dorsolateral prefrontal cortex circuit, a region of the brain that is important for thinking and mood [3]. It is also a circuit

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