The post-translational addition of lipid moieties to proteins is a key regulatory mechanism that affects the localization, trafficking, solubility, and degradation of target proteins. One such modification is S-palmitoylation, the reversible thiol esterification of cysteines catalyzed by a family of proteins known as palmitoyltransferases (PATs). Although first described more than 30 years ago and associated with many diseases, palmitoylation remains largely unexplored. In this Paper of the Week, David Mitchell and colleagues combined biochemical and genetic approaches to elucidate the mechanism and kinetics of the yeast PAT Erf2-Erf4 (which modifies Ras2), providing valuable insight into an important, yet overlooked, biological process. They found that the reaction consists of two steps: an autopalmitoylation of the PAT, with palmitoyl-CoA acting as the palmitate donor, to create a palmitoyl-Erf2 intermediate followed by transfer of the lipid moiety to the Ras2 substrate; in the absence of Ras2, the palmitoyl-Erf2-Erf4 complex undergoes a cycle of hydrolysis and re-palmitoylation. Mutational analysis indicated that the conserved DHHC motif found within PATs constitutes the catalytic core of the enzyme and is essential for both autopalmitoylation and palmitoyl transfer.

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