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Title:	Activation of a ubiquitin fold containing pre-mRNA splicing regulator Sde2 by deubiquitinating enzymes Ubp5 and Ubp15 in Schizosaccharomyces pombe
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Abstract:	The genetic information in eukaryotes flows into protein-coding messenger RNAs through transcription and pre-mRNA splicing. A multi-megadalton protein complex, spliceosome, removes non-coding introns and joins exons to generate translatable mRNAs. It is made of five small nuclear ribonucleoproteins (snRNPs) and more than 200 proteins. In addition, many protein/RNA interactions and post-translational modifications play key roles in regulating the machinery. Ubiquitin and ubiquitin-like proteins (UBLs) are post-translational modifiers functioning in protein degradation, cell cycle, transcription, immune defence, as well as in splicing regulation. Ubiquitin or UBLs share a β- grasp fold and are synthesized as precursor molecules which get processed and activated by deubiquitinating enzymes (DUBs) or UBL-specific proteases respectively. These enzymes are highly substrate specific and are essential for ubiquitin and UBL associated pathways. In my thesis work, we report the mechanism of activation of a novel ubiquitin-like protein Sde2 by deubiquitinating enzymes (DUB) Ubp5 and Ubp15. Sde2 is an intron-specific pre-mRNA splicing factor required for splicing of selective pre-mRNAs in Schizosaccharomyces pombe. The structure of Sde2 has an N-terminal ubiquitin-like fold (Sde2-UBL) followed by a conserved GG~KGG motif and a C-terminal helical domain (Sde2-C). The precursor gets processed at the GG~K site by Ubp5 and Ubp15. Processing of Sde2 precursor is required for its association with the spliceosome; thereby, processing defective mutants of Sde2 show ∆sde2-like splicing defects. The Sde2-UBL is essential for generating the functional Sde2-C with a lysine at its N-terminus. Chromosomal mutations of this lysine resulted in reduced recruitment of another splicing factor Cay1 in the spliceosome and also showed splicing defects. Strikingly, S. pombe Ubp5 and Ubp15 cleave both Sde2-UBL and ubiquitin which are less than 20% identical to each other. However, a homolog of these DUBs in humans, USP7, processes ubiquitin but not Sde2. By swapping the domains of USP7 with Ubp15, we have narrowed down a region in Ubp15 that is responsible for its dual specificity towards Sde2-UBL and ubiquitin. Thus, we have demonstrated that two DUB paralogs activate distinct UBLs with roles in diverse processes related to the ubiquitin system and pre-mRNA splicing. Finally, I will also discuss how these two processes might be connected in the biological system.
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