IS-AC-2-1 Methylation analysis of DNA mismatch repair genes using DNA derived from peripheral blood of patients with endometrial cancer：epimutation in endometrial carcinogenesis

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[Objective] Germline mutation of DNA mismatch repair (MMR) genes (MLH1, MSH2 and MSH6) is a cause of Lynch syndrome. Methylation of MLH1 and MSH2 has been detected in peripheral blood cell of Lynch syndrome patients with colorectal cancer. This germline methylation is referred to as epimutation, but has not been studied in patients with endometrial cancer. We examined to detect epimutation of patients with endometrial cancer. [Methods] The subjects were 196 patients with endometrial cancer. After approval of the institutional review board, we analyzed methylation of MLH1, MSH2 and MSH6 promoter regions of peripheral blood cell by methylation-specific PCR. Family history was analyzed in each case with epimutation. [Results] MLH1 epimutation was detected in 1/196 patients (0.5%), including in 1/55 (1.8%) with an onset age of less than 50. The patient with MLH1 epimutation developed endometrial cancer at 46 years old and complicated with colorectal cancer, but she did not meet the revised Amsterdam Criteria. No case had epimutation of MSH2 or MSH6. [Conclusion] MLH1 epimutation was detected in a patient with endometrial cancer and may be a cause of endometrial carcinogenesis. Our results indicate that it is important to check for epimutation in endometrial cancer patients without germ cell mutation of MMR genes.

IS-AC-2-2 Anti-tumor effect of inhibition of DNA damage response proteins, ATM and ATR, in endometrial cancer cells

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[Objective] Activation of DNA repair pathways is one of the factors for resistance to chemotherapy in cancer cells. Targeting DNA damage response (DDR) proteins, such as ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), might enhance the cytotoxic effects of chemotherapy. The objective of this study is to clarify the anti-tumor effect of inhibitors to ATM or ATR, combined with doxorubicin in endometrial cancer cells. [Methods] Four endometrial cancer cells (HEC-6, HEC-108, HEC-1B, HEC-50B) were treated with doxorubicin in the presence or absence of an ATM inhibitor (KU55933) or an ATR inhibitor (VE821). Their anti-tumor effects were evaluated by colony formation assay. The levels of phosphorylation of DDR proteins were analyzed by immunoblotting. [Results] The combination of doxorubicin and KU55933, but not VE821, suppressed the number of colony formation, compared with doxorubicin alone. Doxorubicin induced accumulation of p-ATM, p-Chk2 and γ-H2AX, but did not affect the levels of p-ATR and p-Chk1 in immunoblotting. The up-regulation of p-ATM, p-Chk2 and γ-H2AX by doxorubicin was cancelled by KU55933 in a dose dependent manner. [Conclusion] Increased levels of the p-ATM and p-Chk2 might be associated with resistance to doxorubicin. Combination of doxorubisin and an ATM inhibitor can be a promising therapy in endometrial cancer.

IS-AC-2-3 An analysis of short-term recurrent cases following medroxyprogesterone acetate (MPA) therapy for endometrial cancer and atypical endometrial hyperplasia

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[Objective] Medroxyprogesterone acetate (MPA) therapy is a fertility preserving therapy for patients with endometrial cancer (EC) and atypical endometrial hyperplasia (AEH). The problem of this therapy is high recurrent rate. The aim of our study is to clarify the characteristics of cases with short-term recurrence (SR). [Methods] Our study recruited 96 cases (29 AEH and 67 EC) with intrauterine recurrence following MPA therapy from 1998 to 2011. MPA therapy was continued until tumor disappearance, and endometrial biopsy were performed every 3-4 months due to follow-up. We defined SR and long-term recurrence (LR) as recurrence within 6 months and after 12 months after initial MPA therapy. This study was approved by an ethical committee of our institution. [Results] The median treatment period and recurrence free interval (RFI) were 197 days (56-755) and 285 days (41-2171). SR and LR were occurred in 28 cases (29%) and 38 cases (40%). Polycystic ovary (PCO) was complicated more frequently in SR group than in LR group ($p=0.04$). The duration of re-MPA therapy for recurrent disease in SR group was longer than that in LR group ($p<0.01$). However the RFI following re-MPA therapy was no significantly difference between both groups. [Conclusion] SR following MPA therapy may be associated with PCO. Re-MPA therapy after intrauterine recurrence can be performed even in SR group.