Structural Studies of TDE0362: A Virulence Factor in Treponema denticola

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Treponema denticola is a key pathogen of chronic periodontitis. During infection, Treponema denticola thrives within subgingival plaques formed in the periodontal pocket, despite direct interactions with the host immune system. To facilitate host immune evasion, Treponema denticola produces a number of virulence factors, including TDE0362, which cleave host immune proteins. TDE0362 encodes a two-domain protein with two conserved bacterial Ig-like domains at the N-terminus and a C-terminal cysteine protease domain (C362). C362 shows sequence and structural homology to the papain superfamily of cysteine proteases, with highest homology to IdeS, an IgG-specific protease from Streptococcus pyogenes. The survival of Streptococcus pyogenes is dependent on the ability to avoid the innate and adaptive immune responses. IdeS specifically cleaves the hinge region of IgG, dissecting the Fab and Fc domains, providing a defense against Fc-mediated phagocytic killing. Treponema denticola is also resistant to phagocytosis. However, despite the similarity to IdeS, C362 does not cleave IgG, suggesting a different mechanism for this resistance. We utilized Se-methionine incorporated protein in conjunction with SAD phasing methods and synchrotron radiation to elucidate the crystal structure of C362 to 2.19 Å. The structure contains 4 monomers in the asymmetric unit in space group P21. The observed structural architecture is conserved in each monomer and is similar to that seen in the IdeS crystal structure. Each monomer consists of 10 β-strands and 10 α-helices, which are organized into two distinct lobes. In its unliganded state, the putative active site residues are highly mobile, suggesting that substrate binding may be required for stabilization.

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