Crystal structure and function of the CRISPR-Lon protease

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Type III CRISPR defense systems can orchestrate a complex antiviral response that is initiated by the synthesis of cyclic oligoadenylates (cOAs) upon foreign RNA recognition [1]. These second messenger molecules bind to the CARF (CRISPR associated Rossmann-fold) domains of dedicated effector proteins that interfere with cellular pathways of the host, inducing cell death or a dormant state of the cell that is better suited to avoid propagation of the viral attack [2,3]. Here, we report the crystal structure of CRISPR-Lon, the first cOA activated protease. The protein is a soluble monomer and contains a SAVED domain that accommodates cA_4. Further, we show that CRISPR-Lon forms a stable complex with the 34 kDa CRISPR-T protein. Upon activation by cA_4, CRISPR-Lon specifically cleaves CRISRP-T, releasing CRISPR-T_{23}, a 23 kDa fragment that is structurally very similar to MazF toxins and is likely a sequence specific nuclease. Our results describe the first cOA activated proteolytic enzyme and provide the first example of a SAVED domain connected to a type III CRISPR defense system. The use of a protease as a means to unleash a fast response against a threat has intriguing parallels to eukaryotic innate immunity.

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