Analysis of sporadic colorectal cancer using array-based comparative genomic hybridization

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ABSTRACT

Colorectal cancer is one of the most common cancers in Denmark and in the Western world in general, and the prognosis is generally poor. Colorectal cancer is placed third after lung and breast cancer as far as cancer-related death is concerned. Choice of therapy and prognostic considerations still largely depend on pathological staging. However, in recent years array-based technologies and other molecular diagnostic approaches have proved to be very promising tools in the clinical handling of most, if not all, cancers. Array-based comparative genomic hybridization (array CGH) is a relatively new method that enables the detection of copy number changes in a whole-genome approach and is now widely used in cancer research.

Approximately 95% of all cases of colorectal cancer are sporadic. According to the traditional molecular classification of sporadic colorectal cancer, chromosome instable colorectal cancers constitute approximately 85% of sporadic cases, whereas microsatellite instable cases constitute the remaining 15%. Chromosome instable cancers are characterized by gross chromosomal changes as for example copy number alterations, loss of heterozygosity, translocations and inversions. Microsatellite instable cancers are generally characterized by more subtle genomic changes caused by mismatch repair deficiency. These two subtypes of sporadic colorectal cancer do not only differ with respect to molecular profiles, as it has been established that they also differ with respect to several clinicopathological parameters, including prognosis.

The main aims of this PhD project were to compare sporadic chromosome instable and microsatellite instable colorectal cancers with respect to copy number changes using array CGH and to identify potentially important tumour suppressor genes and oncogenes in genomic regions with frequent copy number changes.

The 40 sporadic chromosome instable and 20 sporadic microsatellite instable colorectal cancers analyzed in this study were found to differ significantly at several points, e.g. the chromosome instable samples displayed significantly more copy number aberrations and were generally copy number altered in a higher proportion of the tumour genome than the microsatellite instable samples. Several genomic regions with frequent number changes were identified in samples. The regions harbour many known important and potentially important tumour suppressor genes and oncogenes.

In conclusion, this study strengthened the position of array CGH as a powerful method in the study of molecular and clinical aspects of colorectal cancer.