The 127th iCeMS SEMINAR

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13:30-14:30

DNA Repair Pathways— Guardians of the Genome and Targets for Antitumor Therapy

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Venue: 5th Floor Seminar Room (N-531C)
Institute for Chemical Research, Main Building
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DNA repair pathways are essential to counteract the threat of endogenous and exogenous damage to DNA. While the maintenance of genome stability is key to cellular survival and human health, many agents used in antitumor therapy also damage DNA and repair pathways cause resistance to treatment with these agents. This presentation will illustrate our chemical and biological approaches toward understanding these central issues of DNA repair using two examples. The first part will focus on the regulation of the activity of the structure-specific endonuclease ERCC1-XPF in two pathways, nucleotide excision repair (NER) and interstrand crosslink (ICL) repair. Studies in our laboratory have shown how this enzyme is recruited to the two repair pathways through specific protein-protein and protein-DNA interactions. These results will be discussed in the light of the key role ERCC1-XPF plays in the resistance to cisplatin therapy. Furthermore, the mechanisms by which patient mutations in XPF, affecting its roles in NER and ICL repair, respectively, lead to two distinct genetic disorders, xeroderma pigmentosum and Fanconi anemia, will be illustrated. The second part will describe our efforts to synthesize site-specific DNA interstrand crosslinks formed by the therapeutically important cisplatin and nitrogen mustards. Our approach allows for the synthesis major groove ICLs that induce different degrees of bending and distortion in the DNA. Studies of the structure-function relationships of ICL repair that were made possible by these ICLs and the implications of this work for cancer chemotherapy will be discussed.

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