GENETIC ANALYSES OF TUMOR PROGRESSION IN COLORECTAL CANCER

Kristina Lagerstedt

Department of Surgery, Institute of Clinical Sciences, Department of Chemistry,Institute of Biomedicine, The Sahlgrenska Academy at University of Gothenburg, Sweden, 2009

ABSTRACT

Colorectal tumors are responsible for more than 600 000 deaths per year worldwide and thereby constitute the second most common cause of cancer related mortality. Early detection is related to improved prognosis and identification of genetic biomarkers would meliorate available diagnostic tools. Existing tumor classification systems lack precise monitoring within individual tumor stages in relation to progression. Therefore, we performed genetic characterization of tumor progression by analyses of colorectal tumors and normal colon mucosa. We used combined microarray analysis to obtain a set of candidate biomarkers, starting with genome-wide DNA analyses to screen for tumor-specific aberrant DNA patterns followed by correlations to the associated changes in mRNA and microRNA expression. We also investigated the relation between functional p53 and tumor progression as well as survival in patients with colorectal cancer (CRC). Furthermore, we used high resolution oligonucleotide array based CGH to identify nonpolymorphic structural variation in DNA from normal colon biopsies from patients with confirmed CRC to reveal candidate regions with association to putative familial CRC genetic variants.

Colorectal tumor progression is proposed to follow a step-wise transformation from normal cells into malignant tumors, and therefore we used different stages within this model to summarize our results, in terms of genetic events of potential importance. First, gain in parts of chromosome 20 encompassing *AURKA*, as well as alterations in *p53* (17p13.1), may be involved in the development from adenoma to carcinoma. Second, loss of 18q and gain of 8q harboring *SMAD7* and *PTP4A3* appear to rise during progression defined as early (Dukes A and B) to late (Dukes C and D) tumor stage. Third, distant metastatic potential may be associated to loss of 8p and increased expression of miR-373. Fourth, putative structural variants observed in normal colon mucosa may predispose for the onset of malignant transformation in familial sporadic CRC. Finally, there is a clear relationship between increased properties of aberrant DNA content as well as the number of combined genetic events and tumor progression.

We conclude that correlated changes in DNA and RNA abundance may represent a robust rationale for selection of genetic biomarkers. Moreover, our results also suggest that Dukes D tumors possibly develop in a way that does not fit into the stepwise progression model, illustrated by earlier onset and less genetic aberrations. These results represent a set of genetic events that can hopefully contribute to improved procedures considering diagnosis and prognosis in CRC patients by providing genetic biomarkers.

Keywords: colorectal cancer, tumor progression, microarray, DNA aberrations, structural variation

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Kristina Lagerstedt

Fakultetsopponent:
Professor Dan Grandér
Institutionen för Onkologi & Patologi, Cancercentrum Karolinska
Karolinska Universitets sjukhuset, Stockholm, Sverige

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