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Structural insight into the synergistic activities of NADase and SLO in the pathogenesis of Group A Streptococcus infection

Group A Streptococcus (GAS) is a strict human pathogen renowned for its highly aggressive destruction of host tissues that can lead to life-threatening diseases including streptococcal toxic shock syndrome and necrotizing fasciitis. GAS possesses a unique pathogenic trait to enhance its virulence by utilizing the synergism of two secreted toxins, Streptolysin O (SLO) and NAD+-glycohydrolase (NADase). How NADase and SLO assemble into a complex to synergistically promote intracellular survival and resistance to innate immunity within human cells is a long-standing question. By combining X-ray crystallography and small-angle X-ray scattering (SAXS), we decipher the first structure of NADase/SLO complex and reveal the dynamic nature of the complex in solution. The functionally-relevant conformations of the NADase/SLO complex revealed by SAXS suggest the dynamic interplay between SLO and NADase is fundamental to the functioning of the complex. Moreover, the introduction of a complex-disruptive mutation in GAS genome results in decreased resistance to phagocytic killing in vitro. Furthermore, mice infected with GAS mutant harboring the disruptive mutation displayed reduced skin lesions. This work delivers the structure-functional relationship of the NADase/SLO complex and pinpoints the key interacting residues that are central to the coordinated actions of NADase and SLO in the pathogenesis of GAS infection.

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