Structural Studies of the Human Protein Tyrosine Phosphatase Family and Their Application in Drug Design

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Protein tyrosine phosphatases (PTP) mediate various cellular processes by dephosphorylation of phosphoproteins. The human genome contains about 110 PTP members that are grouped into several subfamilies such as classical, membrane type and dual specificity PTPs. Consistent with their central roles in cellular functions, many PTPs are implicated in human diseases including cancer, diabetes and neuronal diseases. Despite the increasing efforts to develop therapeutic drugs targeting PTPs, the promising drug development has been hampered by the lack of detailed knowledge on the specificity and regulation of each enzyme. Recently, we determined crystal structures of ten novel human PTPs. From the structures, we found that the active site of each PTP has significant diversity, suggesting the potential of specific inhibitor design targeting each enzyme. We are carrying out structure-based inhibitor screening of the PTPs by using chemical libraries. The structures also provide new insight into the mechanism of biological regulation for each enzyme.