Disruption of protein-protein interactions as a novel antiviral strategy

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Antiviral agents currently licensed for the treatment of herpesvirus infections include acyclovir and derivatives, ganciclovir, foscarnet, and cidofovir, which all inhibit herpesvirus DNA polymerases. There is renewed interest in the search for new anti-herpesvirus inhibitors, because of the emergence of drug-resistant viral strains, particularly in immunocompromised patients, and because some of these antiviral agents, e.g. ganciclovir and foscarnet, have toxic side-effects. Since the herpesvirus DNA polymerases represent a major target for antiviral chemotherapy, further studies on these enzymes could be important in developing novel drugs.

A novel strategy that we have recently proposed to inhibit viral replication is based on the disruption of viral protein-protein complexes by peptides that mimic either part of subunits interaction. The exquisite specificity of protein-protein interactions affords the possibility of interfering with them in a highly specific manner. Our research interest has focused on the development of new anti-herpesvirus inhibitors which act by disrupting the interaction between viral enzyme subunits. During the past few years, we have been working on the characterisation of several herpesvirus enzymes, for example HSV-1 ribonucleotide reductase, and HSV-1 and HCMV DNA polymerase. These studies were aimed to characterise protein-protein interactions between herpesvirus enzyme subunits and to identify antiviral peptides that mimic either face of the subunit interaction and therefore are able to disrupt viral protein complexes.

For the HSV-1 DNA polymerase, there is excellent evidence that the interaction between the two enzyme subunits, UL30 and UL42, is essential for viral replication and thus a valid target for antiviral drugs. We recently showed that an oligopeptide corresponding to the 27 C-terminal amino acids of UL30, when delivered into HSV-1-infected cells by a protein carrier, is able to inhibit viral replication by disruption of the UL30/UL42 interaction. This study established proof-of-principle for blocking herpesvirus DNA polymerase subunits interaction as an antiviral strategy.

Recently, our studies demonstrated that the two subunits of HCMV DNA polymerase, UL54 and UL44, most likely interact in a way which is analogous to that of the two subunits of HSV-1 DNA polymerase, and suggested that the UL54/UL44 interaction could also be an excellent target for the development of new drugs. In support of this possibility, we identified a peptide which both disrupted the physical interaction between the two proteins and specifically inhibited the activity of the UL54/UL44 complex.

Although a peptide with antiviral activity is unlikely to be used in medicine, if it provides significant results in culture cell and animal studies, it will provide encouragement for investment to develop a drug that blocks the same protein-protein interaction. Therefore, the identification of peptides interfering with protein-protein interactions relevant to the pathogenesis of viral infections is an important addition to the development of new drugs. With the demonstration that mimetic peptides can block protein interfaces and the advances in designing peptidomimetics from peptide sequences, this novel mechanism for inhibition of viral replication holds great promise as the next generation of therapeutic agents.