I S—33 *PTEN* Alterations in Endometrial Carcinoma and Hyperplasia

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[Objectives] Loss of heterozygosity in chromosome 10q is frequently observed in endometrial cancer. A candidate tumor-suppressor gene, called *PTEN* or *MMAC*1, has been recently isolated from the 10q 23-24 region and found to be mutated in several cancer types that display LOH in this region including endometrial carcinoma. This study was designed to further determine a role of *PTEN* gene in the development of endometrial carcinoma.
[Methods] Informed consents were obtained from all patients. Genomic DNA was extracted from 31 cases of endometrial carcinoma (ECs), 12 cases of simple hyperplasia, 10 cases of complex hyperplasias without atypia and 20 cases of complex hyperplasias with atypia. The entire exons of *PTEN* (exons 1-9) were amplified by PCR using 11 intron-based primer pairs. Single-strand conformation polymorphism was performed as an initial screen. Mutations were subsequently confirmed by direct sequencing.
[Results] Mutations in the *PTEN* gene were observed in 6 of 31 (19%) endometrial carcinomas (three of 17 ECs of grade 1 and two of 9 Ecs of grade 2), 4 of 20 (20%) complex hyperplasia with atypia, but not in any 10 complex hyperplasia without atypia or in 12 simple hyperplasias. Of 10 mutations, eight were in exon 7, one was in exon 1 and one was in exon 4.
[Conclusions] Mutations in the *PTEN* gene plays an important role and perhaps occur as an early event in endometrial carcinogenesis.

I S—34 Expression of a functional endothelin (ET_A) receptor in human leiomyoma

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Objective: In this study, we investigated the biological significance of endothelin (ET) receptor subtypes (ET_A and ET_B) in cell growth of the leiomyoma and myometrium of premenopausal women.
Material and Methods: Specific ET receptor subtypes in human leiomyomas and myometrium were characterized using quantitative receptor and emulsion autoradiography with increasing concentrations of unlabeled ET-1, BQ-123 (a selective antagonist for the ET_A receptor) and S6c (a selective agonist for the ET_B receptor). To test the effect of ET-1, S6c, oestradiol and medroxyrogesterone on stimulation of DNA synthesis in culture of human leiomyoma cells, ^{3}H-thymidine incorporation studies were done.
Results: A single class of high-affinity ^{125}I-ET-1 binding sites was localized in all leiomyoma tissue studied (K_d: 0.53 nM). We identified the presence of both ET_A and ET_B receptor subtypes in the smooth muscle cells of normal myometrium and a higher concentration of ET_A receptor in the leiomyomas. Incubation of leiomyoma cells with increasing concentrations (10^{-13} to 10^{-7} M) of ET-1 and estradiol, induced a marked elevation of DNA synthesis in a dose-dependent manner. During this period, ^{3}H-thymidine incorporation into cells increased about 200% to 300%. Medroxyprogesterone and S6c, failed to stimulate ^{3}H-thymidine incorporation in concentrations up to 10^{-7} M.
Conclusions: The results suggest that the specific ET_A receptor may play an important role during the proliferation of leiomyoma cells. The ET_A receptor, expressed in human leimyomas *in vivo*, is probably associated with autocrine/paracrine mechanisms coupled to DNA synthesis. Also, it may be possible that the ET_A receptor expressed may play an important role during the growths of this tumor, presumably by interacting with the ovarian steroids and other growth factors.