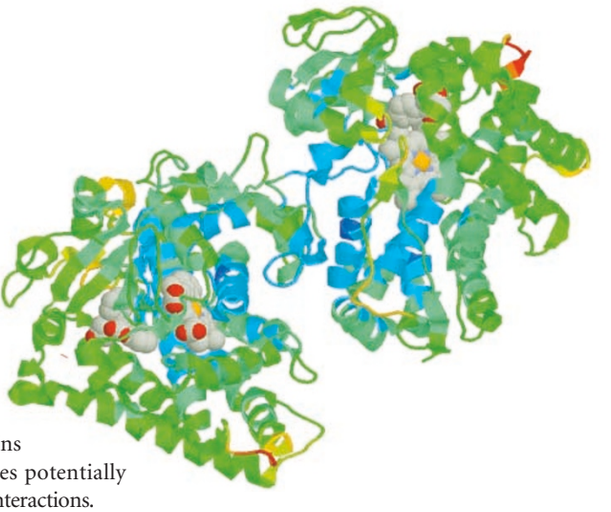
ADME

Atomic views of a human P450



Cytochrome P450 (CYP450) proteins metabolize a wide range of xenobiotics, including environmental compounds and, perhaps most crucially, drugs. Just five human CYP450 proteins metabolize more than 90% of drugs used today (CYP3A4 alone metabolizes up to 50% of all drugs); furthermore, there exist a number of well-known polymorphisms among the CYP450 proteins that are related to differences in ability to metabolize drugs, which can have large effects on drug efficacy and toxicity, as well as drug–drug interactions.

Despite their importance, the structure of a human CYP450 protein has not been widely available, but this dearth has now been remedied with the publication of the crystal structure of CYP2C9 by Harren Jhoti and colleagues in *Nature*. The paper describes the structure of unliganded CYP2C9, and CYP2C9 bound to the anticoagulant drug warfarin. The structure reveals an unexpected binding site, and provides evidence of an allosteric mechanism in the functioning of CYP2C9.

It has been proposed that CYP2C9 preferentially binds small lipohilic substrates through basic residues in an anionic-binding active site. The published structure, however, shows that there are no basic residues in this site that could interact with substrates. Indeed, the residues proposed to participate in anionic binding actually point away from the true binding site, which contains two acidic residues potentially capable of ligand interactions.

Although the structure of CYP2C9 alone is important, the structure of this protein bound to warfarin is potentially much more informative for the purposes of understanding drug–protein interactions in general. The CYP2C9–warfarin structure revealed a number of unexpected points of interaction between the protein and the drug, and also identified a new binding pocket — amino acid residues in this area had been previously identified through mutagenesis studies as contributing to the catalytic activity of CYP2C9, but were not suggested to comprise the binding site.

This new binding pocket is theoretically large enough to accommodate the binding of additional small molecules at the same time as warfarin; CYP3A4 also has the ability to bind multiple ligands, which could be relevant to understanding the mechanism of action of CYP450 proteins in general, and specifically of drug–drug interactions. Furthermore, the mode of binding of warfarin by CYP2C9 indicates a possible allosteric mechanism of action; the authors suggest that determining whether the identified binding site is a 'primary binding site' for substrates, an 'inhibitor-binding site' or functions in an allosteric mechanism is work for the future.

Whereas our previous understanding of CYP450 proteins has generally come from studies of bacterial CYP450s, this paper demonstrates that detailed studies of human CYP450s are likely to throw up a number of surprises, and it will be interesting to see how generally applicable the insights gleaned from this investigation of CYP2C9 are to other CYP450s.

Daniel Jones

References and links

ORIGINAL RESEARCH PAPER Williams, P. A. *et al.* Crystal structure of human cytochrome P450 2C9 with bound warfarin. *Nature* **424**, 464–468 (2003)

FURTHER READING Blundell, T. L. *et al*. High-throughput crystallography for lead discovery in drug design. *Nature Rev. Drug Discov.* **1**, 45–54 (2002)