Detection of the hypennethylation of MLH1 promoter and its clinical application in endometrial cancer screening

2003 Fiscal Year Final Research Report Summary

Detection of the hypennethylation of MLH1 promoter and its clinical application in endometrial cancer screening

Research Project

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13557137

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

展開研究

Research Field

Obstetrics and gynecology

Research Institution

Kanazawa University

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DNA mismatched repair genes / human MLH1 / hypermethylation of promoter sequences / endometrial cancer / molecular targets / cancer screening program / テロメラーゼ

Research Abstract

Silencing of the MLH1 gene by promoter hypermethylation is the main mechanism underlying the microsatellite instability(MSI) phenotype in endometrial cancers. MSI has a key role in the endometrial carcinogesis where mutations of multiple genes have involved.
We have developed the convenient and sensitive method for the detection of promoter hypermethylation in the region 700bp upstream of MLH1 covering 48 CpG sites. The metylation of these sites has been confirmed by bisulfate sequencing. Metylation status was classified as full(over 80% of CpGs are methylated), partial(10-80%) or nonmethylation(less than 10%). Of endometrial cancers examined, 30% were fully methylated, 25% were partially methylated and 45% were not methylated. Analysis of MLH1 by immunohistochemical methods and of MSI revealed that the degree, rather than region-specific methylation of CpG island is critical for decreased MLH1 expression and the MSI phenotype. Among patients with methylated cancers, almost half patients have contained methylated promoters in their normal endometria with profiles similar to those of cancerous lesions, and these were closely associated with the MSI phenotype. In contrast, only a few cases of normal endometria from patients without endometrial malignancies harbored methylated promoters. The present study suggests that hypermetylation of the MLH1 promoter is frequent in the histologically-cofirmed normal endometrium adjacent to cancerous lesions, supporting the notion that hypermethylation of DNA-mismatch repair genes is the initial step that triggers the following various genetic events in the endometrial carcinogenesis. Of course, the genetic events could be candidates for molecular targets in the diagnosis and treatment.
Detection of some molecular targets in a tiny clinical sample might be a useful diagnostic aid in cancer screening.

Research Products (24 results)

All | Other

All | Publications (24 results)

[Publications] Wang Z, Kyo S, Maida Y, Takakura M, Tanaka M, Yatabe N, Koike K, Hayakawa J, Ohmichi M, Inoue M: "Tamoxifen regulates human telomerase reverse transcriptase(hTERT) gene expression differently in breast and endometrial cancer cells."Oncogene. 21. 3517-3524 (2002)

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