Structural Basis of the Disease-related Proteins: Target Oriented Structural Proteomics

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To discover new drugs more quickly and more efficiently, pharmaceutical companies and biotechnology firms are increasingly turning to the genomics and the structural proteomics technologies. Structural-proteomics can provide a foundation for this through the determination and analysis for protein structure on a genomics scale. Among many structures determined by CGI, we will present with the representative examples drawn from our work on novel structures or complex structures of the disease-related proteins. The alpha subunit of Hypoxia-inducible factor (HIF) is targeted for degradation under normoxic conditions by an ubiquitin-ligase complex that recognizes a hydroxylated proline residue in HIF. Hydroxylation is catalysed by HIF prolyl 4-hydroxylases (HIFPH) which are Fe(II) and 2-oxoglutarate (2-OG) dependent oxygenases. Here, we discuss the first crystal structure of the catalytic domain of HIFPH in complexes, with the Fe(II)/2-OG at 1.8 Å. These structures suggest that the L1 region (residues 236-253), which is also conserved in mammals, form a 'lid' that closes over the active site. The structural and mutagenesis analyses allow us to provide a focus for understanding cellular responses to hypoxia and a target for the therapeutic manipulation.