

DNA copy-number alterations underlie gene expression differences between microsatellite stable and unstable colorectal cancers

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Abstract

About 10-15% of colorectal cancers (CRCs) display microsatellite instability (MSI) caused by defective DNA mismatch repair. MSI cancers have characteristic clinical and genetic features, and generally have a better prognosis than microsatellite stable (MSS) tumours. To explore the differences between these two types of tumours, we evaluated changes in gene expression from DNA microarray data that occur consistently in several published samples of primary CRCs and cell lines plus our own data (89 MSI and 140 MSS CRCs). We found good concordance of up- or down-regulation of MSI-associated genes between independent studies of primary CRCs and CRC cell lines ($P < 0.001$ for all pair-wise comparisons). Comparison of array-based CGH and gene expression data revealed that MSI-associated gene expression changes broadly reflect systematic differences in DNA copy-number between (typically near-diploid) MSI tumours and (generally aneuploid) MSS tumours. Divisive analysis clustering based on ranked gene expression intensities of concordant genes successfully separated additional samples into MSI and MSS groups. Classification of single test samples was achieved by scoring against a common reference set, with a sensitivity of 96% and specificity of 85%. We expect this methodology to be useful for constructing other gene-based classifiers that are robust for data from multiple laboratories.

Keywords: Colorectal Cancer, Microsatellite Instability, Gene Expression Signature