

## **Sessile Serrated Adenomas of the Colon Are Associated with Methylation Induced Loss of Cdx2 Expression**

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**Background:** Sessile serrated adenomas (SSAs) are generally characterized by histologic features of gastric mucosa, the immunophenotypic gain of expression of gastric type markers such as Sox2, Muc5A and Muc6, and loss of expression of the intestine-specific transcription factor Cdx2. Our goal was to determine the methylation status of Cdx2 and correlate this parameter to Cdx2 expression in serrated polyps of the colorectum with and without neoplastic potential.

**Design:** We obtained paraffin-embedded samples of hyperplastic polyps (HP) and sessile serrated adenomas (SSA) from the Surgical Pathology Archives. All samples were reviewed and classified by the criteria of Torlakovic et al. (AJSP 2003) into serrated lesions with and without malignant potential for correlation with clinicopathologic features of each patient. Immunohistochemical labeling for Cdx2 was performed using standard methods, and scored for the presence and absence of nuclear labeling as well as the distribution of positive labeling in each polyp. DNA was also extracted from each polyp, bisulfite treated and used for methylation specific PCR (MSP) of the CDX2 promoter. Distributions were compared using the Student's T-test and frequencies were compared using the Chi-squared test, or the Fisher exact test for sample sizes <5. p-values 0.05 were considered significant.

**Results:** A total of 31 SSAs (19 with and 12 without associated low grade dysplasia, LGD) and 17 HPs from 48 patients were studied. There was no significant difference in age (57.59.5yrs vs 61.69.5yrs) or gender (8F:7M vs 16M:16F) among patients with HP versus SSA. However, SSAs were more frequently located in the right/transverse colon (29/31) compared to HPs (1/18, p=0.0001). MSP analyses indicated promoter hypermethylation of the CDX2 promoter in 20/48 polyps (42%). When promoter methylation was compared to polyp histology, the frequency of CDX2 methylation was 3/18 HPs (17%), 4/12 SSAs (25%) and 14/19 SSAs with associated LGD (74%) (p=0.003). CDX2 promoter methylation was associated with loss of Cdx2 labeling in the same serrated polyp. However, Cdx2 labeling was also lost in serrated polyps with normal promoter methylation, suggesting additional mechanisms underlie loss of Cdx2 expression.

**Conclusions:** Loss of Cdx2 expression is frequent in SSAs and in some polyps may be due to CDX2 promoter hypermethylation. Cdx2 loss may contribute to the initiation or progression of sessile serrated adenomas to colorectal adenocarcinoma.