Advances in the biochemistry of urease and related systems

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Urease is a Ni(II)-dependent enzyme involved in the mineralization step of the nitrogen cycle, catalyzing the hydrolysis of urea to give ammonia and carbamate.[1] This reaction causes a pH increase with negative effects for both human health and the environment, therefore the development of urease inhibitors is necessary. The presence of two Ni(II) ions in the peculiar active site cavity renders urease the most efficient enzyme known in nature. X-ray protein crystallography has been applied to the urease-urea complex, allowing us to determine the role of the two Ni(II) ions in i) the stabilization of the reactive hydroxide ion responsible for the urea breakdown, and ii) the orientation-specific binding of the substrate and the tetrahedral transition state prior to product release.[2] Moreover, the extreme sensitivity of urease towards heavy metals led to characterize the enzyme inhibition by Ag(I), Au(I) and Au(III), discovering that a bimetallic cluster blocks urease activity by coordinating to conserved amino acid residues located on a mobile flap involved in the catalysis.[3,4,5] The talk will also describe and discuss recent advances i) in the mechanism of Ni(II) delivery to the urease active site through the poly-chaperone complex UreDFG,[6,7] ii) in the role of HypA at the crossroad between [Ni,Fe]-hydrogenase and urease activation involving the UreE Ni-transport protein,[8] iii) in understanding the structural details of Ni(II) homeostasis in *Helicobacter pylori*, a human pathogen that relies on the activity of urease to survive in the acidic stomach environment,[9] and iv) in understanding the mechanism of urease inhibition by polyhydroxylated aromatics, the most efficient urease inhibitors known so far.[10]

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