Molecular pathogenesis of epigenetic alterations in gastrointestinal cancer and its application to diagnosis and treatment

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【Outline of survey】

Epigenetic alterations such as DNA methylation and histone modification play an important role in inactivation of tumor suppressor genes. However, it remains unclear how methylation contributes to tumor formation and progression. In addition, precise mechanisms of methylation dependent gene silencing are not fully understood. This study aims to understand the molecular mechanisms how epigenetic alterations contribute to tumorigenesis of gastrointestinal cancers. We also try to apply epigenetic alterations to develop novel methods for diagnosis and therapy. To this end, we try to understand molecular mechanisms how DNA methyltransferase inhibitors suppress cancer cells by screening pro-apoptotic genes inactivated by DNA methylation in cancer. We also examine the effects of DNA methyltransferase inhibitors and histone deacetylase inhibitors in vivo, and clarify the most effective drug dose and schedule for therapy. Great attentions have been made to methyltransferase inhibitor worldwide in these days, and there are great demands for experimental results that lead to understand the molecular mechanisms how DNA methyltransferase inhibitors suppress tumor cells. It is also important to develop a screening method to screen more effective inhibitors. Because methylation changes are tumor specific, we can detect alterations in serum or stool. Therefore, DNA methylation can be an important molecular marker for diagnosis of cancer. We try to develop sensitive and high throughput methods to detect DNA methylation, and these methods may be useful to screen the patients with high risk.

【Expected results】

DNA methylation is an epigenetic change that is not associated with change in nucleotide. Therefore, expression of silenced genes can be reversed by treating cells with methyltransferase inhibitors. In the current study, we try to clarify how demethylation of genes occurs in cells, and this information will be useful to develop novel methyltransferase inhibitors. It is also possible to understand the molecular mechanisms of resistance to these drugs. The experimental data obtained in this study will contribute to understand the molecular mechanisms of gastrointestinal cancer, development of novel diagnostic tool, and identification of novel therapeutic strategy. In addition, the information will be useful to understand molecular mechanisms of gene regulation, and epigenetic changes that accompany with inflammation and aging.

【References by the principal researcher】

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【Term of project】 FY 2005 - 2009 | **【Budget allocation】** 85,200,000 yen

【Homepage address】 http://web.sapmed.ac.jp/