がんエピゲノムの解析と診断・治療への応用

Dissection of cancer epigenome as diagnostic and therapeutic targets

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Cancer is fundamentally a genetic and epigenetic disease that requires the accumulation of genomic alterations that inactivate tumor suppressors and activate proto-oncogenes. In addition to genetic mutation or allelic loss, epigenetic gene silencing associated with DNA methylation is recognized as an alternative mechanism by which tumor suppressor genes are inactivated. For example, we have reported that DNA methylation frequently alters the activity in a number of important signaling pathways by silencing expression of genes encoding Wnt antagonists, negative Ras effectors, and p53 targets.

We also found that epigenetic alterations play an important role in the dysregulation of non-coding RNA genes in cancer. Through performing epigenome screening, we identified a number of microRNAs (miRNAs) epigenetically silenced in cancer cells, and showed that these miRNAs play tumor suppressor roles. In addition, we identified epigenetic dysregulation of long noncoding RNA genes which could play a role in tumorigenesis.

Based on the findings above, we tried to clarify the clinical usefulness of cancer epigenome through translational researches. We showed that aberrant DNA methylation could be a useful biomarker to predict and detect cancers. For instance, methylation of the miR-34b/c gene can be a predictive marker of gastric cancer. By combining colonoscopy and molecular analysis, we found that DNA methylation detected in intestinal wash fluids could be a marker of colorectal cancer. Moreover, we showed reported that urinary DNA methylation is useful to detect bladder cancer and predict its recurrence.

To clarify the clinical implication of genetic and epigenetic alterations in colorectal cancer, we performed integrated analysis of colonoscopic, pathological and molecular characteristics in early colorectal tumors. Through these analyses, we identified a novel surface microstructure of precancerous lesions, which could be a marker to predict colorectal cancers with methylator phenotype. We also proved that our integrated analysis is a powerful tool to unravel novel genetic and epigenetic alterations during colorectal tumorigenesis.

These results suggest that dissection of cancer epigenome could lead to better understanding of carcinogenesis mechanism and to improved diagnosis and treatment of cancer.