CRYSTALLOGRAPHIC ANALYSIS OF SMALL MOLECULE BINDING TO HSA: WHAT HAVE WE LEARNED?

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HSA (human serum albumin) is an abundant plasma protein that is remarkable for the broad range of natural and artificial small molecules that it can accommodate. This abundant plasma protein serves to solubilise these compounds and can have a profound effect on their distribution in the body.

Over the past twenty years, protein crystallographers on three continents—armed with the insights of many other biochemists—have fought a long, hard battle with HSA and gradually revealed the structure of the protein in atomic detail. The particular contribution of my group in the past decade has been to focus on structural analysis of the binding small molecules to the protein. To date we have solved over forty structures of HSA-complexes, analysing the binding of endogenous compounds such as fatty acids, hemein, thyroxine and bilirubin, as well as exogenous molecules including drugs (e.g. warfarin, diazepam, ibuprofen), diagnostic reagents (e.g. iophenoxic acid) and marker compounds (e.g. dansylated amino acids).

This work has revealed the locations of an astonishing number of binding sites scattered throughout the protein and allowed us to see the binding conformations of each of their ligands in unprecedented detail. The results give us a new molecular understanding of the drug binding capabilities of the protein and the interactions between drugs and natural ligands. They also provide a rational framework for the analysis of binding measurements, the interpretation of which is often non-trivial as a result of the complex architecture of the protein.

Knowledge of the structure and ligand binding sites, coupled with the development of efficient yeast expression systems for the production of recombinant albumin, has facilitated mutagenic approaches to probe the binding capacity of the protein and to engineer albumin as a carrier protein tailored to novel functions.

My presentation will review briefly the most important highlights of structural analyses of HSA-ligand interactions, focus on the key challenges that have been overcome and look forward to the next phase of high-resolution albumin research.

References: