Overview of carcinogenesis: past, present and future

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In the foregoing articles, the editors of Carcinogenesis have identified the major themes of current carcinogenesis research and assembled an outstanding group of authors to review these areas. I have been asked to provide a historical overview of past accomplishments and describe how these contributed to the broader efforts to overcome the burden of human cancer. My assignment also included a look into the future. As scientists we formulate hypotheses that attempt to predict the future. Occasionally we are successful. The pioneers of carcinogenesis research were remarkably successful in predicting the future. Armed with primitive technology relative to today, these scientists studied the biology of carcinogenesis and conceptualized a framework for cancer pathogenesis that virtually everyone working in cancer research follows today. The current generation has been charged with filling in the details. In the details lay the future. Together with past accomplishments, these emerging details form a remarkable picture of progress in understanding and application, creating realistic and imminent promise to achieve victory in the fight against cancer.

Past accomplishments

The paradigms of cancer pathogenesis

Studies first conducted in animal models and inspired by pathological analysis of human neoplasms confirmed that cancer development is a multistage process in which the summation of events was required to produce a malignant tumor. The concept of initiation described an irreversible consequence of the interaction of a tissue with carcinogens, a change that was often not recognizable as a pathological entity but produced cells that were precursors of the future tumor. Tumor promotion was defined as a reversible process that facilitated the expression of the initiated phenotype. Promotion was distinguished from progression, the former having its influence at the tissue level and the latter representing further phenotypic alterations in initiated cells. Conversion from a pre-malignant phenotype to a malignant cell type was recognized as the major time-dependent stage of cancer pathogenesis, whereas tumor heterogeneity associated with the acquisition of metastatic potential was determined to be a relatively rapid event. These characterizations consumed the first 30 years of organized carcinogenesis research.

With the introduction of in vitro models came greater understanding of the cellular events required for multistage carcinogenesis. The inductive, single-cell origin of cancer, the relationship of mutagenesis to carcinogenesis, and the linear relation of dose to response for chemical exposure were essential findings to support somatic mutations as the basis for cancer pathogenesis. Cultured cells from specific human tissues revealed both the relative resistance of human cells to transformation when compared with corresponding rodent cells and the large inter-individual variation among human tissue donors for responses to carcinogens. At this same time, cells from cancer-prone human patients were found to be particularly susceptible to transformation by oncogenic viruses, indicating directly that the interaction of an oncogenic agent and the host genetic profile were partners in determining the risk for cancer development.

When epidemiological studies of occupational groups and migrants indicated that environmental factors were major causes of human cancer, carcinogenesis research expanded into a more mechanistic era that persists currently. Documentation of pathways for the metabolic activation and detoxification of carcinogens explained the specificity of carcino–macromolecule interactions, illuminated important genetic determinants of cancer risk, and led to the development of methods to detect carcino–macromolecule adducts in human populations. These insights and methods spawned the field of molecular epidemiology and helped to explain the organ specificity of certain carcinogens. The exquisite sensitivity of fetal and newborn animals to carcinogen exposure and the marked variability in cancer susceptibility among animal species and strains focused attention on the search for susceptibility determinants in human populations that is a major research theme today. The emergence of DNA as a critical target for carcinogens was fostered by the discovery of defective DNA repair processes in cancer prone humans. In the intervening years a wider understanding of DNA repair processes has demonstrated the important contribution of DNA structural alterations and the molecules that recognize and repair these alterations to all stages of cancer pathogenesis. Early studies on the mechanism of tumor promotion focused on the role of phorbol esters in skin carcinogenesis. Initially, these studies seemed to lack a more general applicability although phorbol esters were potent phenotypic modifiers of many cell types. The elucidation of the function of phorbol esters as potent activating ligands for protein kinase C was pivotal for illuminating the role of signal transduction pathways, cytokines and hormones and the importance of clonal selection in cancer development.

The fields of chemical carcinogenesis and viral carcinogenesis coalesced with the discovery that many viral oncogenes were altered forms of cellular genes controlling growth, differentiation, mortality or gene expression. It was rapidly determined that these cellular genes could be targets for carcinogen-induced mutations in experimental models, and subsequently it was demonstrated that signature mutations...
occurred in human cancers. The importance of tumor suppressor genes was first recognized from observations of hereditary and spontaneous human cancers. The high frequency of inactivating mutations in these loci inspired the creation of experimental models to study their mechanism of action. Experimental analysis exposed critical pathways controlling cell growth, programmed cell death and differentiated function that counteracted oncogenes. In certain cases these pathways functioned most efficiently in human cells providing an explanation for the relative resistance of human cells to transformation and the frequent requirement for inactivation of both alleles of the tumor suppressor locus for tumor formation.

Validation of hypotheses
Carcinogenesis research has played a critical supporting role in validating hypotheses developed from population studies. In some cases experimental studies have been predictive of cancer risks. The carcinogenic and tumor promoting properties of cigarette smoke and the identification of the offending chemical and gaseous components provided experimental evidence for its potency as a carcinogenic mixture and its organ targeting, and predicted the reversibility of cancer risk with smoking cessation. The potential transplacental carcinogenicity of diethylstilbestrol, and the dangers of vinyl chloride, aromatic amines, polycyclic hydrocarbons and bis(chloromethyl)ether in occupational settings were confirmed experimentally. Breast cancer protection from early pregnancy and breast cancer induction by hormones were demonstrated in experimental animals. The modifying influence of nutrition on cancer induction and the identification of environmental contaminants that contribute to cancer incidence are examples of hazards identified through model systems designed to study chemical carcinogenesis.

Impact of carcinogenesis research on human health
While difficult to quantify, it is a certainty that nutritional modification, environmental cleanup and abatement of occupational exposures have reduced cancer risk. Smoking cessation has had a major impact on lung cancer reduction in men. Recent declines in cancer incidence at a number of organ sites can be attributed to lifestyle changes inspired by insights derived from basic carcinogenesis research. Most gratifying is the emergence of active intervention or chemoprevention to protect high risk individuals from developing cancer. This approach is a direct translation of fundamental knowledge of mechanisms of carcinogenesis. Anti-estrogens, retinoids, inhibitors of the arachidonic acid cascade and sunscreens are having an impact on reducing tumor incidence for at-risk populations, a major triumph for our field.

Emerging opportunities
Impact of carcinogenesis research on biomedical science
The interplay of scientific disciplines is a major factor in the rapidity of biomedical research advances. Contributions from carcinogenesis research have led to important insights in other research areas. In particular, advances in drug development, pharmacokinetics and host responses were accelerated by the discovery of metabolizing enzymes for carcinogens. Genetically determined pathways for carcinogen metabolism are now understood to control the metabolism of a variety of drugs, natural products and environmental contaminants, and genetic polymorphisms are important in drug reactions. The discovery of oncogenes revealed signaling pathways that are implicated in developmental anomalies, aging syndromes, immunological abnormalities and fertility problems. The complex interactions of protein kinase C isoforms, first revealed from interest in tumor promotion, are now recognized to contribute to insulin signaling, immune cytokine receptors and neurological responses, to name a few. The diverse activities of the TGFβ superfamily in wound healing, the integrity of the immune and osseous systems, and morphogenesis were recognized as a consequence of initial discoveries in carcinogenesis research. These examples are by no means inclusive of all the collateral benefits for biomedical science that were generated from carcinogenesis research.

Oncogenesis as aberrant ontogeny
Emerging studies in cancer genetics have revealed human tumors or neoplastic syndromes that are initiated by mutations in essential developmental or patterning genes. Sporadic and hereditary basal cell carcinomas of the skin are the result of mutations in the human homologue of Drosophila patched or other members of the sonic hedgehog patterning pathway. This pathway is important for hair follicle formation, and basal cell tumors are neoplasms evolving from aberrant follicles. Mutations in β-catenin are responsible for the majority of pilomatrixomas, also a tumor of hair follicle origin, and mutations in apc, another member of the WNT developmental pathway, are causative for sporadic or familial colonic polyps. These tumors generally grow slowly and invade locally until late in their clinical course when additional mutations alter the phenotype. Tumors or neoplastic syndromes that may also fall into this category are multiple endocrine neoplasia type 1 (mutations in men1), Cowden’s disease (mutations in pten) and Von Hippel–Lindau disease (mutations in vhl). This growing subfamily of tumor types of diverse tissue origin has in common mutations in tumor suppressor genes and a clinical course characterized by multiple benign tumors of diverse tissue origin that give rise to cancers later in the course of progression. Malignant variants often grow by local extension rather than widely metastasizing. These tumors offer an opportunity to evaluate complementary pathways essential for premalignant progression and malignant conversion during the course of carcinogenesis in patients with multiple lesions.

Endogenous carcinogenesis
Elimination of carcinogens recognized as human hazards and confirmed in bioassays has reduced the cancer risk for exposed populations. However, controversy exists about the impact on cancer rates of more incidental exposures of weaker carcinogens recognized in animal bioassays at maximal tolerated doses. The controversy is amplified when no obvious mechanism of action is detected. The discovery of DNA adducts and mutations induced by endogenous metabolism or natural products has raised the issue of relative contributions of endogenous or natural exposures to cancer risk versus the risk from exogenous contaminants. Current studies have focused on endogenous oxidation reactions and particularly the consequences of nitric oxide generation or lipid peroxidation as important contributors to cancer induction. This is a critically important area for analysis since it will have a major impact on the distribution of public health funds for cancer research and guide the design of cancer prevention strategies. Likewise, awareness that chronic bacterial or viral infections have a major impact in gastric and liver cancer provides both an opportunity for intervention and an approach for cancer prevention.
Imprinted genes and cancer risk

It is estimated that hundreds of genes in the human genome are maternally or paternally imprinted, thus creating a functional haploid state. These genes or their regulatory cofactors would be prime targets for modification by exogenous exposures or endogenous factors during the process of carcinogenesis. A paradigm for this speculation is the maternally imprinted IGF2 locus. Loss of imprinting at this locus is associated with a 1000-fold increase in Wilms’ tumor risk, and 30% of sporadic breast cancers have lost IGF2 imprinting. A number of other human cancers of diverse origin demonstrate loss of imprinting. Among the list of imprinted genes are growth factors and their receptors, raising the possibility that changes in imprinting could influence cell proliferation and provide a selective advantage to tumor cells. Recently an imprinted locus has been identified as the origin for familial hydatidiform mole, a common gestational neoplasm. As the identification of imprinted genes expands and the underlying function and mechanisms of imprinting are delineated, the contribution of imprinted genes to the wider cancer incidence may be clarified, and these genes may serve as early markers for cancer development.

Future directions

Translation

It is clear that we face a future with optimism and opportunity. The labors of three generations of scientists studying mecha
isms of carcinogenesis have reached fruition. We are seeing the reward in rational therapies and prevention strategies. Retinoic acid induces remission in promyelocytic leukemia, and we understand why. In this case, understanding the basic pathogenesis of the disease has resulted in effective treatments. Therapies based on p53 status of tumors look promising, and targeted immunotoxins, now in clinical trials, are designer treatments based on knowledge of cancer phenotypes. Antibodies to erb-b family members are saving lives of patients with advanced cancer. Our understanding of apoptotic and terminal differentiation pathways are yielding new strategies for treatment by genetic or pharmacological methods. Chemoprevention protocols for high risk populations for breast, colon, skin and lung cancer have their basis in understanding mechanisms of carcinogenesis. These can have an immediate impact on cancer incidence. Similarly, changes in nutritional patterns, based on experimental studies, are also contributing to cancer prevention.

We anticipate that methods for early detection of neoplastic lesions, perhaps even at the initiation stage, will come from animal models that are designed to reflect the precise pathogenesis of a particular human cancer. The ability to design rodent models where specific genes or mutated genes are organ targeted and conditionally expressed will provide unparalleled opportunities to define the multistage biology of cancer and the pathways affected. These models will likely reveal mutation spectra, alterations in gene expression and phenotypic markers that will have exceptional value for detecting early lesions. They will also serve as preclinical surrogates for testing therapeutic and prevention strategies. Likewise, animal models will reveal important components of cancer susceptibility traits for particular tumor types. Carcinogenesis studies in designer mice and inbred and congenic strains, together with the elucidation of the entire mouse genome, will accelerate progress in this research area and facilitate translation to the human population.

The impact of technology

We must acknowledge the engineers, computer specialists, chemists and molecular biologists for their contributions to current progress. They have provided us with the tools to scan the genome, inject embryo cells, visualize molecules in real time and screen for biologically active surrogate compounds to name a few important breakthroughs. What does the future hold in technology? The elucidation of the complete human and mouse genomes in the near future will accelerate the understanding of cancer genetics. Microarray technology will reveal interacting pathways and temporal relationships for mRNA and protein expression in normal and cancer cells, exposing new targets for drug therapy. Bioinformatics support for these new techniques will make it possible to interpret data of a magnitude never before contemplated. Imaging techniques developed to detect single molecules will provide real time evaluation of protein–protein, protein–DNA and DNA–RNA interactions and the factors that regulate them, enhancing our understanding of signaling pathways, receptor–ligand function and the control of gene expression. These are the tools needed to understand the details of the molecular anatomy of cancer.

What should we expect for the immediate future?

Funding will direct the answer to this question. Search the National Cancer Institute Bypass Budget, and you will see the near future. This indicates that societal and political considerations are working in concert with scientific opportunities as important and necessary contributors to decisions on cancer research directions. For the year 2000, NCI has focused on four opportunities, and carcinogenesis research is a principal component of each. Priority has been given to cancer genetics, with a particular focus on defining cancer susceptibility states and the interaction of genes and the environment. Support for infrastructure, including informatics and genetic counseling will be provided. Additional priority is given to development of new preclinical models of cancer pathogenesis, designed precisely to study all stages of tumor development and address prevention and treatment. Using developing knowledge of cancer genetics and advanced technology for producing genetically modified mice, this opportunity unites discoveries in human cancer biology and experimental carcinogenesis. The bypass budget will support improvements for diagnostic imaging techniques. Based on rapid advances in technology, this initiative will have immediate clinical results for early cancer detection and monitoring therapeutic effectiveness, its primary purpose. However, one can imagine how these technical advances will also serve the carcinogenesis research community, as we seek to evaluate our new model systems and novel experimental approaches to prevention. The bypass budget also seeks support to define the signature of cancer cells, with the goal of developing markers for early detection of tumors or premalignant cells. Technology has provided us with the tools to make this a possibility, but it has been carcinogenesis research that has allowed us to ask the question.

Through three generations of scientists dedicated to carcinogenesis research, we have enriched our understanding and filled in the details of cancer pathogenesis, developed designer experimental models and rational cancer treatments, and have predicted risks and prevented disease. We can celebrate improv-
ing the public health. Our discoveries may be tempered at times by social and political considerations so it is difficult to predict the rate at which discovery will be translated into application. We still have work to do and remain an integral part of the future efforts. However, this generation of scientists involved in carcinogenesis research will likely see the ultimate rewards: substantial reduction of cancer incidence by prevention strategies, detection and eradication of early lesions before they become life threatening and control of more advanced disease from rational treatment are realistic achievements.

This 20th anniversary of Carcinogenesis marks more than a milestone for the journal or the field of research, it marks a milestone for public health and a reward for the investment in carcinogenesis research.

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