Abstract

The rising threat caused by multiresistant bacterial pathogens establishes an urgent need for novel ways of treatment for infectious diseases. A new concept focuses on the reduction of bacterial virulence rather than viability.[1] The barrel-shaped ClpP protease is a highly conserved virulence regulator in bacterial pathogens. Its inhibition by beta-lactones was shown to lead to a drastic decrease in the expression of virulence factors in Staphylococcus aureus (Sa).[2]

The structural characterization of this tetradecameric serine protease forms the basis for an improved understanding of protein function and inhibition. It was recently shown that SaClpP is able to adopt a compressed, inactive conformation.[3] We have solved the 2.3 Å resolution structure of SaClpP in its closed, active conformation as well as the structure of related enzymes in Listeria monocytogenes.[4,5] Comprehensive mutational analysis was able to pinpoint key residues involved in a catalytic switch and in the intersubunit interaction. By probing the active site serine with a beta-lacton probe, we could show that the tetradecameric organization is essential for a proper formation of the active site. Our data suggest that a highly conserved hydrogen-bonding network links oligomerization to activity. A comparison of ClpP structures from different organisms provides suggestive evidence for the presence of a universal mechanism regulating ClpP activity via conformational selection. We used the active conformation of the protease for docking studies to rationalize inhibitor binding. A hydrophobic pocket next to the active site accommodates aliphatic ?-lacton substituents and leads to an ideal positioning of the electrophilic warhead for reaction with the active site residue.[6] Surprisingly inhibitor binding in these pockets can induce a collapse of the oligomeric complex which leads to a sustainable inhibition.[7]

References

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