Journal of Carcinogenesis

Editorial

Carcinogenesis: The more we seek to know the more we need to know – Challenges in the post Genomic Era

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In spite of all the advances in the treatment of cancer and knowledge of the processes responsible for this disease, there is a gap in understanding the molecular events leading to cancer and mechanisms of action by anticancer agents. Generally speaking, the field of carcinogenesis is far from being completely explored. Many novel ideas and concepts still need to be introduced into the field and the results of several provocative experiments are yet to be disseminated and shared. There is a need and greater scope for multidisciplinary research in the field. A forum for accelerated publication of results and a free access to such publications are very important to the field. These are the considerations that led to the birth of a new online journal, *Journal of Carcinogenesis* http://www.carcinogenesis.com. The journal will branch into six sections each of which is headed by an editor who is an expert in that field.

Diet, Nutrition and Environmental Carcinogenesis

The notion that diet and nutrition influence the development of cancer is not new but today, most scientists and the lay public firmly believe that cancer risk is linked to diet. In 1937, Frederic L. Hoffman noted that "excessive nutrition" was an etiological factor in cancer as well as were fatty and sweetened foods, white bread, and meat [1]. Armstrong and Doll published a landmark paper in 1975 examining cancer incidence and mortality rates world wide in relation to consumption of specific dietary substances which suggested that fat, meat, and animal protein consumption affected the incidence of and mortality from certain cancers [2].

Despite a good deal of research, our understanding of the identity of the food components that promote or prevent cancer is not complete. Thus, one of the major goals of the field of carcinogenesis is to discover time-efficient experimental paradigms that accurately identify dietary factors influencing prevention or development of cancer, and to identify and validate biomarkers for cancer risk in all tissues, particularly in those that give rise to the most common cancers such as lung, breast, colon, prostate, and pancreas. One method of identifying biomarkers is to elucidate the biological mechanisms by which dietary factors influence carcinogenesis. Mechanistic understanding may produce viable biomarkers, which, if validated, could streamline the identification of substances that deserve additional scrutiny.

Diet, Nutrition and environmental carcinogenesis section of the new Journal, *Journal of Carcinogenesis* will publish original research and review articles that advance our understanding of the fundamental linkages between diet and cancer, especially those manuscripts that describe the development or validation of novel biomarkers of carcino-

genesis, define food or nutritional factors that affect cancer development or elucidate the mechanisms by which these factors influence carcinogenesis.

Chemoprevention

Cancers in the organs containing epithelial sites such as breast, colon, prostate and lung represent major preventable causes of mortality in the U.S. population [3]. Epidemiological and laboratory investigations have provided strong, but largely circumstantial evidence that naturally-occurring dietary components may exert protective effects against cancers in these organs in humans [2]. However, a direct clinically relevant mechanistic significance of preventive efficacy for dietary natural phytochemicals depends on extrapolation laboratory results.

Investigations focused on development of human tissue-derived preclinical models, and on identification of mechanism-based genetic, molecular, endocrine and cellular biomarkers specific for pre malignant lesions [4] may provide a viable approach for evaluation of novel naturally occurring preventive agents [5–7]. Such approaches may minimize the need for extrapolation of clinical efficacy of new chemopreventive compounds. Promising agents identified through these preclinical studies can then be rapidly tested via conventional clinical trials.

The section on cancer chemoprevention in the *Journal of Carcinogenesis* encourages submission of manuscripts that are focused on development of novel model systems for multistep organ site carcinogenesis, identification and validation of new mechanistic surrogate endpoint biomarkers for risk of carcinogenesis, and approaches for high-throughput mechanistic screening of carcinogens and cancer chemopreventive agents. We also welcome manuscripts related to evaluation of preventive efficacy of new naturally occurring and synthetic compounds.

Gastrointestinal Carcinogenesis

Gastrointestinal cancers are among the leading cause of cancer deaths throughout the world. During the last decade, adenocarcinoma of the esophagus has been found to increase most rapidly throughout the Western hemisphere. Gastric adenocarcinoma is the second most common malignancy and cause of cancer related deaths worldwide, particularly in Asian countries. Colorectal cancer is the second leading cause of cancer deaths in the United States. It is anticipated that 130,000–200,000 individuals in the United States will be diagnosed annually with colorectal cancer, and more than 56,000 will die of this disease. All of the three above carcinomas, arising from the esophagus, stomach and colon proceed through preneoplastic stages, which, if diagnosed early, would be amenable to significantly improved, long-term survival of the patients and possible cure.

A potential strategy to reduce the mortality rate of esophageal adenocarcinoma is to identify patients at risk in early stage. Increased COX-2 expression in vitro is associated with increased cellular proliferation and decreased apoptosis. These findings may have implications for chemoprevention of adenocarcinoma of the esophagus. Similarly, a novel monoclonal antibody called mAb Das-1 (7E12H12, IgM isotype) has been found to be very sensitive and specific for early detection of metaplastic changes in the distal esophagus and Barrett's epithelium, allowing more effective screening [8].

Inflammatory bowel disease, age, diet low in fiber and high in fat, sedentary life style and of course familial incidence are risk factors for colon cancer [9]. In the colon, adenomatous polyp is a well recognized pre-cancerous condition. The prevalence of adenomas in the United States is approximately 25% by the age of 50 years, although autopsy series suggest that as many as 60% of men and 40% of women may have adenomas by 50 years of age. Molecular genetic studies of Barrett's epithelium, gastric intestinal metaplasia and colorectal tumors have provided significant insight into inherited predisposition and possible clues in the pathogenesis. For colorectal tumors, in particular, where such studies are done more extensively, accumulation of oncogene and tumor suppressor gene mutations appear to be critical to tumor development [10]. A relatively limited number of oncogenes and tumor suppressor genes – K-ras, APC, and p53 genes – have been found to be recurrently mutated in colorectal tumors and intensive studies of the function of these critical genes in normal and neoplastic cell growth continue. A number of other genes, in which somatic mutations appear to be less frequent, have also been identified. These include the β-catenin, DCC, DPC4, SMAD2, TGFβIIR, MSH2, MLH1 genes. Changes in the expression of a variety of genes appear to have a crucial role in the development of cancer and in its clinical course.

Despite significant progress, much work lies ahead before we have a fully developed picture of the pathogenesis of various gastrointestinal cancers. The significance of the cancer cell phenotype of each of the inherited and somatic mutation has not yet been clearly defined. It is very likely that identification of additional oncogenes and tumor suppressor genes together with histogenetic studies will provide important information related to cellular metaplasia in the esophagus, stomach as well as colorectal cancers. At present, there is little understanding of the relationship between dietary and environmental agents associated with any increased risk of gastric and colorectal cancers. The precise role of helicobacter pylori infection of the stomach is also poorly understood. Nevertheless, a hopeful outlook is that significant efforts made during the last decade have provided important insights into the ge-

netic and molecular basis of the esophagus, stomach and colorectal cancers, which will help in the diagnosis, and treatment of patients with these tumors.

We eagerly look forward to receiving the exciting work from various contributors in the field of gastrointestinal carcinogenesis. We are particularly interested in articles that will impact our understanding of many of these cancers at the genetic and molecular level, which will significantly influence the early diagnosis, and more effective treatment of these patients.

Preclinical and clinical studies

At the beginning of the 21st century, we are experiencing a great development in the field of cancer biology and medicine because of the rapid progress of molecular biology and genetics. In particular, the progress in carcinogenesis research has enabled us to develop some new therapeutic and preventive strategies against cancer in addition to traditional chemotherapies. Such a significant advance was possible largely due to the studies of tumor cells at molecular levels during the last 10 years or so. Studies on gene expression profile on the serial steps of carcinogenesis may lead the way to develop effective therapies, so called 'molecular target therapy'. One of the examples includes imanitib mesylate (Gleevec in the US, Glivec outside the US), which is a specific inhibitor for tyrosine kinase in Philadelphia chromosome positive chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST) [11,12]. In the coming years, many candidate drugs will be tested and used with the similar concept and technology. Moreover, technological advances in the field of genomics and proteomics will also usher in new era for the preclinical and clinical studies based on individual and race differences.

In the **Preclinical and Clinical Studies** section of the journal, we welcome you to publish your exciting results in the new era of cancer detection, therapy and prevention from the standpoints of carcinogenesis. We will publish results from original research that makes use of materials from cancer patients to conduct clinical or preclinical studies with a goal to develop new diagnostic and treatment strategy. The manuscripts to be published in this section will include results from the following categories. (a) preliminary results from clinical studies that suggest the potential for extensive future clinical studies and (b) results from experiments using surgical or biopsy specimens for identification of biomarkers of carcinogenesis and measure of efficacy of cancer therapy and potential targets for anticancer drug development [13]. Authors who want to submit hypothesis, ideas on translational research are also encouraged to send their contributions.

DNA Damage and Cell Signaling

Environmental carcinogens interact with DNA, cause mutations, if the function of critical genes is affected by mutation, deleterious effects like cancer may occur [14]. During the past several years, significant progress has been made in understanding the role of carcinogens in cancer initiation and progression [15]. However, appropriate prevention approached for carcinogen-initiated cancers are still not in place. One of the reasons is the lack of sufficient knowledge about the molecular mechanisms of the interaction of carcinogens with genes and the role on these genes in carcinogenesis.

Defects in one or several of the DNA repair pathways can be a determining factor in accumulation of mutations in critical genes involved in the initiation and transformation of normal cells [14]. In clinical practice many chemotherapeutic drugs are the DNA-damaging agents, which induce cell death through apoptosis by increasing DNA damage and decreasing DNA repair [16]. One of the questions of clinical relevance is how we can save normal cells from DNA-damaging effects of the clinically useful chemotherapeutic drugs while increasing the killing of cancer cells? Alternatively and ideally, drugs inducing apoptosis without DNA damaging effect would be highly desired. Addressing these issues will be of immense interest to the readers of the *Journal of Carcinogenesis*.

We will also be interested in publishing those articles that advance our understanding of how DNA damage signals are coordinated among tumor suppressors and proto oncogenes and their gene products and how cell cycle control mechanisms are linked with DNA repair mechanisms [17,18]. We invite papers pertaining to studies addressing how cells exposed to DNA-damaging agents make decision on whether to go to 'safe mode' of cell cycle arrest and call for help from DNA repair machinery or to save the progeny by sacrificing themselves in an apoptotic way. *Journal of Carcinogenesis* will publish articles devoted to basic science and translational aspects of DNA damage and cell signaling.

Genomics and Proteomics

Although many factors may contribute to cancer development, cancer is a genetic disease and is caused by genetic alterations in certain genes. Cancer development is associated with oncogene overexpression and inactivation tumor suppressor genes (TSG). One of the causes of oncogene overexpression is mutation in the regulatory regions or in the genes encoding transacting factors that have regulatory roles on oncogenes. However, the most remarkable genetic alteration causing oncogene overexpression is gene amplification [19–21]. Oncogene amplification can be detected by using methods such as Southern analysis [22] or Comparative Genomic Hybrid-

ization [23] that may quantitatively reveal the gene dosage in the cells.

The other method that may have not been paid attention to is genetic analysis. It is known that DNA sequence polymorphisms, especially, those consist of single nucleotide sequence polymorphisms (SNPs), are present at a high density along the chromosomes [24]. Because of such a high density, many genetic markers are heterozygous for a given patient and in a given chromosomal region. When chromosomal amplification occurs, amplification may not occur on both homologous chromosomes simultaneously. Even if it occurs on both chromosomes, the number of resulting copies of an amplified region may not be equal. In the cases that the difference is very big, only one allele will be detected and the other will not or almost not be detected. If the difference is not that big but significant, one allele will be detected in a significantly larger quantity. These will be considered as loss of heterozygosity (LOH) or allele imbalance and can be conveniently detected by genetic approach that can be used to discriminate the allelic differences.

TSG inactivation may be caused by various reasons. Mutations that cause decrease in gene expression and/or result in inactive gene products are some of the reasons. However, since each cell contains two copies of these genes, the chance of having both copies of a gene inactivated would be very low. With its recognition in 1970 [25], LOH has been shown, by a large number of studies, to play an important role in TSG inactivation, and may be used as a common indication of TSG inactivation or oncogene amplification. LOH has been detected in a number of chromosomal regions indicating the number of genes involved in cancer development could be large. Exhaustive identification of these genes, of course, is one of the major goals for understanding cancer development, which may take years of effort. However, the function of these genes may be studied by correlating cancer morphology and the respective chromosomal locations associated with LOH without knowing the genes and their products.

To be able to understand the genetic basis of cancer thoroughly, two major methodological issues need to be addressed. One is the high degree of heterogeneity in cancer tissue. Many cancer tissues contain proliferative lesions and more advanced malignancy, which may represent different stages of cancer development. On the other hand, certain proliferative lesions or more advanced malignancy may be categorized to be at the same development stages but are present in distinct morphology. Studying these lesions and malignancy individually may allow one to learn the stepwise involvement of the genes during cancer development and different molecular pathways underlying the distinct morphologies. For this reason, it is critical to isolate and study these lesions and malignancy separately using microdissection technique.

The other issue is the involvement of a large number of genes with different chromosomal locations during cancer development. To include these genes in the study, LOH analysis can be used as a common assay. However, since the gene number is large and their chromosomal locations are different or unknown, it is necessary to perform a genome-scale analysis with genetic markers of a high density, or in other words, with a large number of markers. This has been made possible by the recent large-scale discovery of SNPs. However, since the amount of material from microdissection is very small, inclusion of a large number of markers in the study is a serious challenge. Therefore, development of high-throughput assays with high sensitivity is a critical step toward understanding the genetic basis of cancer development in a comprehensive way.

During the past a few years, a large number of studies has been performed to reveal changes in gene expression patterns at either or both mRNA and protein levels. Many of these studies were on a large or genomic scale. However, the authors may have found difficulties to interpret their data. Such an issue could be addressed by associate genetic alterations in the cancer cells with the patterns from gene expression profiling simply because genetic alterations are the primary causes of changes in gene expression. On the other hand, studies on gene expression profiling will provide essential information on the effect of genetic alterations, affected molecular pathways, and biomarkers in these pathways, which maybe used conveniently for monitoring cancer initiation and progression.

Since cancer is a genetic disease, it is critical to introduce genetic approaches into cancer research. The Genomics and Proteomics section of the journal will publish articles describing using genetic approaches or combination of genetic approaches and molecular and cytological approaches to addressing important issues in the field of carcinogenesis. We also welcome manuscripts describing novel technological advances or refinements of existing technologies that advance cancer research. In addition, we will also be interested in publishing articles that present results using any other novel technologies and contribute to enhancement of our understanding of the processes of carcinogenesis.

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