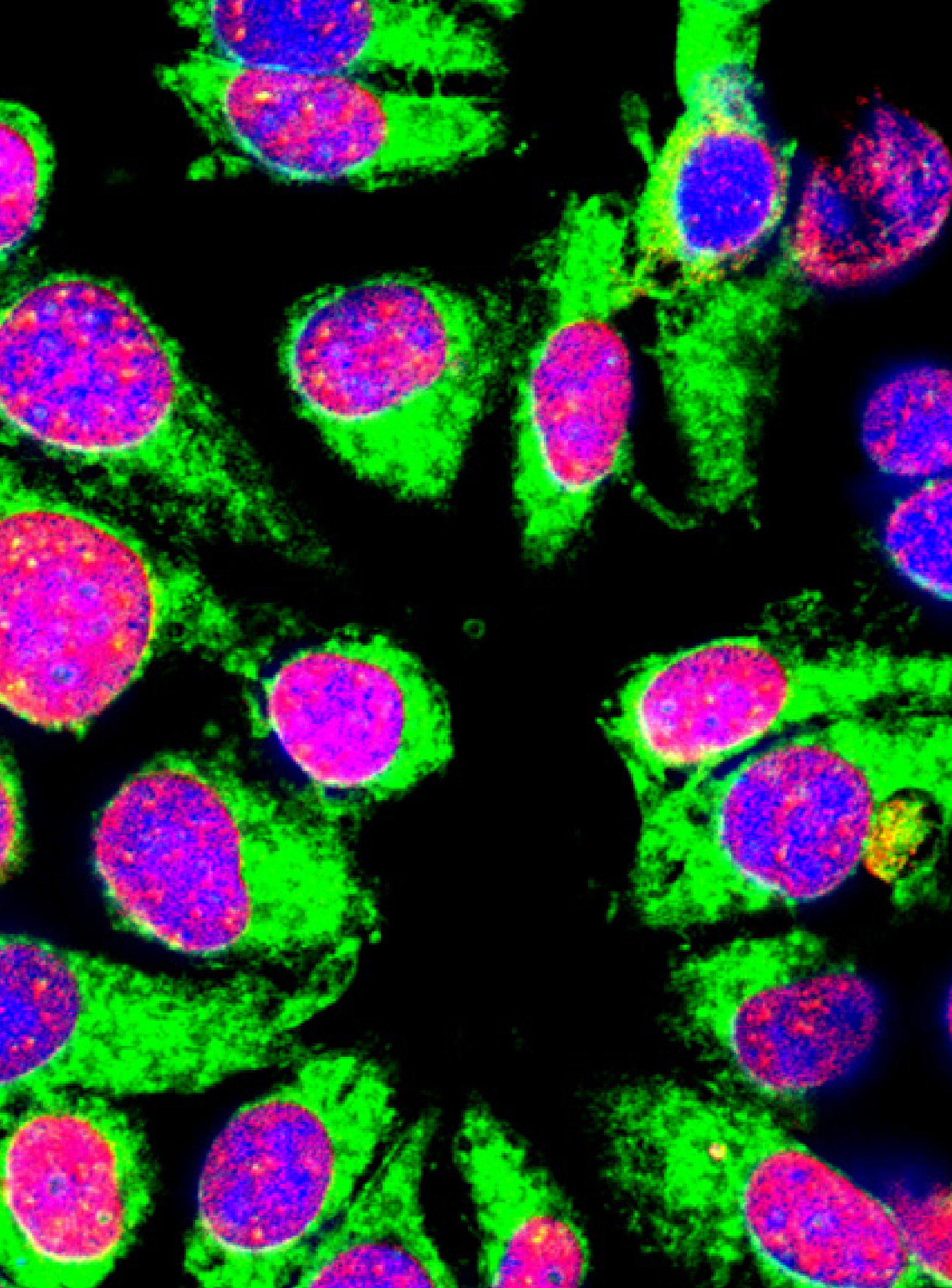


SECTION OF MECHANISMS OF CARCINOGENESIS (MCA)

Section head
Dr Pierre Hainaut

THE MAIN OBJECTIVE OF THIS SECTION IS TO DEVELOP AND CONDUCT STUDIES AIMED AT IDENTIFYING THE MOLECULAR BASIS OF THE BIOLOGICAL PROCESSES INVOLVED IN CANCER CAUSATION. THIS IMPLIES ADDRESSING THE BASIC MECHANISMS OF CARCINOGENESIS THROUGH EXPERIMENTAL STUDIES USING CULTURED CELLS AND ANIMAL MODELS. THE MOST DIRECT OUTCOME OF THIS TYPE OF RESEARCH IS TO IDENTIFY, DEVELOP AND VALIDATE INNOVATIVE BIOMARKERS, WHICH MAY BE APPLICABLE IN LARGE-SCALE STUDIES ON MOLECULAR EPIDEMIOLOGY OR PATHOLOGY. THE SECTION'S SKILLS COVER TWO BROAD CLASSES OF MOLECULAR ALTERATIONS THAT UNDERPIN THE CANCER PROCESS: MUTATIONS AND EPIGENETIC MODIFICATIONS. THE MAIN TARGETS INCLUDE HEPATOCELLULAR CARCINOMA (SEARCH FOR NEW MARKERS AND UNDERSTANDING OF THE MOLECULAR MECHANISMS OF THE SYNERGISTIC EFFECTS BETWEEN DISTINCT ETIOLOGICAL RISK FACTORS), LUNG CANCERS (UNDERSTANDING THE MOLECULAR MECHANISMS OF GENETIC PREDISPOSITION AND OF CARCINOGENESIS IN NEVER-SMOKERS), OESOPHAGEAL CANCERS (IDENTIFYING CAUSAL FACTORS THROUGH MOLECULAR STUDIES IN HIGH-RISK POPULATIONS IN SPECIFIC GEOGRAPHIC AREAS), BREAST CANCERS (UNRAVELLING INTERACTIONS BETWEEN MUTATIONS AND EPIGENETIC CHANGES IN MAINTAINING CANCER STEM CELL STATUS) AND HIGHLY CANCER PREDISPOSING INHERITED MUTATIONS (LI-FRAUMENI SYNDROME). THE SECTION'S WORK IS INTEGRATED, WITH SIMILAR THEMES AND SAMPLE COLLECTIONS BEING STUDIED IN BOTH THE MOLECULAR CARCINOGENESIS GROUP (MOC) AND THE EPIGENETICS GROUP (EGE), THUS FOSTERING A PATTERN OF TECHNICAL AND SCIENTIFIC INTERACTIONS WITHIN THE SECTION AND ALSO WITH OTHER RESEARCH GROUPS. HIGHLIGHTS OF 2011 INCLUDE IMPORTANT ADVANCES IN IDENTIFYING NEW BIOMARKERS OF LIVER CARCINOGENESIS, DEFINING THE MECHANISMS BY WHICH POLYMORPHISMS IN N-ACETYLCHOLINE RECEPTOR GENES CONTRIBUTE TO THE PREDISPOSITION TO LUNG CANCER, UNDERSTANDING THE ROLE OF THE TUMOUR SUPPRESSOR P53 IN BREAST CANCER CELLS' RESPONSE TO ESTROGENS AND NEW STUDIES ON THE EFFECTS OF DIET ON EPIGENETIC DNA METHYLATION PATTERNS.



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The Molecular Carcinogenesis Group (MOC) carries out projects in functional genomics aimed at better understanding the mechanisms of cancer and at identifying biomarkers for early detection. Studies focus on *TP53*, a major tumour suppressor in which the group has acquired a strong international position. This is due in part to the maintenance and dissemination of the IARC *TP53* database, the most cited international resource in the field (<http://www-p53.iarc.fr>). Projects by MOC include: (1) mechanisms of liver carcinogenesis focusing on interactions between p53 and viral oncoproteins on regulating liver cell metabolism and differentiation; (2) role of *TP53* mutations as prognosis and a predictive marker in breast cancer; (3) role of germline *TP53* mutations in a large cohort of carriers from Brazil, where we have discovered a founder mutation which is present in 0.3% of the population; (4) regulation of stem cell status by p53 isoforms; and (5) discovery of new early detection markers for liver cancer. This section highlights some of the significant results in 2011, while our work on the functional significance of polymorphisms in nicotinic acetylcholine receptors (NACHR) for the genetic susceptibility to lung cancer is described in the Section of Genetics.

CANCER IN AFRICA: FROM DESCRIPTIVE EPIDEMIOLOGY TO ENVIRONMENTAL CARCINOGENESIS

Over the past 10 years, MOC has built a network of collaborations in Western and Eastern Africa involving local cancer registries, pathology services, clinical centres and local laboratories handling specimen collections and baseline biological analyses. Highlights of this work include the analysis of trends of incidence of liver cancer in West Africa, investigation on mutations induced by aflatoxin in HBV chronic carriers from rural Gambia and the first study on molecular markers in squamous cell carcinoma of the oesophagus in Kenya, West Africa. The current collaborative network includes projects in Mali (liver cancer, breast cancer, gastric cancer), in Kenya (oesophageal cancer) and in Sudan (oesophageal and liver cancers).

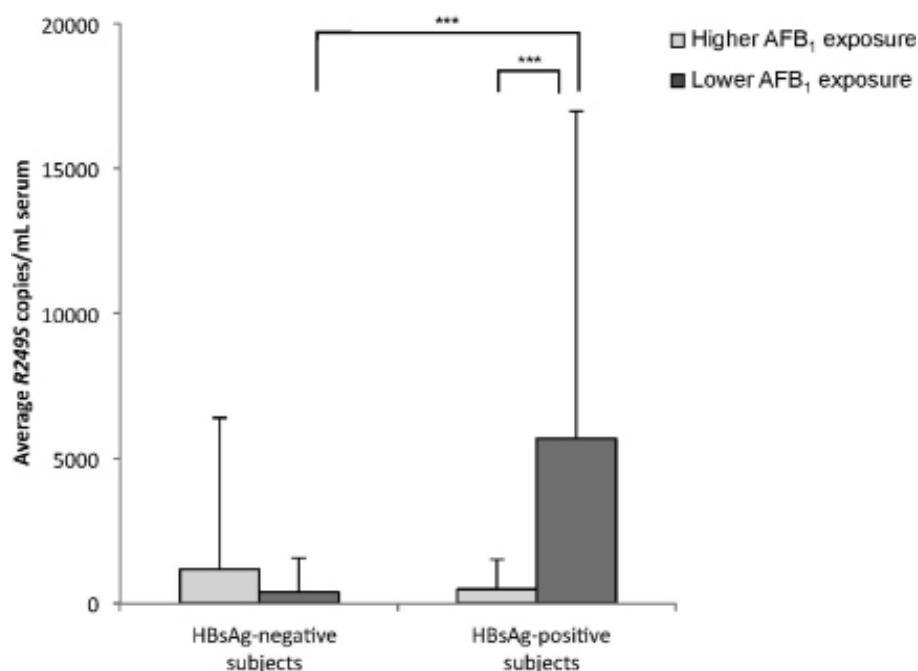
Our studies on recent trends in the incidence of liver cancer in West Africa

have identified a significant increase in women only. We have proposed that this increase might be correlated with the documented increase in female obesity and metabolic disease. Using registration data from Mali and The Gambia, we have investigated the variations in breast cancer incidence and have shown that premenopausal breast cancer remains by far the most common form of the disease. Over the past 10 years, we have developed approaches and detection methods to measure aflatoxin-related mutations in DNA extracted from the plasma of patients with chronic liver disease or liver cancer. To analyse the relationship between detection of aflatoxin-induced *TP53* mutations (R249S) in plasma DNA and consumption of aflatoxin-contaminated food, we have used short oligonucleotide mass analysis to detect R249S levels in plasma DNA in a cross-sectional survey of 473 asymptomatic subjects (237 HBV carriers and 236 non-carriers) recruited in three rural villages in The Gambia over a 10 month period. A seasonal variation was detected with significantly higher levels of mutation in HBsAg-positive

subjects surveyed during April–July than in October–March (Figure 1). HBeAg positivity (a marker of HBV replication) and viral DNA load also varied seasonally with 15–30% of subjects surveyed between April and June being HBeAg-positive, compared with < 10% surveyed during other months. These results suggest that levels of R249S in plasma DNA of asymptomatic subjects are strongly influenced by HB chronic infection status. Moreover, levels of R249S show a seasonal variation that does not match the variations in exposure to AFB1: the peak of R249S in the plasma occurs 3–6 months later than the previously reported peak of exposure to AFB1. This difference may be the consequence of a chain of molecular events determined by the turnover of hepatocytes. These results demonstrate that mutagenesis of *TP53* by AFB1 is a common event in subjects exposed to the toxin, not restricted to pre-cancer or cancer conditions. Thus, it has to be expected that additional genetic and epigenetic changes, subsequent to *TP53* mutation and HBV chronic infection, play essential roles as drivers of hepatocarcinogenesis.

Figure 1. Levels of mutant *TP53* DNA with mutation at third base of codon 249 (R249S, aflatoxin-related mutation) in the plasma of subjects from 3 rural villages in The Gambia, comparing between periods of higher exposure to AFB1 (December–March) and lower exposure (April to–July). The seasonality of R249S release in HBsAg-positive subjects is shown and contrasts with the seasonality of exposure to AFB1.

In Villar *et al.*, 2011.

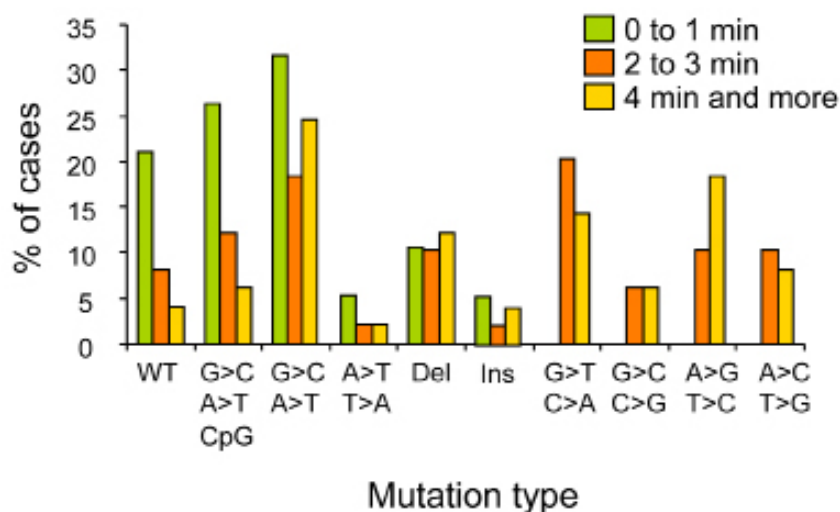


In Kenya we have developed a pilot study on retrospective cases of oesophageal squamous cell carcinoma (OSCC) in the region of Eldoret, which is documented as having a high prevalence of this cancer (detailed incidence data are not available). Studies on *TP53* mutations and HPV prevalence revealed that both biomarkers were infrequent. In contrast with many high OSCC incidence areas, mutations in *TP53* were detected in only about 25% of the cases, whereas HPV was not detected in any of the cases analysed. A similar, low proportion of cases with mutant *TP53* have been previously reported in South Africa (Transkei). Overall, these preliminary data suggest that OSCC from eastern Africa may share common epidemiological and molecular patterns with those detected in South Africa.

OESOPHAGEAL CANCER IN THE ISLAMIC REPUBLIC OF IRAN

We have pursued our long-term effort in analysing patterns of genetic alterations in OSCC from Golestan, Iran, one of the regions of the world with the highest incidence rates for this cancer. Following the detection of a significant association between the immunological detection of PAH-adducts in oesophageal mucosa and risk of OSCC, we have completed an exhaustive analysis of *TP53* mutations in 140 patients recruited in a case-control study. We detected mutations in over 90% of the cases, representing the highest rate of *TP53* mutations ever identified in any form of cancer. The mutations were diverse, suggesting that multiple distinct mutagens and mutagenic mechanisms may contribute to the overall mutation load. Nevertheless, when compared to previously published data on OSCC from other parts of Iran, OSCC from Golestan showed a significantly higher proportion of mutations at bases known as sites of adduction by metabolites of PAH. This is consistent with our previous results that this class of mutagens represents one of the main risk factors in the etiology of OSCC in the region. In addition, we identified significant variations in mutation patterns in relation with hot tea drinking habits, further supporting the notion that thermal injury has a critical impact on mucosal regeneration and DNA repair capacity (Figure 2). These results support the view that OSCC in

Figure 2. Distribution of *TP53* mutation types according to tea temperature, in ESCC cases from Golestan Province, Northern Iran, a very high incidence area of this cancer. Tea temperature was estimated by the time interval between pouring and drinking tea (from 0-1 min to 4 min or more). Our study revealed different mutation patterns related to tea drinking habits. Wild-type *TP53* and G:C to A:T transitions (in particular at CpG sites) were most often seen in subjects who reported drinking tea within 1 minute of pouring. Conversely, transversion mutations (including G:C to T:A mutations which often occur as the result of mutagenesis by PAH adducts) were observed only in subjects who reported a preference for drinking tea with a longer delay (at least 2 minutes after pouring). In Abedi *et al.*, in press



Northern Islamic Republic of Iran is not associated with exposure to a single class of mutagens, but develops in the context of combined effects of thermal stress and exposure to environmental mutagens on a background of susceptibility influenced by genetic and deprivation factors.

p53 ISOFORMS AND CANCER SUSCEPTIBILITY

Following our initial identification of the Delta40 (deltaN) isoform of the p53 protein, we have extended our work on the mechanisms regulating the expression of this isoform. Convergent results from our group and others show that this isoform, which lacks the first 40 amino acid residues of p53 that contains the transactivation domain, is expressed at significant levels in many normal cells and tissues where it may play a critical role in controlling the basal functions of p53 in regulation of stem cell status, proliferation, metabolism and senescence. In collaboration with the groups of JL Mergny and J Hall, we have found that a critical regulatory motif for the control of Delta40p53 expression lies in the intron 3 of *TP53*. This motif consists of a stretch of guanines which was shown to be able to fold into specific secondary structures in p53 pre-mRNA, called G-quadruplexes (G4) (Figure 3). These structures are common in genes

involved in growth control, such as the MYC1 oncogene or HTERT encoding the human telomerase. Mutation of guanines in the G4 affects the splicing of p53 mRNA, leading to the retention of intron 2 and formation of an alternative splicing product that encodes Delta40p53. Significantly, the G4 structure in intron 3 overlaps with a common polymorphism in *TP53*, a 16bp repeat, which has been shown by us and others to have a strong impact on *TP53*-dependent genetic susceptibility. We have previously shown that this polymorphism is a strong modifier of age at cancer diagnosis in carriers of germline *TP53* mutations who are at high risk for familial cancer. Studies in sporadic cancer have shown that the intron 3 polymorphism is associated with an increased risk for many common cancer forms. Therefore, it is possible that genetic susceptibility associated with intron 3 polymorphism may be due to differences caused by this polymorphism in the expression levels of Delat40p53 and in the basal activity of the p53 protein.

DISCOVERY OF NOVEL PLASMA PROTEIN MARKERS FOR EARLY DETECTION OF HEPATOCELLULAR CARCINOMA

In 2007, we launched a long-term effort to discover plasma proteins that could be used for the routine detection and

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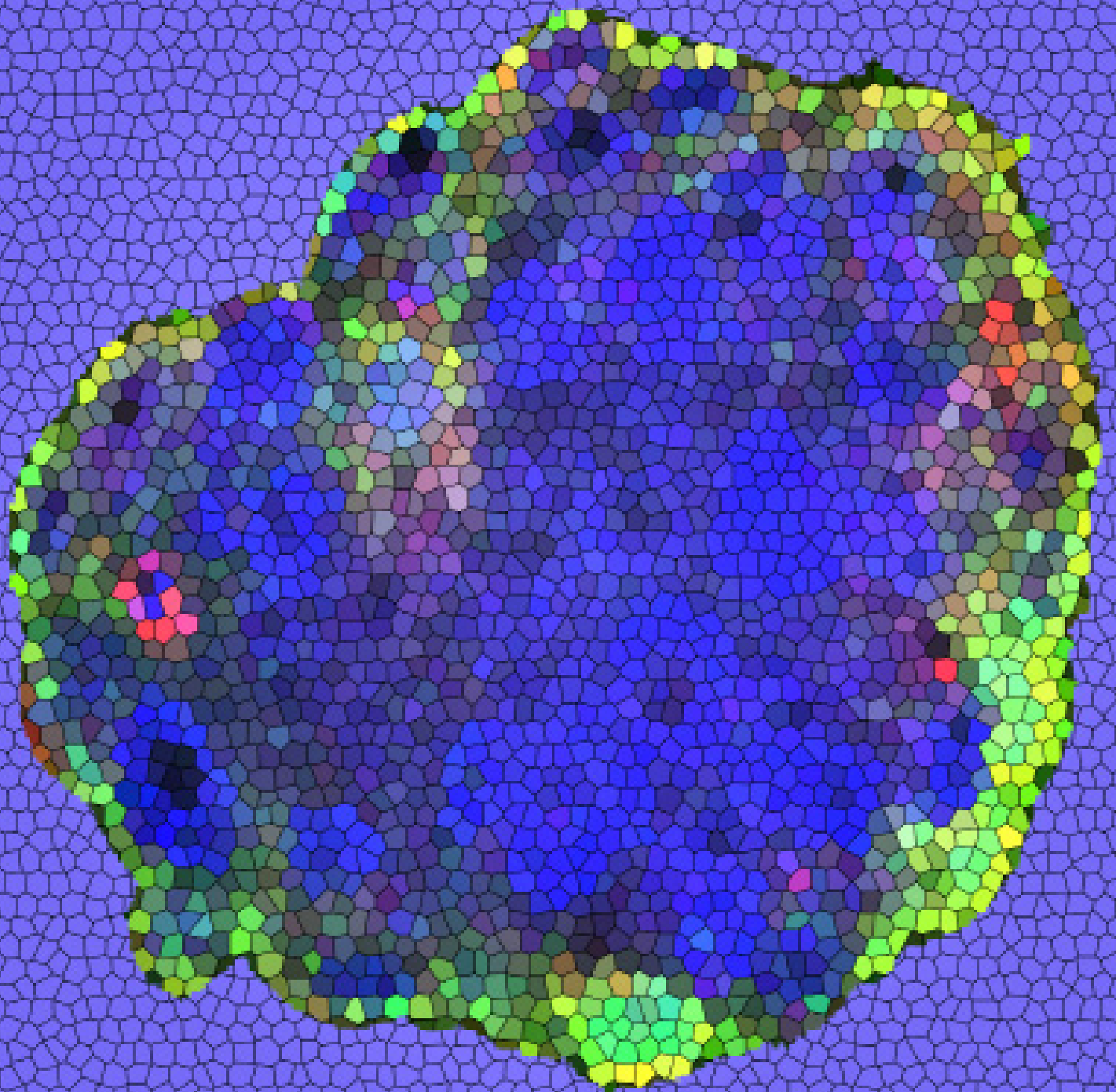
Association pour la Recherche sur le Cancer (ARC), France
Institut National du Cancer (INCa), France
European Community
Ligue Nationale Contre le Cancer, Comité du Rhône, France

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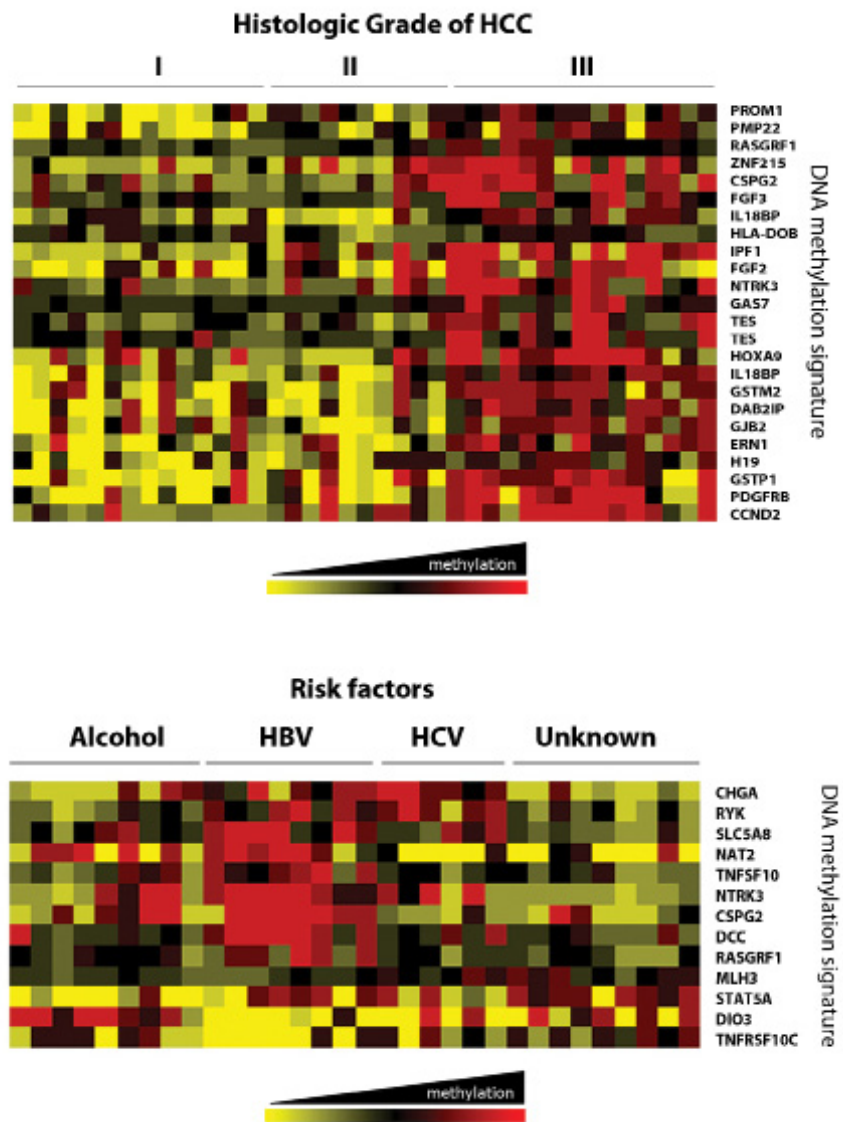
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Over the past decade epigenetics research has become more mainstream, owing to the fact that epigenetic changes have emerged as key mechanisms in cancer development and progression. Although the implication of epigenetic events in cancer is supported by both epidemiological and experimental studies, the precise contribution of epigenetic mechanisms and cellular targets of epigenetic alterations in human cancers are largely unknown. The intrinsic reversibility and ubiquity of epigenetic changes in virtually all types of human cancer make them attractive subjects for biomarker discovery and strategies for cancer prevention (Lima *et al.*, 2010; Krutovskikh and Herceg, 2010; Sincic and Herceg, 2010; Rodríguez-Paredes and Esteller, 2011). The Epigenetics Group (EGE) conducts both mechanistic studies and epigenetic profiling, so as to gain a better mechanistic understanding of tumorigenesis, and to discover and validate new epigenetic biomarkers.

ANALYSIS OF DNA METHYLOME IN HEPATOCELLULAR CARCINOMA REVEALS EPIGENETIC SIGNATURE ASSOCIATED WITH RISK FACTORS AND POTENTIAL CANCER BIOMARKERS

Hepatocellular carcinoma (HCC) is characterized by late detection and fast progression, and it is believed that epigenetic disruption may contribute to its development and progression. A better understanding of the global deregulation of epigenetic profiles (such as DNA methylation states) and how they correlate with disease progression, will aid in the design of strategies for earlier detection and cancer prevention. We characterized the changes in promoter DNA methylation in a series of HCCs, and their respective surrounding tissue, and identified methylation signatures associated with major risk factors and clinical correlates. A wide panel of cancer-related gene promoters was analysed using Illumina bead array technology, and CpG sites were then selected according to their ability to classify clinicopathological parameters. An independent series of HCC tumours and matched surrounding tissue was used to validate the signatures (Hernandez

DNA Methylome changes associated with tumour grade and risk factors in hepatocellular carcinoma



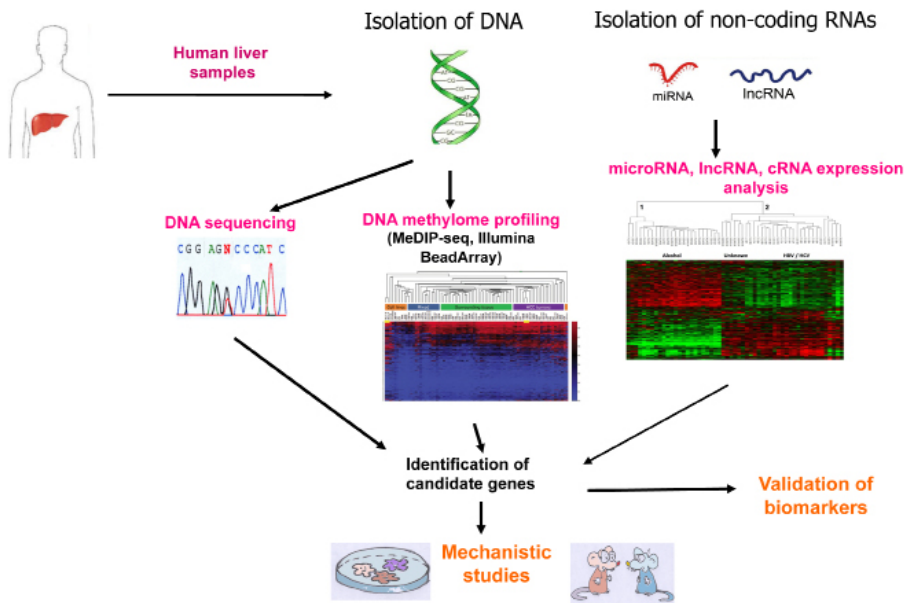
Vargas *et al.*, 2010). While aberrant methylation of a subset of promoters was associated with tumour progression and etiological risk factors, such as HBV or HCV infection and alcohol consumption (Lambert *et al.*, 2010), hypermethylation of an independent panel of genes was strongly correlated with survival after cancer therapy. We have further investigated methylation profiles of the HBV genome in liver samples of different stages of HCC development and in in vitro infected human hepatocytes. We found discrete CpG sites in the HBV genome that are recurrently hypermethylated in cancer but not in chronic hepatitis tissue (Kaur *et al.*, 2010). Our findings suggest that hypermethylation of the HBV genome itself, resulting from deregulated DNA methylation in malignant cells, may

contribute to the occult status of the disease (Kaur *et al.*, 2010). Together, our studies identified specific DNA methylation signatures associated with clinical correlates, as well as the major risk factors, providing information that could be exploited for biomarker discovery in clinics and molecular epidemiology (Hernandez Vargas *et al.*, 2010; Lambert *et al.*, 2010; Herceg and Paliwal, 2011).

ABERRANT DNA METHYLATION LINKS CANCER SUSCEPTIBILITY LOCUS 15Q25.1 TO APOPTOTIC REGULATION AND LUNG CANCER

Nicotinic acetylcholine receptor (nAChR) genes form a highly conserved gene cluster at the lung cancer susceptibility

Experimental strategy for identification of molecular changes associated with hepatocellular carcinoma and risk factors



were modulated by smoking status, consistent with the notion that blood levels of 1-carbon metabolism markers and dietary/lifestyle factors may modify DNA methylation levels in blood cells, and that blood cells can be exploited for the discovery of epigenetic biomarkers of exposures, providing proof-of-principle on the use of blood samples in the context of prospective studies (Vineis *et al.*, 2011).

Impact of dietary regime on methylation patterns in peripheral blood in an intervention study. We conducted a randomized four week intervention trial to test the impact of three dietary regimens on DNA methylation patterns in peripheral white blood cells of heavy smokers (Scoccianti *et al.*, 2011). We found that dietary intervention may induce small but significant modifications in the methylation patterns of long interspersed DNA elements (LINE1), a marker for global genome methylation, whereas several other loci analysed showed low basal levels of methylation with no substantial change after intervention. These results are consistent with the notion that balanced or supplemented diet may contribute to stabilizing normal, endogenous DNA methylation patterns, but does not provide evidence for methylation changes in specific genes associated with this short-term dietary intervention (Scoccianti *et al.*, 2011; Herceg and Vaissière, 2011).

locus 15q25.1. We found that the CHRNA3 gene encoding nAChR3 subunit is a frequent target of aberrant DNA hypermethylation and silencing in lung cancer (Paliwal *et al.*, 2010). Treatment of cancer cells exhibiting CHRNA3 hypermethylation with DNA methylation inhibitors caused demethylation of the CHRNA3 promoter and gene reactivation, whereas restoration of CHRNA3 levels through ectopic expression induced apoptotic cell death. shRNA-mediated depletion of CHRNA3 in CHRNA3-expressing lung cancer cells, elicited a dramatic Ca²⁺ influx response in the presence of nicotine, followed by activation of the Akt survival pathway. CHRNA3-depleted cells were resistant to apoptosis-inducing agents, underscoring the importance of epigenetic silencing of the CHRNA3 gene in human cancer (Paliwal *et al.*, 2010). In defining a mechanism of epigenetic control of nAChR expression in non-neuronal tissues, our findings offer a functional link between susceptibility locus 15q25.1 and lung cancer, and suggest nAChRs as therapeutic targets for cancer detection and chemoprevention (Paliwal *et al.*, 2010; Kraus *et al.*, 2011; Herceg and Vaissière, 2011).

IDENTIFICATION OF EPIGENETIC CHANGES IN PERIPHERAL BLOOD AS BIOMARKERS OF EXPOSURE AND CANCER RISK

The goal of this study is to investigate whether epigenetic changes in peripheral blood (such as WBC and circulating nucleic acids) can be used as intermediate biomarkers for risk factor exposures and different health outcomes.

DNA methylation changes associated with cancer risk factors and blood levels of vitamin metabolites in a prospective study. We tested whether genomic DNA from surrogate tissues, such as blood cells, may be exploited in the discovery of biomarkers of exposure and cancer risk. DNA methylation levels in a panel of candidate genes in blood cells of cases and controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) study were quantitatively determined and the association between lung cancer risk and DNA methylation patterns was examined. We also investigated whether blood levels of vitamin metabolites modify DNA methylation levels in blood cells (Vineis *et al.*, 2011). Our results revealed that DNA methylation patterns in specific genes are associated with the case/control status and that methylation levels are influenced by serum levels of 1-carbon metabolites and vitamin B. Interestingly, these associations

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