Evaluation of nucleosome structure alteration and accessibility change caused by platinum-based antineoplastics

(1. Graduate School of Engineering, The University of Tokyo) ○Xuanyu LIAO,[1] Takafumi Furuhata,[1] Ikuma Arakaki,[1] Akimitsu Okamoto[1]

Keywords : Platinum-Based Antineoplastic, Nucleosome, Enzymatic accessibility

The platinum-based antineoplastic agent represented by cisplatin and its platinum analogs, carboplatin and dichloro (1,2-diaminocyclohexane) platinum (DACH-Pt), is one of the major classes of anti-cancer drugs currently. Their mode of action involves covalent binding to purine DNA bases to cause DNA lesion, which primarily leads to cellular apoptosis.[1] However, intracellular pathways that induce cellular apoptosis are different depending on their chemical structures.[2,3] The cause of the difference in apoptotic pathways between platinum-based antineoplastic agents still remains elusive. This is because studies on the effect of platinum-based drugs on DNA have been lacking from the viewpoint of nucleosome and chromatin accessibility of enzymes that governs biochemical reactions on DNA.

Here, we investigated physicochemical and biochemical properties of nucleosome modified with cisplatin and DACH-Pt which are suggested to have different modes of action in cancer treatment. To this aim, we have reconstituted the model nucleosomes which were site-specifically modified with platinum adducts using Plug-and-play method.[4] Then, we evaluated their thermal characteristics to investigate the chemical properties of the nucleosome altered by platinum modification and their differences depending on the chemical structure of the platinum adducts.

1) L. Kelland, *Nat. Rev. Cancer* **2007**, *7*, 573-584. 2) P. M. Bruno *et al*. *Nat. Med.* **2017**, *23*, 461–469. 3) E. C. Sutton *et al*., *J. Am. Chem. Soc*. **2019**, *141*, 18411-18415. 4) D. R. Banerjee *et al*. *J. Am. Chem. Soc*. **2018**, *140*, 8260-8267.