Structural Biology of Cytochromes P450

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The mammalian cytochrome P450 enzymes are a family of membrane-associated haem-containing proteins which play a major role in the metabolism and subsequence clearance of numerous and diverse xenobiotics such as drug molecules. CYP3A4 is the most important member of P450 family, responsible for metabolising 50 % of drugs while CYP2C9 metabolises some 15 % of all marketed therapeutics. Both enzymes exhibit non-Michaelis-Menten kinetics, including homotropic and heterotropic cooperativity; to predict the *in vivo* clearance of drugs and drug-drug interactions, a better understanding of P450 allostery is required.

In the last few years, a number of mammalian P450 structures have been determined, including CYP2C9 [1] and CYP3A4 [2], both in unliganded forms and in complex with marketed drugs. These crystal structures provide insights into the principles of substrate binding for these promiscuous enzymes, and the structural basis of P450 allostery.

[1] Williams P.A., Cosme J., Ward A., Angove H.C., Vinkovic D.M., Jhoti H., *Nature*, 2003,**424(6947)**, 464-8. [2] Williams P.A., Cosme J., Vinkovic D.M., Ward A., Angove H.A., Day P.J., Vonrhein C., Tickle I.J., Jhoti, H., *Science*, 2004, **305(5684)**, 683-686.

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