RIKEN SEMINAR

〈13th Epigenetics Seminar Series 2017-18〉

Title

Synthetic chromatin acylation promoted by chemical catalyst systems

Our long-term research goal is developing synthetic catalysts that can surrogate enzymes, and using the chemical reactions promoted by the synthetic catalysts in our body as a new paradigm of medicine (catalysis medicine). This research direction should in turn contribute to the progress in green synthesis of functional molecules of high structural complexity in flasks, including drugs. To do so requires powerful chemical catalysts, which can functionalize stable, multifunctional organic molecules, ranging from small molecules to biomacromolecules, under mild conditions with synthetically valuable selectivity.

Toward this goal, we have developed two chemical catalyst systems promoting various acylations on chromatin. One system comprises a clustered DMAP catalyst (8DMAP) and an octa-arginine (8R)-conjugated acyl donor (3NMD-8R), both exhibiting oligocationic characteristics. Due to the coulombic interactions with polyanionic DNA in nucleosomes, both the catalyst and the acyl donor accumulate on nucleosomes, leading to selective acylation at the histone tails, similar to histone acetyl transferases. The other system comprises a thiol-containing DMAP catalyst (DSH) conjugated with a nucleosome-binding ligand. This catalyst activates chemically stable thioesters (including acetyl-CoA) under physiological conditions, and transfers various acyl groups selectively to the proximate amino groups. Specifically, DSH conjugated with a nucleosome ligand LANA (latency-associated nuclear antigen)-peptide (DSH-LANA) selectively promotes both natural (including acetylation, butyrylation, malonylation, and ubiquitination) and non-natural (azido- and phosphoryl labeling) acylations on histone H2B lysine-120 (K120) in recombinant nucleosomes and/or in native chromatin. The residue-selectivity is predictable based on the structure of the nucleosome-ligand complex. Preliminary biologic applications of those two catalyst systems will be discussed. Our chemical catalyst systems may be versatile tools for dissecting the mechanisms underlying regulation of chromatin epigenetics and functions.

Speaker

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●Live telecast from Wako Main

<Kobe: N701-703 Seminar Room, CDB Bldg. A>

<Yokohama: C210/C212, Central Research Bldg.>

<Tsukuba: Moriwaki Hall>

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