s8a.m7.p13.la Structural changes at the copper centre of Azurin in an oxidation-reduction process: an integrated approach combining crystallography and EXAFS. F.E. Dodd[1], K.-C. Cheung[1,2], R.W. Strange[1], Z.H.L. Abraham[3], R.R. Eady[3] and S.S. Hasnain[1] *1.Synchrotron Radiation Department, CLRC Daresbury Laboratory, Warrington, WA4 4AD, UK. 2 Faculty of Applied Sciences, De Montfort University, Leicester, LE1 9BH, UK. 3 Nitrogen Fixation Laboratory, John Innes Centre, Colney, Norwich, NR4 7UH, UK.*
Keywords: metalloproteins.

Crystallographic structures of oxidised and reduced forms of azurin II are reported at 1.75~ resolution [1]. Data were collected using one crystal in each case and by translating crystal after each oscillation range to minimise photo-reduction. Very small differences are observed at the Cu site upon reduction and that these cannot be determined with confidence at current resolution. A comparison with the 3D EXAFS reveals a good correspondence for all the ligands distances except for Cu-His46 where a larger deviation of ~0.12-0.18~ is observed indicating that this ligand is more tightly restrained in the crystallographic refinement at the current resolution. Three dimensional information is obtained for the Cu site in azurin [2] at very high resolution by combining high resolution crystallographic structures and EXAFS data for the oxidised and reduced form of the protein. This combined approach has allowed us to define the subtle structural changes (<0.1~) which take place at the Cu site during a single electron redox process.

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s8a.m7.p14.la Crystal structure of the Stromelysin-3 complexed with a phosphinic inhibitor reveals that its S_1' pocket is a deep opened cavity. A.L. Gall[1], M. Ruff[1], V. Dive[3], M.C. Rio[2], P. Basset[2] and D. Moras[1]. *1: Laboratoire de Biologie et de Génomique Structurales and 2: Laboratoire de Biologie Moléculaire et Cellulaire du Cancer du Sein, I.G.B.M.C., B.P. 163, F-67404 Illkirch Cedex, France; 3: Département d'Etudes et d'Ingénierie des Protéines, C.E.A., F-91191 Gif/Yvette Cedex, France.*
Keywords: X-ray crystallography, matrix metallo-proteinases, Stromelysin-3 (MMP-11).

Stromelysin-3 (ST3) is a matrix metalloproteinase (MMP-11) expressed by the stromal cells surrounding the cancer cells[1]. ST3 is a non-canonical MMP and differs from the other MMPs in both activation pattern and enzymatic activity[2]. It is a marker of bad prognosis: in breast cancer patients, its expression is associated to a poor clinical outcome[3]. In mouse models, its expression induces tumour implantation and its proteolytic activity is essential to enhance tumorigenicity[4]. Therefore ST3 represents an attractive therapeutical target and selective phosphinic inhibitors have been developed[5].

We solved the structure of the complex between the mouse ST3 catalytic domain and a phosphinic inhibitor at 2.6 Å resolution. The asymmetric unit contains six independent molecules related by an imperfect six fold axis. The presence of CHAPS, a non-denaturing detergent, allowed ST3 to crystallize by stabilizing a flexible loop.

The crystal structure of the complex between ST3 catalytic domain and the phosphinic inhibitor reveals that ST3 S_1' pocket is a deep opened cavity. The tense conformation of the bound inhibitor and the presence of water molecules filling this pocket provides basis for the design more potent inhibitors against ST3.

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