

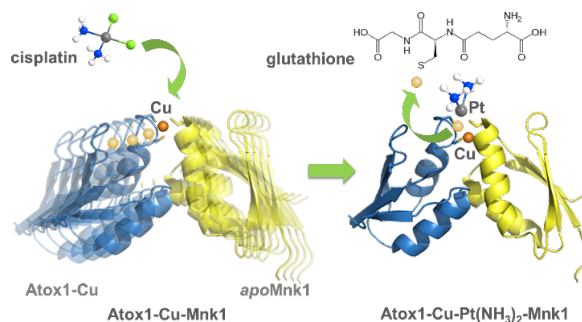


Structural Basis for Inhibition of Copper Trafficking by Platinum Anticancer Drugs.

Rocco Caliendo,^{a,*} Benny D. Belviso,^a Alessia Lasorsa,^b Valentina Mirabelli,^a Maria I. Nardella,^b Giovanni Natile,^b Fabio Arnesano,^b

Proteins involved in copper transport and regulation, such as the human Antioxidant 1 copper chaperone (Atox1), are able to mediate the cellular uptake, sequestration, and efflux from cell of platinum-based drugs, affecting their anticancer activity.¹ X-ray crystallographic investigations have disclosed the Pt binding sites of Atox1, and shown that the metal binding site of the Atox1 dimer is partially occupied by a Pt²⁺ ion, with Cu⁺ ions completing the site occupancy.² Thus, the platinum ion is able to replace partially the copper ion, leading to a disruption of the delicate process that regulates copper level in the cell.

A further recently published study has revealed the structural mechanisms underlying the interaction between Pt-based drugs and two proteins involved in Cu trafficking (Atox1 and the first domain of Menkes ATPase, Mnk1).³ Crystallographic and nuclear magnetic resonance investigations demonstrated that the kinetic inertness of the Pt(II) derivative imparts a bullet time effect to the fast process of copper exchange between Atox1 and Mnk1, by freezing the Cu(I) ion or hijacking it to glutathione, a physiological antioxidant in the biological matrix. Thus, the anticancer drugs cisplatin and oxaliplatin can interfere with the rapid exchange of Cu between Atox1 and Mnk1, with possible consequences on cancer cell viability and migration.



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Riferimenti

- 1 I. H. Hung, R. L. B. Casareno, G. Labesse, F. S. Mathews, J. D. Gitlin, HAH1 is a copper-binding protein with distinct amino acid residues mediating copper homeostasis and antioxidant defense, *Journal of Biological Chemistry* 273 (3) (1998) 1749–1754. doi:0.1074/jbc.273.3.1749.
- 2 B. D. Belviso, A. Galliani, A. Lasorsa, V. Mirabelli, R. Caliendo, F. Arnesano, G. Natile, Oxaliplatin binding to human copper chaperone atox1 and protein dimerization, *Inorganic chemistry* 55 (13) (2016) 6563–6573. doi:10.1021/acs.inorgchem.6b00750.
- 3 A. Lasorsa, M. I. Nardella, A. Rosato, V. Mirabelli, R. Caliendo, R. Caliendo, G. Natile, F. Arnesano, Mechanistic and structural basis for inhibition of copper trafficking by platinum anticancer drugs, *Journal of the American Chemical Society* 141 (30) (2019) 12109–12120. doi:10.1021/jacs.9b05550.

^a CNR - Istituto di Cristallografia, Via Amendola 122/O, 70126 Bari, Italy

^b Department of Chemistry, University of Bari, via Orabona, 4, 70125 Bari, Italy

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