# Structural basis for activation and inhibition of the pro-neurodegenerative NADase SARM1

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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 an octameric nicotinamide adenine dinucleotide ($NAD^+$)- cleaving enzyme whose activation triggers axon destruction [1-3]. Using crystallography, cryo-EM, NMR, biochemical and cellular assays, we demonstrate that SARM1 is activated by an increase in the ratio of nicotinamide mononucleotide (NMN) to $NAD^+$ and show that both metabolites compete for binding to the allosteric armadillo repeat (ARM) domain of SARM1 [4]. We show that NMN binding triggers a reorientation of the ARM domains, which disrupts autoinhibitory intramolecular interactions and enables its catalytic Toll/interleukin-1 receptor (TIR) domains to form two-stranded assemblies [5]. The active site spans two molecules in these assemblies, explaining the requirement of TIR domain self-association for NADase activity and axon degeneration [5]. We also show that a potent orthosteric small-molecule inhibitor of SARM1 undergoes base exchange with the nicotinamide moiety of $NAD^+$ to produce the bona fide inhibitor 1AD and we report structures of SARM1 in complex with 1AD [5]. Our results reveal mechanisms of SARM1 activation, substrate binding and inhibition, and provide rational avenues for the design of new therapeutics targeting SARM1.
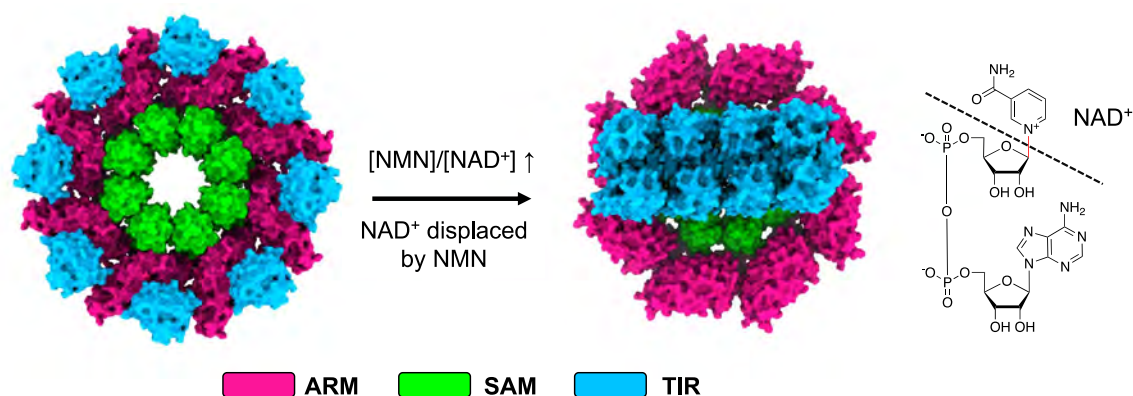
**Figure 1**. SARM1 activation mechanism. Cryo-EM structures of SARM1 in inactive (left) and active (right) states.

[1] Essuman, K. et al. (2017). Neuron **93**, 1334-1343.

[2] Horsefield, S. et al. (2019). Science 365, 793-799.

[3] Wan, L. et al. (2019). Science 365, 799-803.

[4] Figley, M. et al. (2021). Neuron 109, 1118–1136.

[5] Shi, Y et al (2022). Mol Cell 82, 1643-1659.