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Literature Seminar

When: April 22, 2021
Time: 2:30 PM
Location: Microsoft TEAMS

Mycobacterium Tuberculosis Hip1: Biochemical and Structural Studies on a Serine Protease That Delays Immune Responses

Abstract

Tuberculosis (TB) remains a major public health issue with approximately 10 million new cases and 1.4 million deaths from TB reported worldwide in 2019 (WHO 2019).1 Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis, engages a multitude of strategies to escape the first-line host immune responses and replicates within host macrophages.2 The pathogenesis of tuberculosis is determined by a complex interplay between the mycobacterial virulence factors and the host immune responses.2 It is, therefore, critical to delineate and understand the biochemical and molecular functions of Mtb factors that play a role in evading the host immunity.

Hip1 (Hydrolase important for pathogenesis 1), a cell envelope-associated hydrolase, has been found to have an immunomodulatory function by preventing the robust activation of the host macrophages following an infection with Mtb.3 Through its immunomodulatory function, Hip1 controls the magnitude and onset of pro-inflammatory responses elicited by Mtb.3 Key insights into the biochemical and molecular mechanisms which underly the enzymatic activity of the Hip1 have recently been obtained.4 Based on its amino acid sequence, Hip1 was predicted to be a serine protease with a catalytic triad of Ser228, His490, and Asp463 at the enzyme active site.4 The standard serine protease inhibitor 4-(2-aminoethyl) benzene-sulfonyl fluoride (AEBSF) inactivated the enzyme.4 In an effort to identify sources of substrate specificity, cleavage of small peptide p-nitroanilide substrates were characterized with Hip1.4 Further, the Mtb chaperone-like protein GroEL2 was found to be the physiological target for Hip1 activity in Mtb.4 Researchers observed that Hip1 cleaves human GroEL2 within the N-terminus of the protein (between Arg12 and Gly13), releasing a peptide fragment of 12 amino acids.4 Interestingly, this cleavage converts GroEL2 from a cell wall-associated multimeric form into a monomeric form.4 Cleavage of GroEL2 has biological relevance and enhances the dampening of host macrophage responses during Mtb infection.4 X-ray crystallography of Hip1 in its apo form provides a better understanding of the cleavage reaction of Hip1 and also provide an insight into substrate recognition.5 Hip1 was shown to be a two-domain protein, one domain is a mixed (α/β) domain with catalytic residues and the other domain is an alpha (α) only domain.5 Interestingly, a threonine residue, Thr466 is located in the active site close enough to hydrogen bond with residues His490 and Asp463.5 Mutation of this residue to alanine has helped to establish its importance for function.5 The new knowledge on the biochemical and structural features of Hip1 may help in design of drug inhibitors that target the activity of the enzyme to abolish its immunomodulatory function. As a result, new therapeutic strategies against TB can be developed.

References

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