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RATIONAL DRUG DESIGN

We're prodrug!

Prodrugs — those administered in an inactive form due to problems of uptake or degradation — are crucial in the treatment of many diseases, including cancer and viral infections. Nucleoside analogue prodrugs, such as the cancer therapeutic cytosine arabinoside (AraC) and the anti-HIV drug lamivudine (3TC; GSK), are only active in their charged triphosphate form, but they are administered uncharged because entry into cells is inefficient for highly charged molecules. Activation by cellular kinases is required for drug potency, a fact that in many cases limits the effectiveness of these drugs. In the July issue of *Nature Structural Biology*, Arnon Lavie and colleagues solve the structure of human deoxycytidine kinase (dCK), the enzyme responsible for activating prodrugs such as AraC, fludarabine (Fludara; Berlex) and cladribine (Leustatin; R. W. Johnson), and provide insights for the design of both superior prodrugs and of mutant enzymes with enhanced activity.

dCK phosphorylates the natural deoxyribonucleosides deoxycytidine (dC), deoxyguanosine and deoxyadenosine, and its crucial function for the efficacy of prodrug chemotherapy is evident from a direct correlation between the enzyme activity and drug sensitivity in tumour cell lines. Cells lacking dCK activity are resistant to a variety of prodrugs. Furthermore, in animal models, reduction of

tumour size was seen when the cancer drug gemcitabine was administered along with increased dCK activity due to gene transfer. Sabini *et al.* solved the structure of dCK to a resolution of 1.6 Å, in complex with its physiological substrate dC, as well as with the prodrugs AraC and gemcitabine.

The structures explain the different phosphorylation efficiencies observed with various dC analogues and indicate specific modifications to the current cache of prodrugs, which should result in improved drug phosphorylation, and therefore improved therapeutic index of antiviral and anticancer molecules. The authors long-term goal is the structure-based design of mutant enzymes with enhanced activity that can be used with appropriate prodrugs in gene

therapy applications. They demonstrated proof of principle by engineering a dCK mutant that was 50-fold more efficient in phosphorylating dC and fourfold more efficient in activating gemcitabine *in vitro*.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Sabini, E. *et al.* Structure of human dCK suggests strategies to improve anticancer and antiviral therapy. *Nature Structural Biology* **10**, 513–519 (2003)

FURTHER READING De Clercq, E. Strategies in the design of antiviral drugs. *Nature Rev. Drug Discov.* **1**, 13–25 (2002) | Eriksson, S. *et al.* Structure and function of cellular deoxyribonucleoside kinases. *Cell. Mol. Life Sci.* **59**, 1327–1346 (2002) | Yazawa, K. *et al.* Current progress in suicide gene therapy for cancer. *World J. Surg.* **26**, 783–789 (2002)

WEB SITES

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