

Development of an enzyme catalytic-mechanism database: EzCatDB

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An understanding of enzyme catalytic mechanisms from various viewpoints is extremely important in the design of inhibitors. However, despite their extreme importance in catalytic mechanisms, the classification system for enzymes used by the Enzyme Commission (E. C.) does not consider protein sequences and structures. The E. C. classification is based mainly on the entire chemical structure of the substrates and products and on the cofactors involved. Although non-homologous enzymes can catalyze similar reactions, whilst homologous enzymes sometimes adopt different strategies in terms of catalytic mechanisms, the E. C. classification does not reflect such detailed mechanisms in terms of protein structures. Moreover, some enzymes catalyze complex reactions comprising several basic reactions, such as hydrolysis, transfer/elimination/addition of some groups, and isomerization, which are very difficult to express using a single E. C. number.

Conversely, numerous enzyme structures have been determined using X-ray crystallography and NMR, and these have been deposited in the Protein Data Bank (PDB). The PDB not only contains protein structures, but also the various structures of ligand molecules from native substrates/products/cofactors to intermediate/transition-state analogues, which means that the PDB could be a treasury of information on lead compounds. Nevertheless, the relationships between the proteins and ligand molecules are not annotated in the PDB.

I therefore developed a novel enzyme catalytic-mechanism database, **EzCatDB**, focusing on the active sites of enzymes and the reactive parts of their ligand molecules. It specifically addresses the catalytic mechanisms of enzymes and is intended to classify enzymes based on structural information, ligand molecules and proposed mechanisms. This classification can be used to infer correlations between the active-site structures and the catalytic function of enzymes.

References

- (1) Nagano, N.: "EzCatDB: The Enzyme Catalytic-Mechanism Database", *Nucleic Acids Research*, **33** (1) Database Issue, D407-D412 (2005).
- (2) <http://mbs.cbrc.jp/EzCatDB/>

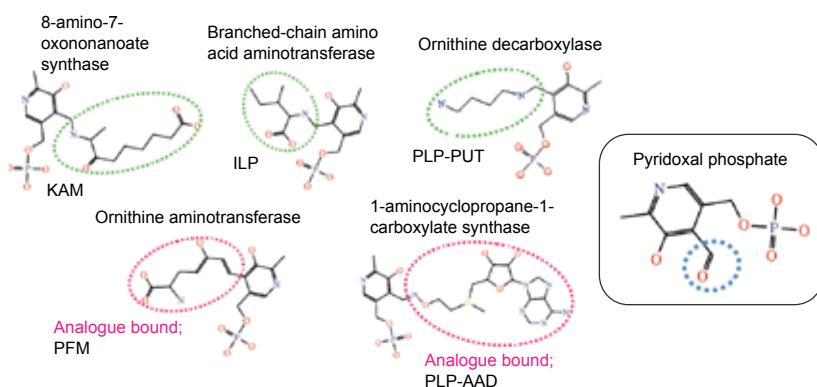


Fig.1

An example of a ligand search: If a search is attempted for enzymes that have "pyridoxal phosphate" bound as a cofactor (shown in the box), and whose PDB data have intermediate molecules or for which analogous compounds have been included, enzymes that meet the conditions can be found ("hit"). Looking at the "hit" data reveals that intermediate compounds or their analogous compounds were found in the corresponding PDB data.

Fig.2

Hierarchic classification of catalytic mechanisms, RLCP: In the EzCatDB, a novel classification of enzyme catalytic mechanisms, which clusters catalytic mechanisms at four levels, has been developed. Here, the classification page for trypsin-like serine proteases is shown. At the bottom of this page, enzyme entries, which belong to this category, are listed along with their links to the corresponding data.