Chemically-Driven Protein Evolution in the Alkaline Phosphatase Superfamily

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The classical image of enzymes is that they are highly specific, with one enzyme catalysing the turnover of one substrate. In recent years, it is becoming increasingly clear that many (if not even most) enzymes are capable of "promiscuous" catalytic activity, with one enzyme catalysing the turnover of multiple, chemically distinct, substrates. It has been suggested that such promiscuity can play an important role in the evolution of enzyme function[1,2]. The alkaline phosphatase superfamily provides a particularly attractive showcase for testing this hypothesis, as the different members not only possess pronounced promiscuous activities, but also, they are "cross-promiscuous", in that the native activity of one superfamily member is often a side activity in another[3]. Moreover, despite their deceptive similarity, the reactions catalysed by these enzymes (namely the cleavage of P-O and S-O bonds) proceed with very distinct solvation and protonation requirements[4], putting tremendous demands on the enzymes that appear to catalyse these reactions within the same active site. We present here a detailed study of two evolutionarily related (but structurally different) members of this superfamily, namely the arylsulfatase from *Pseudomonas aeruginosa*, as well as two related phosphonate monoester hydrolases. We demonstrate that the main driving force for the observed specificity patterns of these highly promiscuous enzymes appears to be the existence of networks of ionizable residues with coupled pK_as, dynamic hydrogen bonding, and flexible electrostatics. Therefore, ultimately, the promiscuity of these enzymes appears to simply arise out of the ability of the non-native substrates to exploit the pre-existing electrostatic pre-organization of the active site towards the native substrate[5,6]. This, in turn provides an example of chemistry-driven protein evolution.

References

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