Involvement of protein methyltransferases and demethylases in oncogenesis

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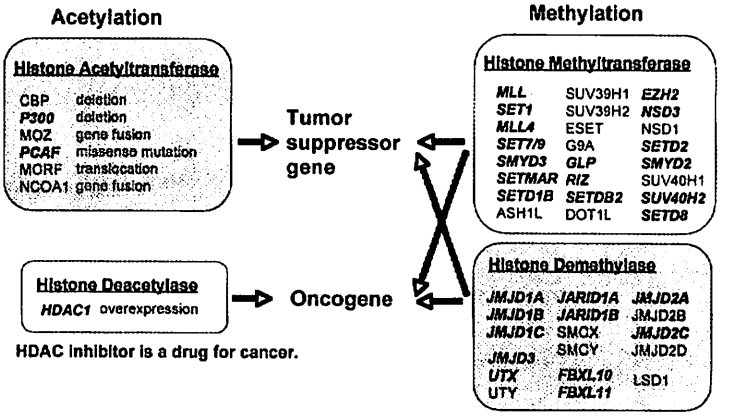
From the tumors of the MuLV-infected Blm mice, we isolated more than twenty candidate tumor suppressor genes that showed the evidences of bi-allelic mutations in the tumors. Those genes included the known tumor suppressor genes and also novel interesting candidates such as Jmjd5 and Fbxl10, the genes encoding JmjC domain containing proteins. Knockdown of Jmjd5 or Fbxl10 expression by each shRNA was shown to confer a mutator phenotype to the cells, suggesting both genes are excellent candidates for tumor suppressor genes.

Recently, several laboratories have shown that the JmjC domain is the signature motif for histone demethylase. Post-translational modification of histones such as acetylation and methylation has been implicated in multiple biological processes including transcription, DNA replication, DNA repair and heterochromatin formation. By the large-scale retroviral insertional mutagenesis, we have so far identified 17 histone methyltransferase genes and 11 histone demethylase genes as potential oncogenes or tumor suppressor genes. These findings provide a unique opportunity to explore the relationship between histone methylation and cancer. Among histone modifications, acetylation has been unambiguously associated with cancer, however, a clear correlation of methylation and cancer has not been conclusively demonstrated yet. Since the inhibitors of histone deacetylases have been developed as anti-cancer drugs, we expect that histone methylation may be the important field to find the new molecular targets for cancer treatment. We have recently found that the expressions of some methyl-modifying enzymes are also deregulated in human lung cancer. Now we are trying to clarify the molecular mechanism of cancer induced by the deregulation of protein methylation.



Target genes identified by retroviral tagging from mouse tumors

Protein methytransferases and demethylases are good candidates of novel molecular targets for cancer