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At the crossroads of biophysics and evolution: protein robustness and evolvability[1] WOUTER HOFF, MASATO KUMAUCHI, Department of Microbiology and Molecular Genetics, Oklahoma State University — Proteins consist of only 20 different amino acids with modest chemical reactivity, but perform a breathtaking range of functions. How do proteins achieve such functional versatility? Novel insights are emerging from research at the interface of protein biophysics and molecular evolution. Proteins are robustness against point mutations: most mutations do not abolish function. How can such robustness be reconciled with the effective evolution of protein function? We examine these issues using photoactive yellow protein (PYP), a prototype of the PAS domain superfamily. High-throughput biophysical measurements of active site properties, functional kinetics, stability, and production level on libraries of PYP mutants reveal that almost all mutants retain photocycle activity, but that the majority of substitutions significantly alter functional properties. Thus, PYP combines robustness with evolvability. The data also reveal the mysterious role of the conserved residues that define protein superfamilies: most PAS-conserved residues are required for maintaining protein production. Asn43, the most conserved residue in PAS domains, regulates PYP signaling kinetics. This residue is often substituted by Ser, Asp, and Thr in PAS domains while retaining two side chain hydrogen bonds. Thus, not residue identity at position 43 but the pattern of side chain hydrogen bonds is conserved.

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