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Systematic Investigation of In Vivo Metabolite-Protein Interactions

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Cell signaling is extensively wired between cellular components to sustain cell proliferation and adaptation. The interaction network is often manifested in how protein function is regulated through interacting with other cellular components including small molecule metabolites. While many biochemical interactions have been established as reactions between protein enzymes and their substrates and products, much less is known about how small metabolites regulate protein functions through allosteric binding. We have established a large-scale systematic approach that couples affinity purification with mass spectrometry to characterize protein-binding small metabolites in budding yeast S cerevisiae, and now extended our effort in cultured human cells. We found both yeast and human proteins bind common metabolites such as sterols and NAD. These metabolite-protein interactions are mostly novel and extensive in yeast (20% proteins scored). We also showed that ergosterol, the fungal version of cholesterol, can regulate the molecular function, protein level, and interactivity of ergosterol-binding protein kinases, suggesting these observed metabolite-protein interactions may have diverse regulatory consequences in different biological processes. The systematic investigation of metabolite-protein interactions will reveal the novel aspects of the molecular mechanisms underneath many diseases, and bear the hope to correct them with new types of intervention.