Stefano Ciurli, J Biotechnol Biomater 2017, 7:4 (Suppl)
DOI: 10.4172/2155-952X-C1-079

Urease inhibitors: Structure and function

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The enzymatic activity of urease, a Ni (II)-dependent enzyme that catalyzes the hydrolysis of urea in the last step of organic nitrogen mineralization, has been the focus of intense research for several decades. The activity of urease has negative consequences for both human health and environment. In particular, urease plays an essential role for the colonization and survival of several deadly ureolytic human pathogens. On the other hand, the large and widespread use of urea as a soil fertilizer for crop production, combined with the high efficiency of soil urease, leads to damage to germinating seedlings and young plants, and gaseous loss of urea N as ammonia, with consequent atmospheric pollution, increase of the green house effects, and decreased efficiency of soil fertilization. The development of potent urease inhibitors, necessary to modulate the catalytic activity of this enzyme, requires the knowledge, at the molecular level, of the mechanism of catalysis and inhibition. In addition, understanding of the assembly mechanisms through which the inorganic Ni(II) ion is taken into the enzyme active site, would provide additional targets for the development of drugs to fight these ureolytic organisms. This approach is even more important considering the increasing number of human pathogens that are becoming resistant to known antibiotics. This lecture will describe how an integrated approach using X-ray crystallography, NMR spectroscopy, calorimetry and light scattering, as well as computer modeling, can provide information for the design of drugs to modulate the enzymatic activity of urease. The fallout of these discoveries has several implications in the economic, social, environmental and medical aspects of everyday life.

Biography

Stefano Ciurli has received his Laurea degree in Chemistry from the University of Pisa (Italy) in 1986, with a thesis carried out at the Dept. of Chemistry of Columbia University (NY), and the PhD degree in Chemistry from Harvard University (Cambridge, MA) in 1990. After two years of postdoctoral studies at the University of Bologna (Italy), investigating the structure and function of Fe, Cu, and Ni metallo-proteins, he became Associate Professor in 1992 and Professor of General and Inorganic Chemistry in 2001. Since then, in addition to pursuing structural investigations on urease, he became interested in the molecular basis of nickel trafficking, approaching, in the most recent years, the metal-mediated protein−DNA interactions involved in nickel-sensing and nickel-dependent gene regulation.

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