遺伝子変異メチル化の定量的検出法の開発と子宮内膜癌発生予知への臨床応用

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雑誌名	平成15(2003)年度 科学研究費補助金 基盤研究(B)研究成果報告書概要
巻	2001-2003
ページ	2p.
発行年	2005-04-18
URL	http://doi.org/10.24517/00056914

2003 Fiscal Year Final Research Report Summary

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

Research Project

Project/Area Number

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

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Project Period (FY)

2001 – 2003

Keywords

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)

[Publications] Maida Y, Kyo S, Kanaya T, Wang Z, Takakura M, Yatabe N, Tanaka M, Nakamura M, Hisamoto K, Ohmichi M, Gotoh N, Inoue M: "Direct activation of telomerase by EGF through Ets - mediated transactivation of TERT via MAP kinase signaling pathway."Oncogene. 21. 4071-4079 (2002)

[Publications] Yatabe N, Kyo S, Kondo S, Kanaya T, Wang Z, Maida Y, Takakura M, Nakamura M, Tanaka M, Inoue M: "2-5A antisense therapy directed against human telomerase RNA inhibits telomerase activity and induces apoptosis without telomere impairment in cervical cancer cells."Cancer Gene Ther. 9. 624-630 (2002)

[Publications] Maida Y, kyo S, Kanaya T, Wang Z, Tanaka M, Yatabe N, Nakamura M, Inoue M: "Is the telomerase assay useful for screening of endometrial lesions."Int J Cancer. 100. 714-718 (2002)

[Publications] Sasagawa T, Robert CR, Khadijeh KA, Sakai A, Inoue M: "Mucosal immunoglobulin-A and G responses to oncogenic human papillomavirus capsids."Int J Cancer. 104. 328-335 (2003)

[Publications] Kyo S, Masutomi K, Maida Y, Kanaya T, Yatabe N, Nakamura M, Tanaka M, Takarada M, Sugawara I, Murakami S, Taira T, Inoue M: "Significance of immunological detection of human telomerase reverse transcriptase."Am J Pathol. 163. 859-867 (2003)

[Publications] Kanaya T, Kyo S, Maida Y, Yatabe N, Tanaka M, Nakamura M, Inoue M: "Frequent hypermethylation of hMLH1 promoter in normal endometrium of patients with endometrial cancers."Oncogene. 22. 2352-2360 (2003)

[Publications] Tanaka M, Kyo S, Kanaya T, Yatabe N, Nakamura M, Maida Y, Okabe M, Inoue M: "Evidence of the monoclonal composition oh human endometrial epithelial glands and mosaic pattern of clonal distribution in luminal epithelium."Am J Pathol. 163. 295-301 (2003)

[Publications] Kyo S, Masutomi K, Maida Y, Kanaya T, Yatabe N, Nakamura M, Takakura M, Sugawara I, Murakami S, Taira T, Inoue M: "Successful immotalization of endometrial glandular cells with normal structural and functional characteristics,"Am J Pathol. 163. 2259-2269 (2003)

[Publications] Kyo S, Kanaya T, Inoue M: "Role of hMLH1 gene hypermethylation in endometrial carcinogenesis. In : Kuramoto H, Nishida M(Eds.)"Cell and Molecular Biology of Endometrial Carcinoma. 232-244 (2003)

[Publications] Nakamura M, Kyo S, Kanaya T, Yatabe N, Maida Y, Ishida Y, Fujii C, Kondoh T, Inoue M, Mukaida N: "hTERT-promoter based tumor specific expression of MCP-1 effectively sensitize cervical cancer cells to a low dose of cisplatin"Cancer Gene Therapy. 11. 1-7 (2004)

[Publications] Yatabe N, Kyo S, Maida Y, Ishida Y, Nishi H, Nakamura M, Kanaya T, Tanaka M, Isaka K, Ogawa S, Inoue M: "HIF-1 mediate activation of telomerase in cervical cancer cells"Oncogene. (In press).

[Publications] Inoue M.: "Current molecular aspects of the carcinogenesis of the uterine endometrium."Int J Gynecol Cancer. 11. 339-348 (2001)

[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)

[Publications] Kyo S, Inoue M.: "Complex regulatory mechanisms of telomerase activity in normal-and cancer cells. How can we apply them for cancer therapy?"Oncogene. 21. 688-697 (2002)

[Publications] Kyo S, Inoue M.: "How to inhibit telomerase activity for cancer therapy."Current Med.Chem.Anti-Cancer Agents. 2. 613-626 (2002)

[Publications] Maida Y, Kyo S, kanaya T, Wang Z, Tanaka M, Yatabe N, Nakamura M Inoue M.: "Is the telomerase assay useful for screening of endometrial lesions."Int.J.Cancer. 100. 714-718 (2002)

[Publications] Kyo S, Masutomi K, Maida Y, Kanaya T, Yatabe N, Nakamura M, Tanaka M, Takarada M, Sugawara I, Murakami S, Taira T, Inoue M.: "Significance of immunological detection of human telomerase reverse transcriptase."Am J Pathol. 163. 859-867 (2003)

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[Publications] Kyo S, Masutomi K, Maida M, Kanaya T, Yatabe N, Nakamura M, Takakura M, Suga¥yara I, Murakami S, Taira T, Inoue M.: "Successful immortalization of endometrial glandular cells with normal structural and functional characteristics."Am J Pathol. 163. 2259-2269 (2003)

[Publications] Tanaka M, Kyo S, Kanaya T, Yatabe N, Nakamura M, Maida Y, Okabe M, Inoue M.: "Evidence of monoclonal composition of human endometrial epithelial glands and mosaic pattern of clonal distribution in human epithelium."Am J Pathol. 163. 295-301 (2003)

[Publications] Kyo S, Kanaya T, Inoue M.: "Role of hMLH1 gene hypermethylation in endometrial carcinogenesis."Cell and Molecular Biology of Endometrial Carcinoma, (kuramoto H, Nishida M(Eds.)(springer-Verlag, New York). 232-244 (2003)

[Publications] Nakamura M, Kyo S, Kanaya T, Yatabe N, Maida Y, Ishida Y, Fujii C, Kondoh T, Inoue M, Mukaida N.: "hTERT-promoter-based tumor specific expression of MCP-1 effectively sensitize cervical cancer cells to a low dose of cisplatin."Cancer Gene Therapy. 11. 1-7 (2004)

[Publications] Yatabe N, Kyo S, Maida Y, Ishida Y, Nishi H, Nakamura M, Kanaya T, Tanaka M, Isaka K, Ogawa S, Inoue M.: "HIF-1 mediated activation of telomerase in cervical cancer cells."Oncogene. (in press. (2004)

URL: https://kaken.nii.ac.jp/report/KAKENHI-PROJECT-13557137/135571372003kenkyu_seika_hokoku_

Published: 2005-04-18