The crystal structure of RTFDC1 reveals a RING-like pseudoheterodimer responsible for pre-mRNA splicing regulation

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The splicing of pre-messenger RNA into mature mRNA by the spliceosome is one of the most dynamic and tightly regulated processes in the eukaryotic cell. While the conjugation of ubiquitin and ubiquitin-like modifiers by RING-type E3 ligases represents a common mechanism for regulating various cellular processes, its involvement in pre-mRNA splicing is not well understood. We have determined the crystal structure of a poorly characterized protein known as Replication Termination Factor Domain Containing 1 (RTFDC1) to a resolution of 2.4 Å. Surprisingly, while RING-like domains are known to function as homo- or hetero-dimers, the monomeric RTFDC1 crystal structure revealed two RING-like domains assuming a dimer-like formation. Comparison of RTFDC1 to the structure of other RING-like dimers reveals a common dimerization interface. Proteomic analysis of the RTFDC1 interactome through proximity-dependent biotin labeling (BioID) in HEK293 cells revealed an enrichment in components of the spliceosome, particularly those belonging to the U2 snRNP. Finally, to identify a direct effect of RTFDC1 on pre-mRNA splicing, we performed mRNA-seq on RTFDC1 knockdown cells. We observed an effect on mRNA splicing involving predominantly intron retention. These results establish RTFDC1 as a potentially novel E3 ligase regulating pre-mRNA splicing.