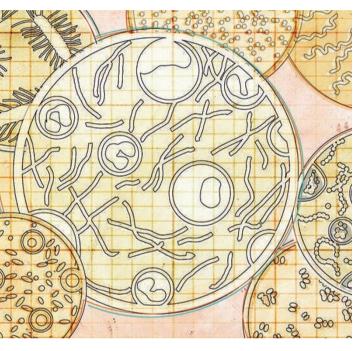
ANTIVIRAL DRUGS

Exposed target for broad-spectrum antivirals



Phosphatidylserine, the most abundant anionic phospholipid of the plasma membrane, has been used as a target to develop a novel broad-spectrum antiviral agent called bavituximab. Strikingly, bavituximab was able to cure overt disease in guinea-pigs infected with a potentially lethal dose of Pichinde virus, a model of Lassa fever virus.

Writing in *Nature Medicine*, Thorpe and colleagues proposed that

the effects of a wide range of viruses on host cells could lead to normally intracellular anionic phospholipids being exposed on the surface of infected cells. To test this hypothesis, they used bavituximab — a chimeric antibody that binds to complexes of the phosphatidylserine-binding plasma protein β_2 -glycoprotein 1 and anionic phospholipids. These experiments showed that infection of mouse cells by Pichinde virus led to phosphatidylserine exposure, and that bavituximab binds to virus-infected cells and infectious virions.

Treatment of guinea-pigs infected with a normally lethal dose of Pichinde virus with bavituximab 6–7 days after infection led to 50% of the animals surviving, and clearance of the virus was observed by day 135. In addition, combination of bavituximab with ribavirin (the current drug of choice for treating Lassa fever) had an additive effect.

The authors also provided evidence for two mechanisms that seem to underlie these effects. First, bavituximab treatment clears infectious virus from the bloodstream. Second, it induces antibody-dependent cellular cytotoxicity of virus-infected cells. As the authors propose, it seems that phosphatidylserine on virions and infected cells might enable viruses to evade immune

recognition and dampen inflammatory responses, and that bavituximab interferes with this 'masking' process.

Finally, the authors explored phosphatidylserine exposure in other viral infections. Exposure was also observed in cells infected with influenza virus, vaccinia, vesicular stomatitis virus and mouse cytomegalovirus (CMV). This indicates that this process is a common feature of enveloped viruses; exposure could also extend to non-enveloped viruses. Furthermore, tests in mice infected with an almost lethal dose of CMV showed that all treated mice survived, in contrast to untreated mice, of which only 25% were alive after 96 days.

In both animal models, bavituximab was well tolerated, and no toxicity was observed histologically. Therefore, targeting phosphatidylserine shows promise as an antiviral strategy. In addition, as phosphatidylserine is a host-derived target, the development of resistance could be limited. Clinical trials of bavituximab are currently underway in patients with hepatitis C co-infected with HIV.

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