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Potential drug target for flesh-eating bug

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Group A streptococcus (GAS), nicknamed the 'flesh-eating bacteria', is a common source of illness in humans. It causes symptoms that range from a sore throat to the fatal destruction of of tissue, and results in death in more than a quarter of cases.

Scientists were aware of the specificity of GAS in humans [1]. But they were unsure what exactly was responsible. Now they are closer to understanding this mystery, raising hopes for future therapies that could tackle GAS. GAS secretes a blood clot-dissolving substance called streptokinase, which makes use of the host´s own mechanism for dissolving blood clots by plasminogen. A recent report has shown that the interaction of streptokinase with human plasminogen is key to the specificity of the human attack [2].

Fatal interaction

The group provide evidence that streptokinase has little or no effect in mammals other than humans. But in animals that were genetically-engineered to produce human plasminogen, streptokinase caused disease.

Heiko Herwald, molecular biologist at Lund University (http://www.lu.se), says: 'Scientists knew about the specificity of streptokinase, but didn't know how important it was.' Previously, scientists thought that other characteristics of the bacteria, such as surface-binding proteins, were equally important for specificity in humans. 'I was surprised – I thought specificity would be due to a whole bunch of factors,' says David Ginsburg, immunologist at Howard Hughes Medical Institute (http://www.hhmi.org) and author of the study.

Clots and no clots

The team genetically altered mice so that they produced human plasminogen. When the mice were infected with GAS, the proportion of mice that became ill or died increased to 75%, nearly four times that of normal mice. 'It had such a dramatic effect,' says Ginsburg.

Suspecting that clot formation acts to bar GAS from the blood circulation system, the team tested whether streptokinase could infect mice without clots. 'When we injected bacteria directly into the blood of normal mice, they became ill,' says Ginsburg. The team also used a snake toxin to dissolve fibrinogen in blood clots. After this, normal mice were much more susceptible to the bacteria, and none of the mice survived after infection. 'This indicates that blood clots in mice prevent streptokinase reaching the blood,' says Ginsburg.

These findings indicate that plasminogen in clots acts to block the attack of the bacteria – except when it is human plasminogen. In this case, streptokinase can specifically target it and break down the clot. This allows the bacteria to enter the blood, causing havoc.

Scientists think there is now a possibility of designing drugs for GAS that inhibit the binding of streptokinase to plasminogen in humans. 'Inhibitors of plasminogen could be a possible drug development target,' says Herwald.

References

1 Gladysheva, I. P. *et al.* (2003). Coevolutionary patterns in plasminogen activation. *Proc. Natl. Acad. Sci. U. S. A.* 100, 9168–9172

2 Sun, H. *et al.* (2004). Plasminogen is a critical host pathogenicity factor for group A streptococcal infection. *Science*, 305, 1283–286

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