Specificity and promiscuity in a superfamily of phosphatases

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In order to identify and assess sequence markers that support structure and specificity, we have undertaken the study of a large enzyme superfamily, comprised mostly of phosphotransferases, the haloalkanoate dehalogenase superfamily (HADSF). Because of the occurrence of the family in all domains of life and the number of homologues within each organism the members provide numerous examples of orthologues to study determinants of specificity and paralogues to study function diversification. Although specificity is often considered the hallmark of enzymes, the occurrence of enzymes displaying substrates promiscuity or substrate ambiguity can offer advantages to the cell. Indeed there may be selective pressures that favor the occurance of promiscuous enzymes. Examples from the HADSF show that promiscuity can provide the cell ways to perform housekeeping functions such as removal of anti-metabolites and a means of bypassing blocked steps in metabolic pathways. Promiscuity also provides the seeds for evolution of new chemistries or new substrates under novel selection pressure. In order to obtain a "panoramic view of promiscuity, we have employed high throughput substrate screening to a diverse set of HADSF enzymes from a sampling of bacteria across phyla. The screen uncovered orthologs of known enzymes and revealed some new pathways and activities. The results highlight that promiscuity is much more prevalent than one might imagine with ~45% of all proteins showing activity against multiple substrates. The structural basis of promiscuity in the HADSF highlights the necessity of a binding surface with multiple enzyme candidate residues to provide potential ligands.