Reconstitution of 'Epi-nucleosomes' with Pinpoint Epigenetic Information

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Epigenetic information on chromatin, such as chemical, reversible and heritable modifications of histones and genomic DNA, play crucial roles in controlling gene expression through alteration of chromatin structure. Epigenetic modifiers/binders are recognized as drug target proteins, particularly after clinical approval of several compounds inhibiting histone deacetylases or DNA methyltransferases as anti-cancer agents. We studied structural and biochemical analyses of human epigenetic factors, such as histone demethylase LSD1 and BET bromodomain protein BRD2, and developed several compounds such as S2101 and BIC1 to inhibit LSD1 and BRD2 proteins, respectively[1-4]. Although epigenetic factors have been widely studied at cellular level through utilization of such compounds and gene knocking-down methods, their biochemical analyses mostly remain at peptide level because of the difficulty in the reconstitution of an epigenetic nucleosome in high purity and high quantity.

We have been developing technology to genetically introduce an epigenetically modified amino acid into a specific site of a protein through 'genetic code expansion'. By taking advantage of this technology along with our unique 'cell-free protein synthesis system', we synthesized histone protein containing acetyl-lysines at designed sites[5], and succeeded to reconstitute epigenetic nucleosomes (epi-nucleosomes) containing designed histone acetylation. In this seminar, I will introduce our technologies regarding reconstitution of 'epi-nucleosomes' with pinpoint epigenetic information.

References

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