Microsatellite instability of selective target genes in HNPCC-associated colon adenomas.

Abstract:
Microsatellite instability (MSI) occurs in most hereditary nonpolyposis colorectal cancers (HNPCC) and less frequently in sporadic tumors as the result of DNA mismatch repair (MMR) deficiency. Instability at coding microsatellites (cMS) in specific target genes causes frameshift mutations and functional inactivation of affected proteins, thereby providing a selective growth advantage to MMR deficient cells. At present, little is known about Selective Target Gene frameshift mutations in preneoplastic lesions. In this study, we examined 30 HNPCC-associated MSI-H colorectal adenomas of different grades of dysplasia for frameshift mutations in 26 cMS-bearing genes, which, according to our previous model, represent Selective Target genes of MSI. About 30% (8/26) of these genes showed a high mutation frequency (> or =50%) in colorectal adenomas, similar to the frequencies reported for colorectal carcinomas. Mutations in one gene (PTHL3) occurred significantly less frequently in MSI adenomas compared to published mutation rates in MSI carcinomas (36.0 vs 85.7%, P=0.023). Biallelic inactivation was observed in nine genes, thus emphasizing the functional impact of cMS instability on MSI tumorigenesis. Some genes
showed a high frequency of frameshift mutations already at early stages of MSI colorectal tumorigenesis that increased with grade of dysplasia and transition to carcinoma. These include known Target Genes like BAX and TGFBR2, as well as three novel candidates, MACS, NDUFC2, and TAF1B. Overall, we have identified genes of potential relevance for the initiation and progression of MSI tumorigenesis, thus representing promising candidates for novel diagnostic and therapeutic approaches directed towards MMR-deficient tumors.