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Journal Club

Structural basis for lack of toxicity of the diphtheria toxin mutant CRM197

Enrico Malito et al.(2012) PNAS, 109, 5229-5234

Abha Jain

Wednesday, February 13, 2013
4:00 pm
Seminar Room

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CRM197 is an enzymatically inactive and nontoxic form of diphtheria toxin that contains a single amino acid substitution (G52E). Being naturally nontoxic, CRM197 is an ideal carrier protein for conjugate vaccines against encapsulated bacteria and is currently used to vaccinate children globally against Haemophilus influenzae, pneumococcus, and meningococcus. To understand the molecular basis for lack of toxicity in CRM197, we determined the crystal structures of the full-length nucleotide-free CRM197 and of CRM197 in complex with the NAD hydrolysis product nicotinamide (NCA), both at 2.0-Å resolution. The structures show for the first time that the overall fold of CRM197 and DT are nearly identical and that the striking functional difference between the two proteins can be explained by a flexible active-site loop that covers the NAD binding pocket. We present the molecular basis for the increased flexibility of the active-site loop in CRM197 as unveiled by molecular dynamics simulations. These structural insights, combined with surface plasmon resonance, NAD hydrolysis, and differential scanning fluorimetry data, contribute to a comprehensive characterization of the vaccine carrier protein, CRM197.