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How can we understand an entire (super)family of proteins?

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Understanding how the functional properties of a protein are encoded in its amino acid sequence remains a formidable challenge. We use photoactive yellow protein (PYP) to determine how structure-function relationships can be obtained for an entire (super)family of proteins. PYP is a model system to study fundamental processes in proteins and a prototype for the PAS domain superfamily. It consists of a 100-residue PAS domain with an additional 25-residue N-terminal extension. PYP exhibits a photocycle that is initiated by *p*CA photoisomerization, followed by proton transfer from Glu46 to the *p*CA and a subsequent protein quake during formation of the pB intermediate. These structural changes are driven by the electrostatic epicenter formed by the buried ionized Glu46 side chain and involve partial protein unfolding, including the release of the N-terminal region. Deletion of the N-terminal region slows down pB decay 1,000-fold. We report results on family-wide structure function relationships in PYP. (i) Transplanting mutations that alter the properties of a highly studied PYP to a different PYP homolog are only partially successful, implying sequence context dependence of functional properties. (ii) We find a direct correlation between the strength of the hydrogen bonding between the *p*CA and Glu46 and functional properties of PYPs. The role of Glu46 as the epicenter for driving large conformational changes during pB formation is conserved. (iii) Across the PYP family the N-terminal region is negatively charged while the PAS core is positively charged. The resulting charge-charge interactions are critical for the function the N-terminal region. (iv) We find that residues conserved in the PAS domain superfamily exert their effects through conserved patterns of side chain interactions.