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Towards a systems understanding of the ubiquitin-proteasome system: from substrates to functions and mechanisms

Abstract

Selective protein degradation is involved in most cellular processes, from cell division to differentiation and signaling, and contributes to proteome homeostasis through removal of unnecessary or abnormal proteins. The ubiquitin-proteasome system (UPS) plays a key role in selective protein degradation, whereby a cascade of ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-protein ligase (E3) enzymes marks proteins with polyubiquitin chains for degradation at the proteasome. Generally, each E3 enzyme is responsible for ubiquitination of a specific set of proteins. Deubiquitinating enzymes (DUBs), which remove ubiquitin marks and replenish the pool of free ubiquitin, are involved at various stages of the targeting and degradation processes. Despite the central role of the UPS in protein degradation and its association with various human diseases, many UPS components remain poorly characterized, various E3 ligases have no known substrates and the functions of DUBs are not well understood. I will describe our ongoing efforts to comprehensively characterize the UPS in the budding yeast S. cerevisiae through proteomic approaches designed (i) to identify substrates and functions for the various UPS components and (ii) to dissect the specificity determinants of select degradation pathways.