ABSTRACT

The JAMM (JAB1/MPN/Mov34 metalloenzyme) motif is a conserved amino acid sequence, EX(n)HS/THX(7)SXXD, found in proteins from all domains of life. Eukaryotic proteins possesing a JAMM motif are responsible for the selective hydrolysis of iso-peptide linkages involving ubiquitin and ubiquitin-like proteins and often exist as subunits of large complexes. The iso-peptidase activity of JAMM proteins plays a major role in key points of regulation in the ubiquitin system. In particular, the JAMM motif of CSN5 of the COP9 signalosome is responsible for the cleavage of the ubiquitin-like Nedd8 from SCF ubiquitin ligases. A homolog of CSN5 in the lid subcomplex of the 19S proteasome regulatory particle, Rpn11, cleaves ubiquitin from proteasome substrates as they are processed by the proteasome. In order to understand the mechanism underlying iso-peptide bond hydrolysis by the JAMM motif, we have solved the crystal structure of a JAMM domain protein from *Archaeoglobus fulgidus*, AfJAMM. The JAMM motif forms a thermolysin-like active site on a cytidine deaminase fold. We have demonstrated through biochemical analysis of mutations in the JAMM motif of Csn5 that the mechanism of hydrolysis is similar to that of thermolysin. To achieve an integrated understanding of a JAMM domain protein within its cognate complex, we have purified and crystallized the lid subcomplex of the 19S proteasome regulatory particle for structural studies.