MS09-O2

Structure, function, and inhibitors of the Helicobacter pylori acid acclimation system, an essential component for chronic infection

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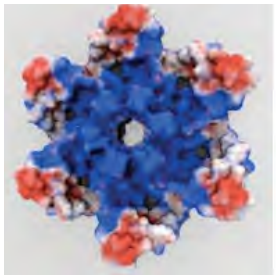
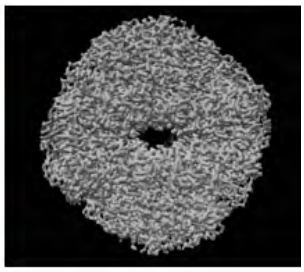
Half the world's population is chronically infected with *Helicobacter pylori*, causing gastritis, gastric ulcers and an increased incidence of gastric adenocarcinoma. Its proton-gated inner-membrane urea channel, *Hp*UreI, is essential for survival in the acidic environment of the stomach. The channel is closed at neutral pH and opens at acidic pH to allow the rapid access of urea to cytoplasmic urease. Urease produces $NH_3$and CO_2, neutralizing entering protons and thus buffering the periplasm to a pH of roughly 6.1 even in gastric juice at a pH below 2.0. Here we report the structure of *Hp*UreI, revealing six protomers assembled in a hexameric ring surrounding a central bilayer plug of ordered lipids. Each protomer encloses a channel formed by a twisted bundle of six transmembrane helices. The bundle defines a previously unobserved fold comprising a two-helix hairpin motif repeated three times around the central axis of the channel, without the inverted repeat of mammalian-type urea transporters. Both the channel and the protomer interface contain residues conserved in the AmiS/UreI superfamily, suggesting the preservation of channel architecture and oligomeric state in this superfamily. Predominantly aromatic or aliphatic side chains line the entire channel and define two consecutive constriction sites in the middle of the channel. The novel hexameric channel structure provides a new paradigm for the permeation of urea and other small amide solutes in prokaryotes and archaea. Our high-throughput screens have identified sub-micromolar inhibitors of *H. pylori*'s acid acclimation system. Follow-up microsecond-scale unrestrained molecular dynamics studies provide a detailed mechanism of urea and water transport by *Hp*UreI. In parallel we have determined the structure of the 1.1 MDa cytoplasmic urease complex by cryo EM to 3.1 Å resolution.





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MS09-O3

Structure determination of lytic polysaccharide monooxygenases interactions with substrate

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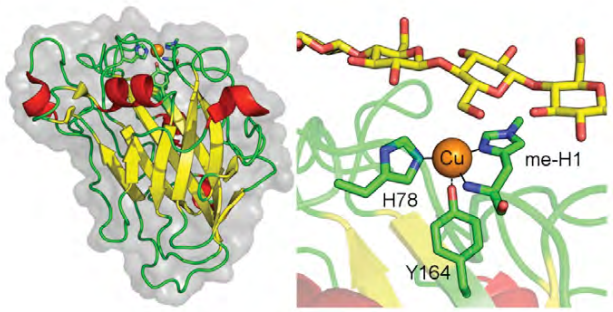
Lytic Polysaccharide Monooxygenases (LPMOs) are copper-dependent enzymes discovered within the last ten years, which oxidatively degrade recalcitrant polysaccharides of the plant cell wall, making chains available for further degradation by hydrolytic enzymes. LPMOs show great potential as a key component in formulation of efficient enzyme cocktails for biomass conversion, and as such, for the production of bioethanol [1]. Very little experimental information on the interactions of LPMOs with their substrates was available until recently. A combined biochemical, crystallographic and spectroscopic study elucidated the interactions between a family AA9 LPMO of the filamentous fungus *Lentinus similis* (*Ls*AA9A) and cellooligosaccharides [2].

More recently we have focused on a detailed comparative study of the substrate interactions and activity of *Ls*AA9A and *Collariella virescens* (*Cv*AA9A)[3]. In this presentation we will focus on the interactions of the LPMOs with cellooligosaccharides and hemicelluloses studied by X-ray crystallography. We thank the CESBIC consortium for initiating this project, and the Novo Nordisk foundation HOPE project (grant number: NNF17SA0027704).



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Keywords: Lytic Polysaccharide Monooxygenase, Complex structures, Cellooligosaccharides.