Synopses of papers

Chinese and Irish Advanced Gastric Carcinomas Have a High Incidence of APC Gene Abnormalities.

D Butler, A Graze, M Leadz and E Kay.
Department of Pathology, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin 9.

The adenomatous polyposis coli gene (APC) is commonly mutated in a number of cancers including Familial Adenomatous Polyposis (FAP). The gene product is a cytoplasmic protein that plays a role in cellular adhesion and intercellular communication. Advanced gastric carcinomas from 49 patients, 23 Chinese and 26 Irish, were selected from pathology files in Shenyang, China and Dublin, Ireland. PCR was used to amplify DNA extracted from microdissected tissue using three fluorescently labelled microsatellite markers flanking and internal to the APC gene. Loss of heterozygosity (LOH) and microsatellite instability (MI) were detected using a Visible Genetics Open Gene DNA Sequencer. The relationship between APC gene deletion and the following clinicopathological parameters were evaluated: 1) Patient nationality; 2) Patient sex and 3) Tumour differentiation.

Overall 65.3% of gastric carcinoma cases had LOH at one or more microsatellite loci. More of the Irish patients had LOH (59.2%) when compared with the Chinese patients (0.9%, P > 0.05). Microsatellite instability was recorded in 12.2% of patients. The frequency of deletion at the DSS2 locus was found to be statistically different between the Chinese and Irish patients (P < 0.05).

The finding of such a high percentage of APC abnormalities in the advanced gastric carcinoma cases examined, highlights the importance of this region in the progression of gastric cancers.

Is dietary folate acid- and alcohol intake associated with promotent methylation of tumor suppressor- and DNA repair genes in sporadic colorectal cancer?

Manon van Engeland1, Anton de Goeij1, Matty Weijenberg1, Adriana de Bruin1, Piet van den Brand2, Stephen Baylin3 and James Herman4. Departments of Pathology1 and Epidemiology4, University Maastricht, The Netherlands; Johns Hopkins Oncology Center1, Baltimore, Maryland, USA.

Sporadic colorectal cancer (CRC) is characterized by genetic alterations as well as epigenetic changes. The latter comprise global hypomethylation of the genome and promoter hypermethylation of genes involved in carcinogenesis. Epidemiologic studies point to diet as an important risk factor for sporadic CRC. However, the reported associations between dietary factors and the occurrence of genetic and epigenetic changes are weak or nonexistent. Colorectal carcinogenesis has been shown to be associated with promoter hypermethylation of several tumor suppressor genes and DNA repair genes. This aberrant methylation is assumed to be influenced by folate acid and alcohol intake.

The purpose of this explorative study is to determine the methylation status of promoter regions of the tumor suppressor genes p16, p16, APC, RASSF1A and PHIT as well as the DNA repair genes MMR and O6-MGMT in a series of 122 CRC samples from patients with high or adequate folate acid/low alcohol intake (n=61) vs. low folate acid/high alcohol intake (n=61). The colorectal carcinomas for this study are derived from the prospective Netherlands Cohort Study on Diet and Cancer, which started in 1986 and includes 25,279 men and 62,573 women who completed a self-administered questionnaire on diet, other environmental risk factors, medical history and family history of cancer. The entire cohort is being followed up for cancer by record linkage to the cancer registries in the Netherlands. After 7.3 years of follow-up, archival paraffin blocks from 780 CRC patients have been retrieved from pathology labs in The Netherlands, of which 122 cases are selected for this study. Methylation status of the promoter CpG islands is determined by methylation specific PCR (MSP) and are correlated to folate acid and alcohol intake.

Results of this study indicate that low folate acid/high alcohol intake may be involved in CRC carcinogenesis by promoter hypermethylation of tumor suppressor genes and DNA repair genes, which may lead to genetic alterations in CRC key genes.