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Structural basis for an autoubiquitination-targeted lysine by E2-E3 complex

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Tripartite motif (TRIM) proteins are involved in a broad range of cellular processes associated with pathological conditions, such as innate and antiviral immunity and in oncogenic processes (1). Notably, TRIM proteins constitute the largest subfamily of RING-type E3 ubiquitin-ligases, with around 100 members in humans (2). TRIM21, also commonly referred to as Ro52 or SSA was first identified as a major autoantigen in the autoimmune diseases SLE and Sjögren's syndrome. We have shown that RING-domain specific autoantibodies from patients with Sjögren's syndrome impair TRIM21-mediated autoubiquitination by blocking the E2-E3 interaction (3). In the present study, I will show our crystal structure of human TRIM21 (residue 1-91), comprising its extended RING domain, in complex with the human E2 conjugating UBE2E1 enzyme, as well as the structure of the unbound E2 enzyme. The structure presents a first snapshot of how the ubiquitin-targeted Lys61 of TRIM21 is captured bona fide in the UBE2E1 active site, where specific conserved E2 residues, including the "gateway" Asp163 and the "swing door" Asp133, position the incoming lysine for ubiquitin ligation. A crystal structure-derived series of snapshots, together with congruent analysis by NMR, SAXS, structure-directed mutations, modelling and functional assays, jointly show how allosteric activation supports specific lysine targeting and selective ubiquitination. This work significantly extends our understanding of E3-mediated facilitation of substrate recognition, and provides a molecular platform for improved understanding of the structural distinction between sumoylation and ubiquitination inherent to E2s.

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