Functional Analysis of Histone Modification Enzymes during Chemically Induced Hepatocarcinogenesis

○Shigehiro Osada (Grad. Sch. of Pharm. Sci., Nagoya City Univ.)

Carcinogenesis is induced by accumulation of genetic and epigenetic changes, which lead to cellular dysfunction. It has been clear that epigenetic changes are equally important for the multistage carcinogenesis. The best-studied epigenetic mechanism for cancer development is DNA methylation and less attention has been focused on histone modification. Nucleosome, the fundamental unit of chromatin, consists of approximately 147 base pairs of DNA and histone octamers. Histone modification (acetylation, methylation, phosphorylation, etc.) is important for the regulation of gene function including transcription, DNA replication and DNA repair. Aberrant activity or mis-targeting of chromatin modification enzyme activities leads to unexpected cellular responses and induces carcinogenesis.

In order to address the relation between carcinogenic and toxic activities of chemicals and chromatin modification activities, chemical hepatocarcinogenesis was induced by Solt-Farber procedure, and the expression level of histone acetyltransferases (HATs) in liver was observed. We demonstrated that expression levels of P300 and CBP, cAMP-response element-binding protein binding protein, were decreased during chemical hepatocarcinogenesis, whereas expression of monocytic leukemia zinc finger protein (MOZ), a member of the MYST (MOZ, Ybf2/Sas3, Sas2, and Tip60) acetyltransferase family, was induced. Although MOZ gene frequently is rearranged in leukemia, we were unable to detect MOZ rearrangement in the carcinogenic liver. Next, we examined the effect of MOZ on hepatocarcinogenic-specific gene expression. Glutathione *S*-transferase placental form (GSTP) is a well-known tumor marker that is specifically elevated during hepatocarcinogenesis. We found that exogenous MOZ induced GSTP expression in rat hepatoma H4IIE cells. I will discuss our recent progresses on the aberrantly expressed HATs and tumor maker gene expression.