Interactions of Cancer Susceptibility Genes and Environmental Carcinogens

American Association for Cancer Research (AACR)-International Agency for Research on Cancer (IARC) Joint Conference

Recent advances in molecular biology have created new opportunities to identify and control the causes of human cancers. To summarize current knowledge and explore future research opportunities, an interdisciplinary meeting conference entitled “Interactions of Cancer Susceptibility Genes and Environmental Carcinogens” was held. An international panel of experts presented insights into carcinogenic processes in overviews, summary lectures, and 6 sessions on the following topics: human cancer epidemiology; biomarkers of individual susceptibility; mechanisms of transgenerational carcinogenesis; experimental models of genetic susceptibility; genetic instability; and DNA damage and repair. The small size of the meeting (limited to 175 participants) and its interdisciplinary theme were particularly helpful in fostering scientific exchange. A total of 78 posters were also presented with the participation of many young investigators.

Historically, research on cancer causation was conducted primarily by two independent groups of investigators. Epidemiologists studied human populations to identify patterns and determinants of cancer occurrence, with emphasis on environmental risk factors. Concurrently, laboratory investigators studied mechanisms of carcinogenesis in animal and in vitro experiments. Early efforts to bridge the two approaches were often unproductive due to limitations in knowledge and technology. However, newly available tools of molecular biology and genetics have made human subjects and tissues the preferred experimental model for many studies of cancer etiology and development. These studies have already generated many exciting discoveries which were summarized by the speakers and in posters at the Conference.

L. Wattenberg (University of Minnesota, USA) discussed the current status of chemoprevention research. Among natural and synthetic agents, one class of compounds acts by blocking carcinogens from reaching critical target sites during the stages of tumor initiation and promotion. Another class acts as suppressive agents that prevent evolution of the carcinogenic process to a malignant state. Suppressive agents can act by inducing cell differentiation (e.g., retinooids), blocking genotoxic events such as oncogene activation (terpenes), and selectively inhibiting cellular proliferation (antihormones). Chemoprevention can target the general population or high-risk groups. Minimal toxicity of the therapy might be acceptable to high-risk subjects but is usually unacceptable to the entire population. Biomarkers and intermediate end points are needed in order to develop optimal dosage regimens and evaluate the likely efficacy of chemopreventive agents being considered for trials in which prevention of cancer is the end point. Such trials frequently are a major undertaking so that information enhancing the likelihood of success is critical.

L. Tomatis (International Agency for Research on Cancer, Lyon, France) discussed transgenerational carcinogenesis and reviewed the epidemiological and experimental evidence for the effect(s) on the progeny of the preconceptional exposure of parents, in particular the male parent, to an environmental carcinogen. Most of the epidemiological studies were related to occupational exposures. A positive correlation between certain occupational exposures and an increased risk of childhood cancer in the progeny was confirmed in several but not all studies. Some of the discrepancies in the observations could be related to the insufficient qualitative and quantitative information on exposures. Several experimental results pointed to an increased cancer risk in the progeny of male mice or rats exposed to a chemical carcinogen or to ionizing radiation before mating. In the experimental model the increase in tumor incidence was observed rather late in life. The corollary to these epidemiological and experimental observations is that a preconceptional exposure to a carcinogen/mutagen may contribute, at least in part, to what is generally described as inherited predisposition to cancer.

C. Harris (National Cancer Institute, Bethesda, MD) discussed the role of the p53 tumor suppressor gene in the process of carcinogenesis and in the epidemiology of cancer. The majority of p53 mutations are missense mutations and they occur at high frequency in human tumors, resulting in increased stability of the p53 protein and affecting the function of this protein in cell growth and in controlling neoplastic transformation. The type and the affected nucleotide sequence of these mutations are also indicative of exposure to environmental carcinogens. Dietary exposure to aflatoxin B1 is related to G to T transversions at codon 249 in hepatocellular cancer; UV light is correlated with transition mutations at pyrimidine dimers; G to T transversions are prevalent in various tumors attributable to cigarette smoke; and mutations at A-T base pairs are associated with vinyl chloride in hemangiosarcomas of the liver. These mutation spectra are consistent with the knowledge on the DNA damage and repair resulting from corresponding exposure to the carcinogens. Inactivation of p53 function can also result from endogenous mechanisms of mutagenesis or by interaction with other cellular (Mdm2) and oncoviral proteins (E6) from human papilloma virus. Mutations of p53 affect various cellular processes, namely genetic stability, DNA repair, programmed cell death, and control of the pool of proliferative cells, that have direct bearing on the neoplastic process. The voluminous data accumulated on genetic changes in human cancers were discussed in reference to their relevance in human cancer risk assessment.

Discussing the contribution of environmental and endogenous agents to mutation induction in target cells and genes associated with human cancer, M. F. Rajewsky [Institute for Cell Biology (Cancer Research), University of Essen Medical School, Germany] focused on molecular parameters determining the genomic “fingerprints” of exposure to defined DNA-reactive carcinogens. The types and codon specificity of carcinogen-induced mutations are dependent upon the chemical reactivity of individual carcinogens and the molecular nature of the resulting DNA lesions, the sequence context and presentation of target nucleotides in chromosomal DNA (transcriptionally active versus silent genes), and the efficacy and toposelectivity of lesion-specific DNA repair. DNA repair capacity differs significantly among various cell types and is an important rate-limiting factor in cancer development. Highly sensitive methods have been established to detect specific carcinogen-DNA adducts and to measure their repair kinetics. Using monoclonal antibody-based immunoanalytical techniques, defined DNA alkylation products can now be quantified in...
individual cells and gene sequences with a sensitivity of 1 modified base in $10^{-7}$-$10^{-9}$ of their unmodified counterparts. These approaches allow us to examine the occurrence of early molecular and cellular changes in the natural history of carcinogenesis as well as to improve the resolution power of epidemiological studies aiming at the identification of environmental risk factors or of individuals at high risk of developing particular forms of cancer.

T. Mäkelä (Whitehead Institute for Biomedical Research, Cambridge, MA) described a new type of DNA rearrangement involving L-myc and a new gene, rif, in small-cell lung cancer. Oncogenic activation of the myc genes occurs in various human cancers by either gene amplification or chromosomal translocation. The rearrangements of L-myc and rif genes (located in chromosome 1p32 approximately 480 kilobases apart) join exon 1 of the rif to a region upstream of L-myc, resulting in the formation of a rif-L-myc fusion protein. These rearrangements are associated with amplification of these regions, which also contain highly repetitive sequences indicating that the rearrangements are probably the result of homologous recombinations between similar repeats in this region. It was also observed that coamplification of L-myc and rif without apparent rearrangement in either gene occurs in several in small cell lung cancers. This indicates that an identical chimeric rif-L-myc protein is formed through independent genetic lesions. Current studies are assessing the functional role of the fusion transcript in transgenic mice and embryonic stem cells.

T. Heidmann (Institut Gustave Roussy, Villejuif, France) discussed the mobility of endogenous retroviruses and retrotransposons in higher eukaryotes and its relevance in the process of carcinogenesis. Mobile genetic elements are present up to 10% of the genome in mammals and their transposition could be an important source of "endogenous mutagens." Methods are now available to assess the transposition rate in mammalian cells using "indicator genes" that detect the transposition of any structure into which they are inserted, provided that transposition is a "retrotransposition" (retrotransposition of DNA sequences through an RNA intermediate into a new and distant location in the genome). The mechanism of intracellular transposition of endogenous murine retrotransposons was characterized and their transposition rates in normal 3T3 and tumor cell lines were analyzed. These studies are now extended to transgenic mice containing marked IAP sequences as a transgene. These various approaches should permit the determination of the contribution of these elements in the induction of "insertional mutagenesis" and/or genetic instability in the mammalian cells and be helpful in determining the effect of environmental agents in the mobilization of these elements.

T. D. Tlsty (Lineberger Comprehensive Cancer Center, Chapel Hill, NC) examined the role of viral proteins involved in malignant transformation to investigate cell cycle cellular pathways that may be perturbed during loss of genomic stability. Recent studies have identified cellular proteins which are targets for the viral oncoproteins, stressing the importance of these cellular proteins in controlling neoplasia. Among the targets of the viral oncoproteins are the products of the p53 and retinoblastoma (Rb) tumor suppressor genes. We demonstrate that the expression of human papillomavirus type 16E6 and E7 oncoproteins in normal, mortal cells disrupts the integration of the network of signals that maintain genomic integrity. E6-expressing cells, in which cellular p53 protein is bound and degraded, exhibited alterations in cell cycle control and displayed the ability to amplify the endogenous CAD gene when placed in the drug N-(phosphonacetyl)-l-aspartic acid. Expression of E7, which complexes with a variety of cellular proteins including Rb, resulted in a p53-independent alteration in cell cycle control, massive cell death, and polyploidy upon N-(phosphonacetyl)-l-aspartic acid treatment. These results demonstrate that the viral proteins disrupt cellular processes that safeguard the genome and growth of normal cells. Alterations of these controls are being examined in cells from patients that are predisposed to neoplasia.

L. Aaltonen (University of Helsinki, Helsinki, Finland) described the occurrence of instability of short tandem repeats (replication error or RER²) in HNPPC and in sporadic colorectal cancer. The studies based on families of HNPPC demonstrated that the RER phenomenon is associated with the cancer susceptibility gene that was recently mapped to chromosome 2p. Furthermore, RER was seen in tumors derived from families showing negative lod scores to 2p suggesting that more than one gene may cause the RER phenotype. Preliminary studies indicate that RER in sporadic tumors is strongly associated with proximal tumor location. HNPPC tumors also favor proximal colon, but not as overwhelmingly. In fact the difference in the site distributions of sporadic RER+ and HNPPC tumors was statistically significant suggesting different etiologies in proximal and distal RER+ tumors. Tumors of the endometrium, stomach, kidney, ovaries, small intestine, and hepatobiliary system are also characteristic of HNPPC syndrome. RER was shown to occur in at least tumors of the endometrium and stomach.

C. Barrett (National Institute of Environmental Health Sciences, Research Triangle Park, NC) described the use of rodents in studies of genetic susceptibility to carcinogens. Animal models facilitate screening for causal agents, mechanistic studies, and mapping and positional cloning of susceptibility genes. Transgenic mice are particularly useful for studies of carcinogenic mechanisms in inherited susceptibility genes. Inherited susceptibility to colon cancer in humans and rodents has been found in mutation carriers of the same gene (e.g., APC). Allelic losses in rodents have been detected in regions corresponding to losses detected in human breast cancers, such as chromosome 17p distal to p53 and the 17q region of the BRCA1 (breast cancer 1 gene) locus. Some correlations were found for loss of heterozygosity lung cancer in humans and rodents, but loss of heterozygosity is infrequent in rodent liver cancers. Heterozygous p53 knockout studies in mice with low baseline cancer rates show that exposure to genotoxic carcinogenic agents induces a high frequency of early onset tumors, whereas nongenotoxic agents have minimal carcinogenic effects.

H. C. Pitot (University of Wisconsin, Madison, WI) discussed the genetic changes occurring during hepatocarcinogenesis in rats following treatment with chemical carcinogens or radiation and in transgenic rats harboring the albumin promoter-enhancer-SV40 T-antigen transgene. The induction of hepatocellular carcinoma in the rat can be dissected in three distinct stages, initiation, promotion, and progression. The "progressor" activity of the various inducing agents has been examined and it was observed that they possess the common characteristic of inducing clastogenesis. Karyotypic changes also occur in early stages of chemically induced hepatocellular carcinomas, showing a prevalence of over 50% of tumors with a trisomy of a short segment of the long arm of chromosome 1 (q41.1-q43.3) as well as a significant number of deletions of all or portions of the short arm of chromosome 3 and of the long arm of chromosome 6. In the hepatocellular tumors developing in the SV40 T-antigen transgenic mice, the same karyotypic abnormalities at a similar frequency were noted. These data indicate that the genetic program for the stage of progression in hepatocellular carcinoma in rat is not dependent on the carcinogen used in their induction.

B. Mechler (German Cancer Research Centre, Heidelberg, Germany) described the use of the fruitfly Drosophila as a particularly suitable organism for dissecting the genetic components controlling carcinogenesis. The fruitfly Drosophila has been used as a model system for studying the molecular basis of cancer development. In Drosophila, the tumor suppressor gene p53 ortholog, p53Dm, has been shown to play a key role in regulating cell proliferation and apoptosis. Mutations in p53Dm can lead to uncontrolled cell growth and tumorigenesis, similar to what is observed in human cancer. This model system allows for the study of genetic factors involved in cancer development and progression, providing insights into the underlying mechanisms of carcinogenesis.

The abbreviations used are: RER, replication error repeat; HNPPC, hereditary nonpolyposis colorectal cancer; NER, nucleotide excision repair; hUBF, human upstream binding factor; MEN2, multiple endocrine neoplasia syndrome type II; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; AFB1, aflatoxin B1.
These findings suggest that p127 is a major component of a pathway that lethal(2) giant larvae gene is the prototype of the tumor suppressor protein of 523 amino acids characterized by seven internal repeats. Among the components of the p127 complexes a serine kinase has been identified which specifically phosphorylates p127 on multiple sites and displays characteristics similar to those of protein kinase A. These findings suggest that p127 is a major component of a pathway mediating intercellular communication and directly controlling cell proliferation as well as cell polarity.

D. Bootussa (Erasmus University, Rotterdam, the Netherlands) examined the role of NER in preserving the genetic integrity and in preventing the deleterious effects of genotoxic agents in diseases such as cancer and other diseases. NER mutants display high sensitivity to UV light and numerous chemicals as well as elevated levels of induced mutagenesis. By transfection-correction cloning strategy some six complementing human NER genes (called ERCC for excision repair cross-complementing) have been identified. The phenotypic consequences of ERCC mutants are relevant in inborn human diseases, namely xeroderma pigmentosum, Cockayne’s syndrome, and trichothiodystrophy, that are characterized by hypersensitivity of the skin to UV light and the development of various clinical manifestations, in particular skin cancer, in xeroderma pigmentosum but not in Cockayne’s syndrome or trichothiodystrophy syndromes. Recently it was discovered that the ERCC 3 gene product or piT! is a cytoskeletal protein forming a network in the cytoplasm and undercoating the plasma membrane at junctional sites. Whether soluble or bound to the plasma membrane p127 is always recovered in an oligomerized form. Among the components of the p127 complexes a serine kinase has been identified which specifically phosphorylates p127 on multiple sites and displays characteristics similar to those of protein kinase A. These findings suggest that p127 is a major component of a pathway mediating intercellular communication and directly controlling cell proliferation as well as cell polarity.

C. Sapienza (Ludwig Institute for Cancer Research, La Jolla, CA) summarized data on genomic imprinting. Nonrandom retention of paternal alleles has been found in human Wilms’ tumor, retinoblastoma, osteosarcoma, and soft tissue sarcoma. There is preferential retention of the paternal allele in these tumor cells. In addition new evidence suggests an imprintor on the X chromosome that acts as a mutator in retinoblastoma. This recessive imprintor is not transmitted by males, and effects are manifest in females. Analysis of retinoblastoma incidence, by sex, shows slight male predominance overall. However, a new bilateral hereditary case in a previously unaffected family is much more likely to be a male. There is no difference by sex in unilateral sporadic retinoblastoma. In new retinoblastoma families with an affected father, there are fewer female offspring and a higher proportion of affected sons (offspring of affected males tend to be male affected and there are fewer daughters). A mutation in the imprintor gene on the X chromosome is postulated to be lethal in females who do not survive.

U. Wintersberger (University of Vienna, Vienna, Austria) considered effects of DNA damage on successive generations of proliferating yeast cells. The DNA damage might be lethal, affect progression through the cell cycle, or generate variants by mutation or gene conversion. Pedigree analysis of the behavior of progeny of yeast cells exposed to a DNA-damaging agent showed that the cell cycle is retarded to varying degrees in repair-proficient cells. Some agents affect the first G1 phase, whereas other agents cause extensive desynchronization through the cell cycle. After several generations, loss of some lines is observed. Therefore, lethal events can occur at first or later generations, as in cells exposed to ethylating agents. Further, the use of the Luria-Delbrück fluctuation assay together with a newly developed computer simulation program showed that the rate of a gene conversion event, yeast mating type switching, was enhanced for several generations after DNA damage. The yeast cell data might further understanding of human carcinogenesis.

D. Malkin (Hospital for Sick Children, Toronto, Ontario, Canada) described the occurrence of cancer in carriers of germline p53 mutations. These studies began as descriptive reports of multiple forms of cancer that aggregate in a few rare families. The cancers that occurred excessively in affected families include soft tissue sarcomas and osteosarcomas, breast cancer, leukemia, brain tumor, and adrenocortical carcinoma. Eventually the p53 gene was examined in these families because of the wide spectrum of cancers associated with somatic p53 alterations. After germline mutations were found in several of these families, researchers proceeded to investigate germline mutations in sporadic (nonfamilial) cancer cases. Among children with diverse childhood cancers, isolated cases with germline mutations have been found, primarily in very early onset cases. Work is in progress to develop rapid screening assays that can be utilized to study larger human populations. A screening assay in yeast has been developed and is being tested as a clinical diagnostic tool.

C. Kemp (Beatson Institute for Cancer Research, Glasgow, United Kingdom) discussed the role of oncogenes and tumor suppressor proteins forming a network in the cytoplasm and undercoating the plasma membrane at junctional sites. Whether soluble or bound to the plasma membrane p127 is always recovered in an oligomerized form.
genes in tumor initiation, promotion, and progression. In a skin system in transgenic mice expressing an activated H-ras, the oncogene was found to act as an initiating event. In addition, data on DMBA/TPA treatment in p53 knockout mice showed that the skin papilloma growth rate was not increased in hemizygous or null mice compared with control mice, suggesting that loss of p53 is not an initiator. However, null mice developed skin carcinomas at a very high rate and early in life, and heterozygous mice had an intermediate rate of carcinoma. H-ras mutations were found only in carcinomas and rarely in papillomas. The findings suggest that p53 is important in progression from papilloma to carcinoma. Carcinomas in null mice have early metastases and were markedly undifferentiated. For liver tumors, however, the numbers of preneoplastic lesions and tumors were similar in wild type and heterozygous p53 mice treated with diethylnitrosamine. None of the heterozygote mice had loss of the second p53 alleles in their benign liver tumors. The relevance of tissue-specific and carcinogen-specific mutations in both oncogenes and tumor suppressor genes was discussed.

F. Li (Dana-Farber Cancer Institute, Boston, MA) reviewed studies of familial childhood cancers that have identified members of an important class of cancer-associated genes, the tumor-suppressive genes. Inherited mutations have been found in the Rb gene for childhood retinoblastoma, the WT1 gene for Wilms’ tumor of the kidney, and the p53 gene in some families with Li-Fraumeni syndrome. Retinoblastoma has been the prototypic hereditary cancer in humans. Penetration of the gene is high and the relative risk in carriers exceeds 10,000-fold above the baseline population frequency of the disease. A recent study of more than 1600 survivors of retinoblastoma confirmed that hereditary cases have a marked excess of second primary cancers. The results show that germline Rb mutations can be disposed to cancers other than retinoblastoma and that radiotherapy further increases the risk of second neoplasms. Analyses of gene-environmental interactions can create future opportunities for cancer control to avoid of environmental carcinogens, early detection, and participation in chemoprevention trials.

V. Beral (University of Oxford, Oxford, United Kingdom) discussed the role of hormonal factors for breast cancer in women with a family history of the disease. The BRCA1 susceptibility gene on chromosome 17q is present with equal frequency in men and women, but breast cancer is limited to females. The finding indicates that female sex hormones might be critically important in breast cancer development in susceptible women. Data also indicate the following: breast cancer risk increases with early menarche; reproduction alters risk; and oophorectomy reduces risk. In addition, exogenous hormones in oral contraceptives and hormone replacement therapy might increase risk in young women, but the data in the literature are inconclusive. The Collaborative Group in Hormonal Factors in Breast Cancer was organized two years ago, and identified 50 studies of exogenous hormones and breast cancer. Preliminary analyses have been performed on 38 studies with 36,000 cases. Data are available in each study on breast cancer occurrence in mothers and sisters and show that approximately 10% (4000 subjects) have an affected mother and/or sister. The results, when available, should overcome the problems of reporting bias and small numbers and reveal whether family history modifies risk of oral contraceptive use.

B. Ponder (University of Cambridge, Cambridge, United Kingdom) discussed MEN2. Clinical features of the disease include medullary thyroid carcinoma, parathyroid adenoma, pheochromocytoma, and other features. MEN2 is present in 25% of all medullary thyroid carcinoma cases. Three MEN2 subtypes have been identified, and all are mapped to chromosome 10q11.2. This is the location of the protooncogene, Ret, which is somatically activated in papillary thyroid carcinoma and expressed in several neuroectodermal tissues. Ret knockout mice develop a Hirschsprung-like disorder. In MEN2A and familial medullary thyroid carcinoma, germline Ret mutations have been found in one of five cysteine residues in a cysteine-rich region in the extracellular domain of the protein. Correlations are found between mutational site/type and the spectrum of tissue involvement. Codon 634 mutations are more common in MEN2A families than in other families. Missense mutations at codon 634 that generate arginine are associated with parathyroid involvement or disease. Ret mutations appear to be dominant, and the second allele appears to be intact in tumors. Ret mutations are being sought in MEN2B because the disorder maps to chromosome 10q11.

N. Caporaso (National Cancer Institute, Bethesda, MD) defined molecular epidemiology as the study and identification of mechanisms that connect environmental exposure and cancer development. Among cigarette smokers who are exposed to an established human carcinogen, only 1 in 10 subjects develop lung cancer. Lung cancer is also known to occur in families, and segregation analyses suggest a role of heredity in early onset disease. Interest has centered on debrisoquine metabolism by the cytochrome P-450 enzyme, CYP2D6. Extensive metabolizers by phenotype analysis are overrepresented among lung cancer cases. Multiple case-control studies involving genotype and phenotype analyses show a relative risk of 1.8 among extensive metabolizers. However, these studies involve use of a drug to measure metabolism, and participation rates in many studies is only 25%. Therefore, selection bias might be the reason for the reported excess risk. Association with a rapid metabolizer is greater for histological types of lung cancers other than adenocarcinomas. These studies are complex and require well-defined populations, validated laboratory approaches, quantification of exposures, and adequate statistical power.

G. Lenoir (International Agency for Research on Cancer, Lyon, France) summarized the chromosome 17q mapping status of the BRCA1 gene for breast and ovarian cancer. Both of these cancers are known to have a familial component due in part to inheritance of autosomal dominant gene(s) with high penetrance. Initial mapping of BRCA1 to chromosome 17q was reported in 1990. The gene is not only important as the inherited defect in some families but may also be involved as somatic mutations in nonhereditary cases. An international collaborative study of 214 families shows that approximately 45% of families with early onset of breast cancers are linked to chromosome 17q. A much higher fraction of breast-ovarian cancer families are linked to the locus. Linkage data are being used to evaluate individual cancer risk in female relatives in these rare families. Isolation of the BRCA1 gene and identification of additional susceptibility genes for breast cancer will greatly broaden the population of women who can be examined for high risk of breast cancer and potential interventions.

R. Montesano (International Agency for Research on Cancer, Lyon, France) reviewed the evidence of the interaction between environmental chemical agents and viral infections in the etiology of human cancers. Epidemiological evidence indicates that some 15% of human cancers are attributable to viral infections, particularly some human papilloma viruses in the case of cervical cancer and HBV infection in HCC. It is also evident that a small proportion of the infected individuals will eventually develop cancer, indicating that other risk factors are involved. Recently informative markers, namely aflatoxin-albumin adduct and mutations at codon 249 (AGG— AAG) of the p53 gene, have become available to assess recent past exposure to aflatoxins, a major risk factor for HCC in certain parts of the world. Studies in The Gambia and some parts of China show that a high proportion of these populations are exposed to high levels of aflatoxins. Studies in HBV-transgenic mice indicate that chronic hepatitis results in an increased expression of some P-450 drug-metabolizing enzymes and this is paralleled by an increased binding of AFB1 to albumin. Further studies are needed to determine the relevance of this finding to human disease.
liver DNA. Field studies are supportive of this mechanism of interaction between AFB1 and HBV infection.

P. Cerutti (Swiss Institute for Experimental Cancer Research, Epalinges sur Lausanne, Switzerland) examined the presence of specific mutations into hotspot codons of proto-oncogenes and tumor suppressor genes in premalignant tissues in individuals at high risk of cancer. A large fraction of HCC from Qidong (China) contains a specific G to T transversion in the Third position of codon 249 of the p53 tumor suppressor gene. This particular mutation is observed more rarely in HCC from other areas of East-Asia and almost never in HCC from Western countries and Japan. In order to better understand its role in the pathogenesis of HCC, Cerutti and collaborators compared the load of codon 249 AGT mutations in nontumorous liver tissues from HCC patients from Qidong, urban Thailand, and the United States. The loads of codon 249 AGT mutations were strongly elevated in all specimens from Qidong, were slightly elevated in one biopsy from Thailand, but did not exceed background levels in specimens from the United States. Therefore, they paralleled the levels of food contamination with AFB1 in these areas and are in support of AFB1 as the causative mutagen. The presence of elevated loads of codon 249 AGT mutations in nontumorous liver tissue from HCC patients from Qidong suggests that the mutagenic event occurred early in hepatocarcinogenesis and that cells carrying this mutation have undergone clonal expansion in the nonmalignant tissue.

B. Weinstein (Columbia University, New York, USA) provided a final overview of this meeting, emphasizing the relevance of the findings discussed to the development of new strategies for cancer prevention. He briefly reviewed the exciting advances being made in the identification of inherited factors that influence interindividual variation in cancer susceptibility and their interplay with multiple external factors in the process of multistage carcinogenesis. He stressed that in view of this complexity even a single type of human cancer, for example colon cancer, can be caused by different factors in different individuals and that the resulting tumors can, therefore, display different mutations in cellular oncogenes and tumor suppressor genes. This heterogeneity will probably mandate different approaches to primary and secondary prevention in different subpopulations. He also reviewed recent evidence that in addition to cellular oncogenes (which often act through agonist-induced pathways of signal transduction) and tumor suppressor genes (which function through a variety of mechanisms), cyclins and related genes involved in controlling the progression of cells through the cell cycle constitute a third repertoire of genes that can be mutated or deregulated during multistage carcinogenesis. These changes may be particularly important in the process of tumor progression, thus contributing to the frequent amplification of genes and karyotypic instability of malignant tumors. He also stressed the need to elucidate not only the genetic mutations associated with multistage carcinogenesis but also the epigenetic distortions that occur in signal transduction, gene expression, gene imprinting, and differentiation. The latter events, although poorly understood, may play a critical role in the action of tumor promoters, the process of hormonal carcinogenesis, and the action of certain chemopreventive and cancer therapy agents (e.g., tamoxifen, the retinoids, and nonsteroidal antiinflammatory agents). Another important area of future study relates to the question of organ specificity in the action of specific inherited cancer susceptibility genes, including the Rb, p53, APC, and hMSH-2 genes. Insights into this question might contribute to a better understanding of the mechanisms by which mutations in these genes predispose to cancer and to novel approaches for prevention in individuals who harbor mutations in these genes. Finally, he stressed that with the increasing identification of mutated genes that predispose individuals to cancer development, there is an urgent need to establish at major medical centers throughout the world expertise and resources for performing the related assays (efficiently and with precision), for developing preventive measures for individuals who are at high risk, and for genetic counseling when this is appropriate. Thus, the current explosion of information on the interplay of inherited and environmental factors in human cancer causation provides exciting challenges and opportunities for cancer prevention.

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