Organometallic Chemistry in Anticancer Metallodrug Research: Understanding Site-selective Protein Metalation

Christian G. Hartinger

University of Auckland, School of Chemical Science, Auckland 1010, New Zealand
c.hartinger@auckland.ac.nz

The approaches taken to develop novel metal-based anticancer agents have considerably changed over the last 50 years since the discovery of the platinum drugs and focus now on compounds that interact with proteins overexpressed in tumor cells, show novel modes of DNA interactions or accumulate with higher selectivity in tumors, to name a few. Bioactive metal complexes are often considered promiscuous in their binding to proteins, in that they interact with a variety of proteins and a multitude of amino acids on a protein surface can be metallated. This confuscates the identification of specific interactions of relevance and bioactivity, as not all metalation events will contribute equally or may even be detrimental. The exception to this observation is the organometallic anticancer agent plecstatin-1, which was found to bind to plectin.[1]

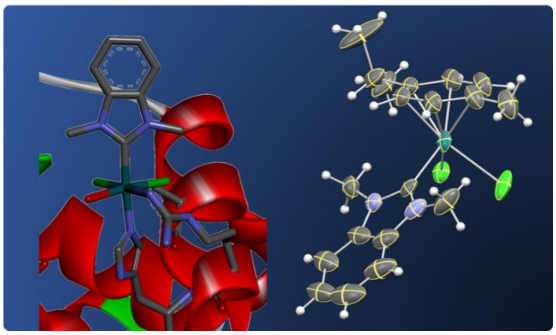

Figure 1. Unexpected adducts formed between anticancer organometallics and proteins.

In this contribution, I will discuss concepts we use in anticancer metallodrug design (Figure 1) and metallomics strategies to interrogate their modes of action. I will focus on the impact of ligand structures on the binding of their organometallic complexes to proteins,[2] which will be complemented by observations of unexpected reactions and surprising behavior in the presence of these biomolecules.[3] These studies lead us to develop an improved understanding of the driving forces for protein surface metalation and selectivity for some sites over others. Overall, it appears as a combination of parameters contributes to the selectivity of binding, including primary and secondary protein structures, steric demand of metal complex co-ligands and the presence of surface grooves with complementary features to those of the binding metal moieties that facilitate hydrophobic and/or electrostatic interactions.

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