Distinctive Spatiotemporal Stability of Somatic Mutations in Metastasized Microsatellite-stable Colorectal Cancer.

Abstract:
A multistep model of disease progression and genomic landscape has been firmly established for colorectal cancer (CRC) primaries, but the genetic makeup of related metastases and the dynamics of genetic changes during metastatic progression are scarcely known. To address these issues, we used multigene high-coverage next-generation sequencing of 24 microsatellite-stable CRC primaries, matched normal tissue, and related multiple metastases to nodes, liver, lung, and brain with a CRC-specific gene panel to infer the degree of clonal evolution during metastatic progression of the disease. Somatic mutations were detected in 40% of CRC-related genes, and we observed a striking 100% genetic concordance between primary and multiple secondary sites for APC, KRAS, FBXW7, PIK3CA, BRAF, SMAD4, and ACVR2A. Except for true de novo mutations in 4 cases (affecting SYNE1, CTNNB1, TP53, and PTEN), all remaining cases (84.4%) shared the genetic lesions of the primary tumors with all investigated metastases irrespective of the site of metastasis or time lapse between primary tumor resection and the occurrence of metastatic spread. Putative biomarkers and druggable
targets were identified in 25% of the cases. Our data proves that genetic alterations occurring early in CRC carcinogenesis are remarkably stable during metastatic progression, indicating (i) a very low degree of genetic heterogeneity between primary and multiple secondary sites with respect to CRC driver mutations and (ii) that genetic interrogation of archived primary tumor samples appears to be sufficient for the application of cancer precision medicine in the metastatic setting.