Title:	Sde2 is an intron-specific pre-mRNA splicing regulator activated by ubiquitin-like processing
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Abstract:	The expression of intron-containing genes in eukaryotes requires generation of protein-coding messenger RNAs (mRNAs) via RNA splicing, whereby the spliceosome removes non-coding introns from pre-mRNAs and joins exons. Spliceosomes must ensure accurate removal of highly diverse introns. We show that Sde2 is a ubiquitin-fold-containing splicing regulator that supports splicing of selected pre-mRNAs in an intron-specific manner in Schizosaccharomyces pombe. Both fission yeast and human Sde2 are translated as inactive precursor proteins harbouring the ubiquitin-fold domain linked through an invariant GGKGG motif to a C-terminal domain (referred to as Sde2-C). Precursor processing after the first di-glycine motif by the ubiquitin-specific proteases Ubp5 and Ubp15 generates a short-lived activated Sde2-C fragment with an N-terminal lysine residue, which subsequently gets incorporated into spliceosomes. Absence of Sde2 or defects in Sde2 activation both result in inefficient excision of selected introns from a subset of pre-mRNAs. Sde2 facilitates spliceosomal association of Cactin/Cay1, with a functional link between Sde2 and Cactin further supported by genetic interactions and pre-mRNA splicing assays. These findings suggest that ubiquitin-like processing of Sde2 into a short-lived activated form may function as a checkpoint to ensure proper splicing of certain pre-mRNAs in fission yeast.
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