

Epigenetic fingerprint in endometrial carcinogenesis: The hypothesis of a uterine field cancerization

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Transcriptional silencing by CpG island hypermethylation plays a critical role in endometrial carcinogenesis. In a collection of benign, premalignant and malignant endometrial lesions, a methylation profile of a complete gene panel, such steroid receptors (ER α , PR), DNA mismatch repair (hMLH1), tumor-suppressor genes (CDKN2A/P16 and CDH1/E-CADHERIN) and WNT pathway inhibitors (SFRP1, SFRP2, SFRP4, SFRP5) was investigated in order to demonstrate their pathogenetic role in endometrial lesions. Our results indicate that gene hypermethylation may be an early event in endometrial endometrioid tumorigenesis. Particularly, ER α , PR, hMLH1, CDKN2A/P16, SFRP1, SFRP2 and SFRP5 revealed a promoter methylation status in endometrioid carcinoma, whereas SFRP4 showed demethylation in cancer. P53 immunostaining showed weak-focal protein expression level both in hyperplastic lesions and in endometrioid cancer. Non-endometrioid cancers showed very low levels of epigenetic methylations, but strong P53 protein positivity. Fisher exact test revealed a statistically significant association between hMLH1, CDKN2A/P16 and SFRP1 genes methylation and endometrioid carcinomas and between hMLH1 gene methylation and peritumoral endometrium ($p < 0.05$). Our data confirm that the methylation profile of the peritumoral endometrium is different from the altered molecular background of benign endometrial polyps and hyperplasias. Therefore, our findings suggest that the methylation of hMLH1, CDKN2A/P16 and SFRP1 may clearly distinguish between benign and malignant lesions. Finally, this study assessed that the use of an epigenetic fingerprint may improve the current diagnostic tools for a better clinical management of endometrial lesions.