Letter to the Editor

Spectral karyotyping and SNP microarray analysis define uniparental disomy (UPD) as a novel mutational mechanism in MSI- and CSI-colorectal cancers *

Sir,

Spectral karyotyping greatly improves recognition and definition of chromosomal aberrations [1]. In previous studies, we applied spectral karyotyping to a number of colorectal cancer cell lines derived from metastatic and primary tumors [2]. As expected, we observed complex marker chromosomes and pronounced chromosomal instability (CSI) in tumors devoid of microsatellite instability. In contrast, microsatellite instable (MSI) tumors uniformly displayed stable karyotypes [3]. Likewise, a newly characterized adenoma cell line lacked karyotypic alterations [4].

Recently, we complemented our spectral karyotyping studies by SNP-array analyses of multiple MSI- and CSI-cell lines [5]. Results were verified by the analysis of 15 primary MSI- and 15 CSI-tumors (unpublished data). SNP analysis greatly facilitated the interpretation of complex chromosomal alterations of CSI-cell lines. Monoallelic regions could be correlated with sites of inactivated tumor suppressor genes and activated oncogenes. Some of the genes relevant for colon carcinogenesis are inactivated by allelic loss (e.g. p53, SMAD4). Monoallelic regions with increased copy number may represent oncogene loci activated by allele-specific amplification (e.g. Cyclin D1 in CSI-cell lines). Monoallelic regions without copy number alterations fulfill the criteria of uniparental disomy (UPD). In the tested colorectal cell lines and primary tumors, UPD appears to instrumental in the inactivation of early-acting tumor suppressor genes, including APC in CSI- and hMLH1/hMSH2 in MSI-cellular phenotypes. Our results suggest that following initial mutational inactivation of one of the APC or hMLH1/hMSH2 alleles the remaining wild-type allele is deleted, concomitant with re-duplication of the mutated allele. Alternatively, UPD may have arisen through some type of gene conversion. In addition to the APC and hMLH1/hMSH2 chromosomal sites, 6pter → p22 was also found to be frequently altered by UPD in primary MSI tumors, suggesting a candidate tumor suppressor gene in this region.

We conclude that the combination of spectral karyotyping and SNP-array analysis permits the detection of UPD. UPD represent a novel type of genetic change that may cause inactivation of early acting tumor suppressor genes involved in the generation of microsatellite- and chromosomal instability of colorectal tumors.

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References
