DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY COLLOQUIUM
UTAH STATE UNIVERSITY

Nov. 10 2021

2.1 Å Crystal Structure of the Mycobacterium Tuberculosis Serine Hydrolase, Hip1, in its Anhydro-Form (Anhydrohip1)

The 2.6 Å crystal structure of the apo form of Hip1 (hydrolase important for pathogenesis) was previously reported, however, very little is known regarding the active site architecture of this M. tuberculosis (Mtb), serine hydrolase drug target. To begin mapping the active site of Hip1, we co-crystallized Hip1 with the irreversible, serine protease inhibitor, 4-(2-aminoethyl)-benzenesulfonylfluoride (AEBSF), since the analogue, phenylmethylsulfonyl fluoride (PMSF), exhibited no inhibition of the enzyme. We obtained crystals that diffracted to 2.1 Å but to our bewilderment, we did not observe any electron density for the inhibitor in the omit map for the Hip1-AEBSF complex. Rather, in the vacant active site, the catalytic Ser228 is converted to dehydroalanine (dAla), thus yielding anhydrohip1.

Here we present a comparative analysis of the crystal structures of anhydrohip1 and Hip1 and provide a mechanism for the conversion of the enzyme to the anhydro-form through reaction with AEBSF. With the aid of molecular docking, we propose an explanation for the differential inhibition of Hip1 by AEBSF and PMSF. We also present a preliminary definition of the S2 subsite of the protease and delineate a mechanism for a ligand-induced conformational change within this subsite.

Finally, we expand upon the previous demarcation of the proposed lipid binding pocket in the α-domain of the enzyme. We believe that this detailed analysis of the structures of anhydrohip1 and Hip1 provides valuable information useful for the structure-based drug design of novel Hip1-directed Mtb therapeutics.

4-5PM (MDT) | ESLC, Room 046 | Zoom
https://usu-edu.zoom.us/j/89128547168?pwd=U0ZEUHN4Y0E2YUlxQ2ZRWXJERW9udz09
Zoom Meeting ID: 891 2854 7168
Zoom Passcode: 641921

Nathan Goldfarb, PhD
UTAH VALLEY UNIVERSITY

Host: Sean Johnson

College of Science
UtahStateUniversity