TRIM21-mediated lysine capture in the UBE2E1 active site shows substrate-targeting mode of a ubiquitin-conjugating E2

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TRIM21, a RING-containing E3 ubiquitin-ligase of the TRIM (tripartite motif) protein family, is a major autoantigen in autoimmune disease and a modulator of innate immune signalling. We report the 2.86 Å crystal structure of the complex of the human TRIM21 extended RING domain with the human E2 conjugating UBE2E1 enzyme, supported by NMR, SAXS and functional analysis. Crystal structure snapshots describe the unconstrained capture of a ubiquitin-targeted lysine into the UBE2E1 active site by functionally critical residues specifically conserved in ubiquitin-conjugating E2s. We show in structural detail how the lysine acceptor targeted for ubiquitination remodels amino acid side chains in the active site region and, consequentially, induces structural changes extending to the E2-E3 direct interface, including the so-called "linchpin" residue required for ubiquitination but distant from the active site. Our work supports an activating role of the substrate as a trigger of catalytic activity and significantly contributes to our understanding of the molecular basis for specificity in lysine targeting by ubiquitin-conjugating E2s.