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Deciphering atypical ubiquitin signals using pathogen-derived E3 ligases

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Abstract

Ubiquitin is a small 8 kDa protein that is appended onto lysine residues of proteins as a post-translational modification, and functions in regulating diverse cellular processes. Through its own lysine residues or its N-terminus, ubiquitin can be joined into one of eight distinct polymeric chains using multiple ubiquitin monomers. Extensive research has led to an understanding of the cellular functions for some of the eight chains, but the biology of the remaining chains remain mysterious. Ubiquitin chains are generated by the incredibly diverse E3 ubiquitin ligating enzymes, each of which contain some level of specificity for a particular ubiquitin chain. One obstacle impairing the study for some of the mysterious chains is the lack of a known eukaryotic E3 ligase that generates the chain preferentially. Fortuitously, many pathogenic bacteria have convergently evolved E3 ligases to co-opt the ubiquitin system of eukaryotic hosts to aid in establishing infection, enabling an alternative approach to study ubiquitin chain ligation. Here, we use protein mutagenesis techniques on E3 ligases from enterohemorrhagic Escherichia coli, Salmonella Typhimurium, and other pathogenic bacteria to explore the structural determinants of the mysterious Lys6-linked ubiquitin chains. Further, we report and utilize a novel E3 ligase with strong preference for Lys6-linked chain ligation, greater than that of any E3 ligase to our knowledge. Dysregulation of the ubiquitin cycle is implicated in numerous cancers, neurodegenerative diseases and autoimmune disorders, and by exploring the elusive Lys6-linked ubiquitin chain, our work expands the toolbox for decoding the ubiquitin system and its contributions to human health.