Up close and personal: anti-herpes drug development

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Researchers have identified a small molecule that inhibits the interaction between the subunits of herpes simplex virus (HSV) DNA polymerase. This molecule, they say, provides a starting place for the development of new antiviral drugs, not only for HSV but also for cytomegalovirus (CMV).

Hidden enemy

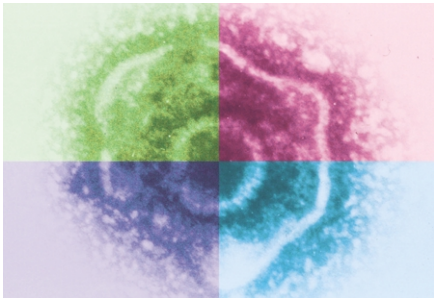
HSV-1 and HSV-2 infections are very common – most adults have antibodies to HSV-1 and/or HSV-2. Although the cold sores and genital lesions caused by these herpesviruses are painful, HSV infection or reactivation in healthy adults is not life-threatening. In immunocompromized patients, however, HSV infections are more serious.

HSV infections are usually treated with the nucleoside analog acyclovir, which inhibits viral DNA polymerase. But, says Donald Coen, Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Boston (http://www.hms.harvard.edu), 'acyclovir-resistant HSV develops in 5–10% of immunocompromized patients.'

Towards a new HSV therapeutic

A potential target for a new HSV therapeutic is the interaction between the catalytic subunit of HSV polymerase (Pol) and its processivity subunit (UL42), which is significantly different from the equivalent interaction in other viral and cellular polymerases. 'A few polar residues form hydrogen bonds between Pol and UL42 and mutation of any of these residues disrupts the Pol–UL42 interaction and inhibits polymerase function,' explains Coen. 'This led us to ask whether a small molecule could do the same.'

As they report in *Chemistry and Biology* [1], the researchers have found a molecule that specifically inhibits the physical interaction of Pol and UL42 and inhibits viral replication at concentrations below those that were cytotoxic. 'This molecule is too toxic to go into patients,' cautions Coen, but it might be possible to make less toxic derivatives that retain their antiviral activity.



'This is important work in that it identifies a small molecule that can inhibit a protein–protein interaction in HSV,' comments Howard Marsden, formerly Principal Scientist at the Medical Research Council's Institute of Virology in Glasgow, UK (http://www.vir.gla.ac.uk). 'However, this is only a "hit". It's a long way from here to a lead compound,' a journey that might not be justified given the availability of acyclovir.

More importantly, say Marsden and Coen, the current work is a platform from which to search for new drugs to treat CMV, another herpesvirus. CMV infections are treated with gancyclovir, says Marsden, 'the serious side-effects of which are only acceptable because CMV infections can be life-threatening in immunocompromized patients.'

Protein–protein interactions: a good drug target?

Coen and Marsden both believe that selective disruption of protein–protein interactions, which are crucial to most biological processes, is a good strategy for drug discovery. But, says Andrea Cochran, Senior Scientist in Genentech's Protein Engineering Department, South San Francisco (http://www.gene.com), drug companies are sceptical about this approach: interesting early results have often failed to progress to a drug candidate. Nevertheless, many companies, including Genentech, are investigating the approach. In February 2004, for example, researchers at Hoffman-La Roche described a small-molecule inhibitor of the MDM2–p53 interaction that could lead to a new anti-cancer therapy [2], and the recent Horizon Symposium Maine, USA (http://www.nature.com/horizon) included a session on targeting protein–protein interactions for drug discovery.

So how soon might this approach yield new drugs? Few examples are likely in the next five years, says Cochran. However, given the increased appreciation of the importance of protein–protein interactions in many areas of biology, 'within 10–15 years there will certainly be some examples,' she concludes.

References

1 Pilger, B.D. *et al.* (2004) Identification of a small molecule that inhibits herpes simplex virus DNA polymerase subunit interactions and viral replication. *Chem. Biol.* 11, 647–654

2 Vassilev, L.T. *et al.* (2004) *In vivo* activation of the p53 pathway by small-molecule antagonists of MDM2. *Science* 303, 844–848

1359-6446/04/$ – see front matter PII: S1359-6446(04)03195-2