Bacterial cell wall degradation by a staphyloccocal autolysin

Thilo Stehle, a,b Sebastian Zoll, a Interfaculty Institute of Biochemistry, University of Tuebingen, Tuebingen (Germany) b Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN 37232 (USA). E-mail: thilo.stehle@uni-tuebingen.de

Treatment of hospital-acquired Staphylococcus infections remains a challenge as the number of strains with multiple antibiotic resistances has increased steadily over the last decades. This emphasizes the need for a new class of antibiotics that act on new targets. The major autolysins AtlE and AtlA of S. epidermidis and S. aureus, respectively, represent such targets. Both enzymes take over pivotal roles in cell division where they are responsible for the separation of daughter cells.

The high-resolution structure of AmiE reveals for the first time detailed insights into the enzymatic function of a staphyloccocal peptidoglycan (PGN) hydrolase and thereby provides the basis for the formulation of a likely mechanism of catalysis [1]. With the synthesis of PGN fluorescent substrates, a method was established that offers the option to produce substrates of defined length and high purity [1,2]. Easy modifiability of the synthetic substrates also allows probing the influence of amino acid substitutions on substrate recognition. It could be demonstrated that the presence of a third amino acid in the peptide stem as well as the isoform of glutamine in the second position are key motifs and essential for recognition by AmiE. These findings could also be confirmed in a docking model. Structural comparisons with other proteins sharing the amidase-fold reveal common features in the substrate grooves, which points to an evolutionary conserved mechanism of PGN recognition.

Contrary to previous assumptions according to which the cell wall binding region (CBR) of the AtlE amidase contains only two repeat domains, the structure of R₁₄ reveals the presence of four highly similar domains that belong to the family of SH3 domains. The sequence and structural similarity between every second repeat in the CBR is higher than between adjacent ones. A distinct patch of conserved residues could be located on opposite sides of each repeat in the R₁₄ tandem repeat. These areas might serve as binding pockets for negatively charged ligands such as teichoic acids. We are currently examining this possibility.

Small angle x-ray scattering (SAXS) experiments of AmiE-R₁₄ and R₁₄ reveal that the hinge region between the catalytic domain and the first repeat module is more flexible than the second one separating R₁₄ from R₁₄. In conjunction with the available structural data, it is now possible to draw a plausible mechanism of cell wall interaction in which the flexibility of the first linker ensures access of the catalytic domain to several PGN cleavage sites. The second linker serves to separate the two tandem repeats of the CBR. This creates a binding groove in R₁ that can easily be modulated by movement of the RT-loop. In comparison to its counterpart in R₁, the RT-loop of R₁ is not engaged in any contacts with the preceding domain.


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