New insights into the structural features and functional relevance of human cytochrome P450s

Shu-Feng Zhou
University of South Florida, USA

To date, the crystal structures of 17 human cytochrome P450s (CYPs) have been solved. These include CYP1A2, 2A6, 2A13, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2R1, 3A4, 8A1, 11A1, 17A1, 19A1, 21A2, & 46A1. The determined structures of all human CYPs show the characteristic CYP fold as observed in other members of the CYP superfamily, with the lengths and orientations of the individual secondary structural elements being somewhat similar to each other. However, remarkable differences in the structural features of these CYPs have been observed and this may contribute to the substrate specificity and inhibitor selectivity of individual CYPs. For example, in the CYP1A2 (PDB No. 2HI4) structure, both helix F' and G' are 310 helical fragments instead of typical α-helices. In addition, the CYP1A2 structure is different from those of CYP2 and 3 members in the length and local structure of loop regions connecting conserved secondary structure elements since they share <40% identity of sequence. In the 2HI4 structure in complex with α-naphthoflavone, the compact active site is closed without clear solvent or substrate access channels with a relatively small volume of the cavity of 375 Å³, which is 44.2% larger than that of CYP2A6 (260 Å³), but smaller than that of CYP2D6 (~540 Å³) and CYP3A4 (1386 Å³). In contrast, it is known that CYP3A4 and 2C8 possess much more open active sites, with cavity volumes of 1,385 Å³ and 1,438 Å³, respectively. Although the active site volume of CYP3A4 is similar to that of CYP2C8, the shape of the active site cavity differs considerably due to differences in the folding and packing of portions of the protein that form the cavity. Compared with CYP2C8, the active site cavity of CYP3A4 is much larger near the heme iron. CYP3A4 contains an unexpected peripheral binding site located above a 7-Phe residue cluster, which may be involved in the initial recognition of substrates or allosteric effectors. The elucidation of the structures of human CYPs and the functional relevance has important implications in drug design and development. A good drug candidate should have a low affinity to CYPs that are subject to significant induction, inhibition and polymorphism.

Biography
Shu-Feng Zhou, M.D. & Ph.D., is presently a Professor of Pharmacology and Molecular Medicine, Associate Vice President of Global Medical Development, Associate Dean of International Research, and Chair of the Department of Pharmaceutical Sciences, Colleges of Pharmacy and Medicine, University of South Florida, Tampa, Florida. He has published more than 320 peer-reviewed papers in biomedical journals, which has been cited more than 7,500 times by colleagues with an H-index of 44. He is the editor or editor-in-chief of 16 medical journals and the editorial board member of 34 biomedical journals. To date, he has trained 24 Ph.D. students, 12 M.Sc./Honors students, 14 postdoctoral staff and 15 visiting doctors from other countries.

szhou@health.usf.edu

http://dx.doi.org/10.4172/2161-1025.S1.008