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# Nucleosomes and Cisplatin

Vincent Murray[1,*]
[1]School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW 2052, Australia
*Correspondence: v.murray@unsw.edu.au
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In order to form a covalent complex with DNA inside human cells, cisplatin has to overcome the protective environment of a nucleosome, where DNA is complexed with histone proteins. Todd and Lippard (2010) expand our understanding of this process by describing the structure of a nucleosome containing a Pt-DNA adduct, which has important implications for more effective chemotherapeutic drug development.

Many cancer chemotherapetic agents interact with DNA inside tumor cells as part of their mechanism of action. Intracellular DNA is tightly packaged in the form of nucleosomes and other chromatin structures. However, this complex cellular environment is widely ignored in cisplatin-DNA experiments. The protein-DNA complexes found in chromatin would be expected to alter the interaction of the drug with DNA inside cells compared with purified DNA. As part of our growing understanding of this process, Todd and Lippard (2010) have investigated the interaction of cisplatin with a nucleosome core at atomic resolution using X-ray crystallography. They also examined the transcriptional effects of a cisplatin/nucleosome complex.

Richmond and colleagues (Luger et al., 1997) published the first X-ray crystal structure of a nucleosome at atomic resolution. The nucleosome consists of a central octamer core of histone proteins with DNA coiled around the outside of this protein core. Electrostatic interactions are prominent in maintaining this complex, with arginine residues interacting with the minor groove of DNA as well as hydrogen bonding observed at multiple sites between the histones and DNA.

Cisplatin is a very successful antitumor drug that mainly forms intrastrand crosslinks with consecutive guanine residues in DNA. There are two main ways that the interaction of cisplatin with nucleosomes can be investigated (Figure 1). First, Pt-DNA adducts are produced and then nucleosomes are formed on the Pt-DNA complex. This is the process used by Todd and Lippard (2010) in their paper. Second, nucleosomes are formed on a DNA sequence and then cisplatin is reacted with the nucleosome complex.

This latter strategy more closely mimics the interaction of cisplatin with DNA inside human cells, whereas the former strategy can provide more detailed information at atomic resolution.

The latter strategy has been employed by a number of groups to investigate cisplatin nucleosome interactions. Galea and Murray (2002) found that cisplatin had a 1.3-fold tendency to form adducts in the linker region of the nucleosome compared with the nucleosome core. They also found that a number of cisplatin analogs had a larger differential between linker and core (Galea and Murray, 2010). The interaction of other antitumor drugs with nucleosomes has also been investigated; bleomycin is probably the best known example. Bleomycin damage to DNA is affected in a crucial manner by chromatin structure, with bleomycin preferentially causing single- and double-strand breaks in the linker region of the nucleosome.

In this issue, Todd and Lippard (2010) have produced an X-ray crystal structure of a 1,3-d(GpTpG) Pt adduct incorporated into a nucleosome. Surprisingly, the Pt adduct does not appreciably distort the nucleosome structure. The DNA bending caused by the Pt adduct is integrated into the bending required by the DNA to wrap around the histone octamer core. The Pt adduct results in bending toward the major groove; this is synchronous with the nucleosomal bending at this position in the structure. The presence of the Pt adduct also caused directed rotational positioning of the nucleosome core so that the Pt adduct faces inward toward the histone octamer core (Ober and Lippard, 2007). In this protected setting, the adduct is shielded from repair and explains the ten-fold lower efficiency of

repair when the 1,3 Pt adduct is present in a nucleosome (Wang, et al., 2003).

There are several implications from this nucleosome work for the further development of cisplatin analogs with clinical potential. Cisplatin is a relatively small molecule, and most analogs will be larger and may not be able to sterically fit into the nucleosome structure. It is worth noting that carboplatin, which is the main clinically utilized analog of cisplatin, produces exactly the same adduct on DNA as cisplatin. Galea and Murray (2010) showed that increasing the size of a cisplatin analog resulted in a reduced ability to form adducts in the nucleosome core. Cisplatin analogs with an attached intercalator moiety had the largest differential between core and linker adduct formation, probably due to the need of the intercalator to alter the DNA structure before Pt binding. These studies would argue that a successful cisplatin anticancer analog would have to produce a lesion that is similar in size or identity to that of cisplatin. Future molecular modeling of novel cisplatin analogs bound in a nucleosome could be highly beneficial in the development of clinically successful cisplatin analogs.

The 1,2 intrastrand crosslink is the most prevalent crosslink produced by cisplatin, and it would be exciting for Lippard and colleagues to produce an X-ray crystal structure of this adduct. In a previous paper, Ober and Lippard (2008) found that the 1,2 intrastrand Pt crosslink produced more distortion than the 1,3 intrastrand crosslink when present in a nucleosome and hence may result in more restrictive structural requirements for the 1,2 crosslink in a nucleosome.

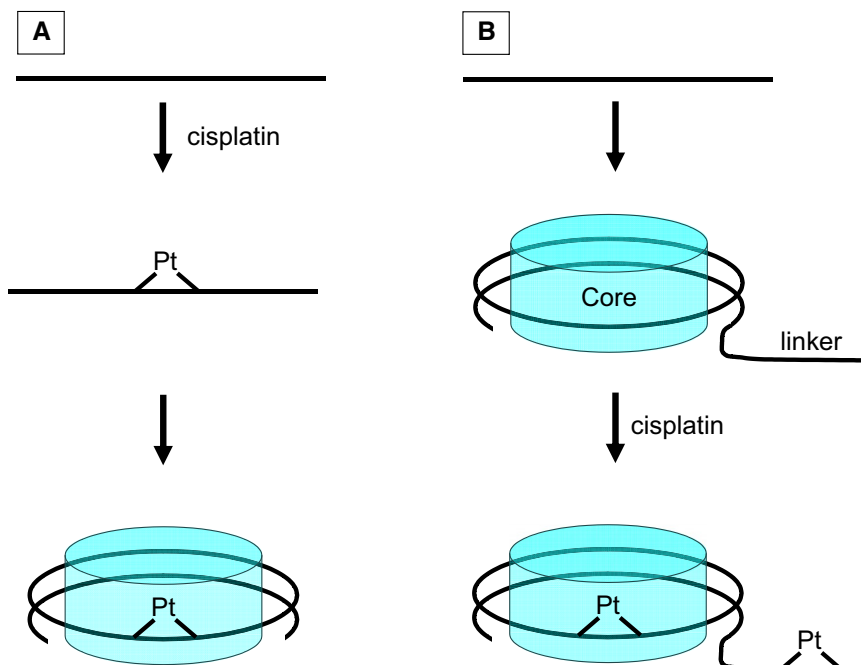In addition, the Pt-DNA crosslink appeared to be located in a region of the

**Figure 1. Two Procedures for Investigation of the Interaction of Cisplatin with Nucleosomal DNA**
(A) Cisplatin adducts are formed on a defined DNA sequence, an octamer of histones is added, and a Pt-nucleosome complex is produced.
(B) A nucleosome is constructed on a defined DNA sequence, the nucleosome is treated with cisplatin, and the Pt-DNA adducts are analyzed.

"crowded" with protein-DNA interactions, in order to see if sections of the nucleosome are more accommodating of the cisplatin adduct.

In conclusion, Todd and Lippard's paper is a landmark paper in our understanding of how cisplatin is an effective cancer chemotherapetic agent. It appreciably adds to our understanding of the interaction of cisplatin with DNA inside cells and has several important implications for the development of more efficient cisplatin analogs.

nucleosome that had a more open structure that could more easily accommodate a Pt crosslink. Only one DNA strand is present at this position compared with two DNA strands in the other three-quarters of the nucleosome structure. It would be interesting to investigate a Pt adduct in a region of the nucleosome that was more

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# Epigenetics Gets Sweeter:
# O-GlcNAc Joins the "Histone Code"

John A. Hanover[1,*]
[1]Laboratory of Cellular and Molecular Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892-0851, USA
*Correspondence: jah@helix.nih.gov
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*O*-GlcNAcylation has now been added to the growing list of histone modifications making up the multifaceted "histone-code" (Sakabe et al., 2010). The sites of *O*-GlcNAc-histone modification hint at a role in chromatin remodeling, thus adding to mounting evidence that *O*-GlcNAc cycling sits atop a robust regulatory network maintaining higher-order chromatin structure and epigenetic memory.

The hexosamine signaling pathway integrates cellular nutrient stores by regulating the synthesis of UDP-GlcNAc, a key metabolite required for the dynamic *O*-GlcNAc modification of nuclear and cytoplasmic proteins. Previous studies have directly linked *O*-GlcNAc cycling to signaling, transcription, and translation, as well as to RNA and protein stability