Uncovering The Molecular Basis for SARM1 Activation

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The NADase SARM1 (sterile alpha and TIR motif containing 1) is a key executioner of axon degeneration and there is great interest in understanding SARM1 as a key driver of multiple neurodegenerative diseases. In this talk we will describe how a combined approach of X-ray crystallography and cryo-EM uncovered the molecular mechanism of SARM1 activation.
These studies, supported by mutational analysis, reveal a model in which SARM1 undergoes a significant conformational rearrangement upon activation, allowing the formation of the NADase site.
Initially, the structure of apo SARM1 was characterised in the autoinhibited state via cryo- EM. These datasets revealed an octomeric ring held together by oligomerization of the SAM domain with the active TIR domains held on the circumference via contacts with the autoinhibitory ARM domain.
Through biochemical studies, we demonstrated activation of SARM1 through the increase in the NMN/NAD+ ratio, suggesting an agonist function for the mononucleotide NMN. However, elucidation of the active form of SARM1 required stabilisation of the activated complex through the binding of an alternative dinucleotide in the orthosteric site. These structures reveal that the ARM domain undergoes a contraction and reorientation upon binding to NMN, stimulated by the stabilisation of a loop within the NMN binding site. This movement disrupts contacts between the ARM and TIR domains, liberating the TIR domain to adopt a new position in a two-stranded oligomeric assembly. The substrate binding site was observed to span two TIR domain monomers within this assembly, aligning with sites previously identified in crystal structures of the isolated TIR domain.
Supporting these data, mutations in the ARM domain rendered the enzyme insensitive to NMN activation.
Together, these results explain the mechanisms of SARM1 activation and substrate binding, and provide a model for activation of SARM1 for the stimulation of axon degeneration.