Crystal and Cryo-EM structures provide insight into how pro-neurodegenerative SARM1 is activated and cleave NAD+

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Axonal degeneration is responsible for disease progression and accumulation of disability in many neurodegenerative conditions. Sterile alpha and Toll/interleukin-1 receptor motif-containing 1 (SARM1) is a nicotinamide adenine dinucleotide (NAD^+)- cleaving enzyme whose activation triggers axon destruction [1-4]. Loss of the biosynthetic enzyme NMNAT2, which converts nicotinamide mononucleotide (NMN) to NAD^+, activates SARM1 via an unknown mechanism. Using crystallography, cryo-EM, NMR and biochemical assays, we demonstrate that SARM1 is activated by an increase in the ratio of NMN to NAD^+ and show that both metabolites compete for binding to the autoinhibitory N-terminal armadillo repeat (ARM) domain of SARM1 [5]. We show that NMN binding disrupts ARM-TIR interactions in the full-length SARM1 octamer, enabling its TIR domains to self-associate and form a catalytic site capable of cleaving NAD^+ [5]. These structural insights identify SARM1 as a metabolic sensor of the NMN/NAD^+ ratio, define the mechanism of SARM1 activation, and may enable a path to the development of allosteric inhibitors that block SARM1 activation.

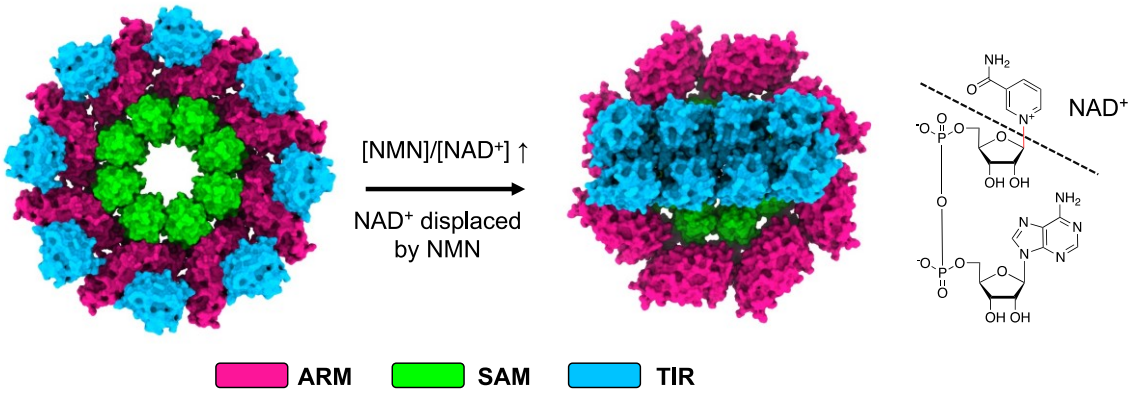

Figure 1. SARM1 activation mechanism. Left: Inactive cryo-EM structure of SARM1. Right: Model of activated SARM1 with oligomerised TIR domains capable of cleaving NAD^+.

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