194 Poster

The influence of the Ataxia-Telangiectasia mutated G5557A polymorphism on cervical cancer development

S. Oliveira[1], H. Sousa[1], D. Pinto[1], A.L. Pinto-Correia[1], J. Moutinho[2], R. Medeiros[1]
[1]Instituto Português de Oncologia do Porto FG EPE, Grupo Oncologia Molecular, Porto, Portugal; [2] Instituto Português de Oncologia do Porto FG EPE, Gynaecology Department, Porto, Portugal

Introduction: DNA double strand break (DSBs) is one of the most serious threats to the integrity of the eukaryotic genome. One key protein that responds rapidly to this threat is Ataxia-Telangiectasia Mutated (ATM) protein kinase.

Integration of Human Papillomavirus (HPV) DNA into the host genome is recognized as an essential step for the cell transformation and cervical cancer development. The aim of this study was to analyse the role of the ATM G5557A polymorphism in cervical cancer development.

Material and Methods: We developed a retrospective study considering 484 cervical specimens of women from the northern Region of Portugal, using a real-time polymerase chain reaction methodology (assay C__26487857_10). Statistical analysis was performed using SPSS software.

Results: No statistically significant differences were found, regarding the influence of the G5557A polymorphism with cytological classification, the presence or absence of HPV16 or other oncogenic high-risk HPV types ($p>0.050$). However, the ATM 5557A allele was found to influence the age at which the progression from LSIL to high-grade or invasive cervical cancer occurs (43.0 vs 59.0 years old; $p=0.001$).

Conclusion: Our study reveals, for the first time, that ATM 5557A allele may influence cellular transformation leading low-grade lesions to progress to high-grade or invasive cervical cancer.

195 Poster

Association of Simian Virus 40 (SV40) with human breast carcinomas in Tunisian women

M. Hachana[1], M. Trimeche[1], S. Ziadi[1], K. Amara[1], R. Gacem[1], R. Zaghdoudi[1], M. Mokni[1], S. Korbi[1]
[1]University Hospital Farhat-Hached, Department of pathology, Sousse, Tunisia

Background: Breast carcinoma is the most common women's cancer worldwide, and the major cause of cancer mortality among women. Breast carcinoma is a multistep disease, and viral infection may play a role in one or more of the steps in its pathogenesis. Simian Virus 40 (SV40), which belongs to the polyomavirus family, is able to induce various specific tumor types in hamsters and other rodents, and to transform cells from different species. Over the last several years, different laboratories have reported the presence of SV40 in several types of human tumors. The present study was undertaken to investigate whether the SV40 is implicated in human breast carcinoma.

Methods: One hundred and nine invasive breast ductal carcinoma cases from Tunisia were tested for the presence of SV40 on paired tumor and normal frozen tissue specimens. Detection of SV40 genomic DNA was performed by polymerase chain reaction (PCR) assays targeting the Tag, the regulatory, and the VP1 regions. Immunohistochemistry was used to assess estrogen receptors, progesterone receptors, HER2, and P53 expression. The expression of large and small T-antigens of SV40 was investigated using Pab108 monoclonal antibody. We also examined the relationship between the presence of SV40 and clinicopathological data.

Results: Specific SV40 DNA sequences were detected by PCR in 24/109 (22%) of tumor and in only 2/109 (1.8%) of the matched non-tumoral tissues. Immunohistochemistry study has confirmed the presence of SV40 in tumor cells in all SV40 positive cases. Regarding clinicopathological data, we found that SV40-postive tumors were more frequently detected in patients aged over 50 years than in younger patients (34.7% vs. 12.7%; $p = 0.006$). With regard to immunohistochemical parameters, a significant correlation was found between SV40 presence and the accumulation of P53 protein (32.7% vs. 13.3%; $p = 0.015$). Furthermore, SV40 presence is inversely correlated with HER2 overexpresion (3.7% vs. 28%; $p = 0.008$).

Conclusions: In summary, our study demonstrates the presence of SV40 in a significant proportion of human breast carcinomas and provides data supporting a functional effect for this virus in these tumors. Further studies are required to elucidate the role of this virus in the pathogenesis of breast carcinoma. Additional investigations are necessary to evaluate the prevalence of SV40 in high risk breast carcinoma populations.

196 Poster

Does cooked Western diet initiate colon carcinogenesis in rats?

F. Dépeint[1], S. Taché[1], N. Naud[1], R. Santarelli[1], F. Pierre[1], W.R. Bruce[2], D.E. Corpet[1]
[1]Institut National de Recherche Agronomique, UMR Xénobiotiques, Toulouse, France; [2] University of Toronto, Nutritional Sciences, Toronto, Canada

Background: Only a handful of studies have investigated the role of nutritional factors on colon carcinogenesis without prior chemical initiation. A synthetic Western diet (WD), representative of nutrient imbalance in Western populations, induces colonic tumours in mice, but not in rats (Newmark et al., 2001). Also, a heat-treated diet initiates aberrant crypt foci (ACF), putative precursors of colon cancer, in the colon of F344 rats (Dépeint et al, submitted). Hypothesis: We speculated that WD heated for 1h30 at170°C (CWD) can induce more colonic ACF than regular WD (NWD). We have also tested if ACF initiation was due to (i) Maillard compounds (MAL), (ii) lipid peroxides (PER), or (iii) vitamin deficiency (VIT), each achieved by heating or depletion of specific fractions of the WD diet. Material and Methods: F344 rats (n=20 per group) were fed one of the five WD-derived diets described above or a control AIN76 diet (AIN) for 130 days, without giving a colon carcinogen. Faecal water and urine samples were assayed for lipid peroxides and cytotoxicity. After 130d on experimental diets rats were sacrificed and their colon scored for inflammation and ACF formation. Lipid peroxides and mutagenic factors formed during the heating process were also measured directly in the diet. Results: Rats fed the CWD diet gained less weight than other rats, and showed obvious symptoms of rectal inflammation. The end of study is planned in April 2008, and full biomarkers and ACF data will be presented in Lyon, July 2008. Conclusion: Faecal thiobarbituric acid reactive substances (TBARS) and cytotoxicity have been correlated with ACF outcome (Pierre et al, 2003). Endogenous biomarker data collected strongly support the hypothesis of an increased risk associated with heat treatment of the diet. They also suggest a possible role of inflammation during the process, and that Maillard compounds may play a more important role in colon carcinogenesis than lipid peroxidation. No clear risk of vitamin deficiency has been found so far. However ACF data are needed for firm conclusion, and will help discriminate between the factors. Cooking is a common step in food processing. This study will shed some light on the risk associated with cooked foods and the investigation goes beyond the traditional culprits such as carcinogens produced during meat cooking, which are not involved here.

197 Poster

E2F2 - a potential new molecular marker for colon carcinogenesis

C. Nicolet[1], A. Neuville[2], J.M. Flaman[3], M.P. Gaub[4], D. Guenot[1]
[1]INSERM, U682, Strasbourg, France; [2] CHU Hautepierre, Anatomo-Pathologie, Strasbourg, France; [3] INSERM, U614, Rouen, France; [4] CHU Hautepierre, Laboratoire de Biologie Moléculaire et Biochimie, Strasbourg, France

Colon cancers are classified in tumours of microsatellite instability phenotype (MIN) which results from mismatch repair gene alterations and in tumours of chromosomal instability phenotype (CIN) which present mostly aneuploidy. The genetic alterations found in CIN tumors are greatly heterogeneous suggesting that the signaling pathways required for colon carcinogenesis could be more complex than currently proposed. This could account for the development of tumors resistant to chemotherapy and for the difficulty to find efficient anticancer agents. Also, the heterogeneity of the cohorts analyzed could explain why despite numerous published studies, no molecular markers for tumour progression and metastatic invasion or for sensitivity to chemotherapy are available. To define a genomic profile of alterations linked to the tumour progression, a pan-genomic CGH array (aCGH) to detect genome deletions and amplifications at a high level of resolution has been performed on 62 CIN colon tumours. Among several alterations, a microdeletion in 1p36.12 region has been observed for 46/94 (49%) of the tumors of all clinical stages. This genomic region includes several genes and among them, E2F2. E2F family members are key regulators of the cell cycle, and the disruption of the pathway controlling E2F appears to be a necessary step in human oncogenesis as E2F family members can activate or repress transcription, stimulate or inhibit proliferation, and promote or suppress apoptosis depending on the context. Real-time PCR showed that deletion of the E2F2-targeting probes correlated with a decreased gene copy number and as a complement quantitative multiplex PCR of short fragment (QMPSF) showed that only one copy of the gene was deleted. Sequencing of the 8 exons did not evidenced gene mutation but a polymorphism in exon 4 was found. At the level of the gene gene expression, E2F2 mRNA was decreased in distal tumors but increased in proximal tumors. As E2F1, E2F2 and E2F3 have redundant functions in controlling cell cycle progression, messenger expression for E2F1 and E2F3 were also