Unraveling the protein ruthenation by antimetastatic metallodrugs: High-resolution X-ray structures of the adduct formed between hen egg-white lysozyme and NAMI-A at various time intervals

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Proteins play a crucial role on the observed pharmacological profile of metal ion complexes, with several studies providing evidence that DNA is not necessarily the primary and/or the only target. In this context, the low cytotoxicity and the anti-metastatic activity of the Ru(III) coordination compound NAMI-A ((ImH)[*trans*-$RuCl_4$(dmso-S)(Im)], Im=imidazole) have been ascribed to its interaction with proteins [1]. To investigate the protein metalation sites of NAMI-A we employed hen egg white lysozyme (HEWL) as a model protein [2] and studied their binding mode at several time points by X-ray crystallography.

We obtained four X-ray co-crystal structures of NAMI-A with HEWL at near-atomic resolutions of 0.98 – 1.07 Å (PDB IDs: 7BCU, 7BCX, 7BD0, 7BDM). The structures obtained after soaking of HEWL crystals with NAMI-A for 1.5 h, 8 h and 26 h revealed three Ru(III)-species bound at the interface of the proteins within the unit cell, whereas the structure obtained after a soaking time of 4 days revealed a "naked" ruthenium ion bound to His15 of lysozyme. The presence of the metal, chloride ions and DMSO-sulfur atoms was verified by anomalous scattering mapping, which allowed us to follow the hydrolysis of NAMI-A from its intact form at 1.5 h, to intermediate species at 8 h and 26 h, until the fully aquated Ru(III) species bound to HEWL at 4 d. Further studies of protein ruthenation using bovine serum albumin are currently underway.

References:

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