REVIEW

Genetically Determined Susceptibility to Cancer

By Paul A. Marks

This review summarizes evidence for genes that exist in humans that affect susceptibility to cancer. It is not possible yet to precisely describe the relationship between so-called “cancer gene(s)” and carcinogenesis. Among the questions that remain open is the nature of the events that must occur in individuals with a cancer gene before clinically significant cancer develops. Regardless of the nature of such events, there is evidence that a genetically determined factor can be important in the initial or early steps in malignant transformation of cells. A major challenge in cancer research in the coming years will be the characterization of “cancer gene(s).” Such studies will have profound implications not only for understanding the nature of carcinogenesis, but also for the development of new approaches to detection and treatment of cancer.

Over the past several years, important progress has been made in our understanding of the relationship of genetically determined factors to the development of cancers. It is clear that as we define, at a molecular level, genetic mechanisms involved in cancer, we will advance our understanding of carcinogenesis and will be able to rather precisely define the role of certain environmental agents, such as chemicals, viruses or physical agents, in this process. In turn, these understandings will provide new approaches to prevention, diagnosis, and treatment of cancer. This review discusses evidence for genetically determined susceptibility to cancers in human subjects.

Some Characteristics of Human Cancer

The incidence of cancer in human subjects increases with age. The relationship of cancer to age, based on deaths from malignant neoplasms of all types between the ages of 25 and 80, is linear when the data are plotted on a logarithmic scale (log–log plot). This relationship has been interpreted as consistent with carcinogenesis involving multiple events and that cancer will not occur until each of these events, perhaps only the early steps of which involve alterations in DNA, have occurred.

It may require years to accumulate these events. This is suggested by data indicating that a lag period of 5–30 yr or more may occur between the initial recognized exposure to a potential carcinogen and the appearance of a cancer. This lag period has been shown for a number of carcinogens, such as ionizing radiation and those related to smoking. The relationship between age and the incidence of cancer, as well as the lag period in appearance of cancer, are consistent with the suggestion that cancer is the result of a multistep process. These observations, of course, do not tell us the nature of the steps that may be involved in carcinogenesis. It is also worth pointing out that a progressive increase in the incidence of cancer with age does not necessarily imply that the population is homogeneous with respect to susceptibility to cancer, since this observed relationship is compatible with a mixture of susceptibilities varying over 50–100-fold.

Mendelian Inherited Traits and Human Cancer

Over the past 10 yr, there has been a substantial increase in our recognition of hereditary conditions that predispose to cancer in humans. Peto has...
suggested that individuals with genetically determined increased susceptibility to cancer can be classified into three broad groups. Group 1 includes those with genetically determined increased risk for cancer of a 100-fold or more. Such conditions include recessive traits such as xeroderma pigmentosum and ataxia telangiectasia, as well as dominant traits such as familial polyposis coli, neurofibromatosis, and retinoblastoma. Only a small proportion of human cancer involves such a large genetic risk factor. Group 2 includes those with a genetic predisposition that increases risk by 10–100-fold over the general population. This group may include a substantial proportion of all cancer patients. Group 3 includes individuals whose genetic risk is increased less than 10-fold; the risk to this population is at present very difficult to detect.

There is increasing evidence that for every specific type of cancer there may be a genetically determined factor, as well as a nonhereditary form. At least two and possibly as many as five genetic forms appear to increase susceptibility to colon cancer, including familial polyposis coli. It has been estimated that forms of colon cancer associated with a genetically determined increased susceptibility account for about 10% of all human cancers of the colon in the United States. Another common form of cancer for which there is evidence of genetic factors is breast cancer. At least three forms of breast cancer in which increased susceptibility owing to a genetic factor exists have been suggested, based on patterns of associated tumors, namely, breast cancer associated with ovarian cancer, breast cancer associated with endometrial cancer, and breast cancer associated with brain tumors or sarcomas. As much as 10% of all breast cancer in the United States may be associated with genetic factors. Some of the strongest evidence for the role of genetic factors in determining breast cancer derive from the recent studies of King, who used linkage analysis to establish genetic transmission of at least one form of breast cancer. In 14 families identified at high risk with respect to breast cancer, the pattern of occurrence of breast cancer was found to be consistent with the inheritance of an autosomal dominant allele, which greatly increases susceptibility to the disease. Linkage analysis in these families at high risk for breast cancer indicated that the marker gene, glutamate pyruvate transaminase (GPT), is closely linked to a dominant allele increasing susceptibility to breast cancer. GPT is polymorphic in humans, and it is the type-2 GPT that is found to be closely linked to the allele increasing susceptibility to breast cancer in the families studied by King and her associates. The GPT locus has been provisionally mapped on chromosome 10. Unfortunately, no other marker that is polymorphic in white populations has been located on this chromosome to permit confirmatory studies of this linkage relationship. King's studies predict that women carrying this susceptibility allele have a 12% risk of breast cancer by age 35, a 50% risk of breast cancer by age 50, and an 87% risk of breast cancer by age 80, while their female relatives who do not carry the susceptibility allele have no increased risk of breast cancer over that of the general population. Fathers can carry the susceptibility allele and pass the increased risk to their daughters. GPT typing cannot be used as a screening test for breast cancer in the general population. GPT gene simply marks the chromosomal region where a susceptibility gene of still unknown function may be located in these families at high risk for breast cancer. In the general population, there is no association between a woman's GPT type and her risk for breast cancer.

Any estimate of the overall contribution of genetic factors to the burden of cancer in our society is, at present, impossible. We have an inadequate understanding of the interaction between genetic factors and environmental hazards for cancer.

MUTAGENESIS AND CARCINOGENESIS

Ames and his colleagues have demonstrated that substances known to be carcinogenic in man and/or animals can be mutagenic in bacteria. Those substances known to be carcinogenic may not be directly mutagenic, as Ames demonstrated that the majority of these agents require activation to be mutagenic. The majority of so-called precarcinogenic agents must undergo metabolic alterations in the body to active carcinogens. Thus, an extensive body of data has accumulated indicating a strong correlation between carcinogenic activity and mutagenic activity. Additional evidence for the relationship between mutagenesis and carcinogenesis is the observation by Cleaver that repair of DNA damaged by ultraviolet light, which occurs in normal human cells, is defective in patients with xeroderma pigmentosum. The genetically determined defect in DNA repair in cells of patients with xeroderma pigmentosum make them several thousand times more susceptible to skin cancer than normal subjects. It is interesting to note that the repair defect in xeroderma pigmentosum patients does not result in any obvious increase in the incidence of other common cancers, such as lung, colon, or breast cancer, in these patients. Consistent with genetic factors playing a role in increased susceptibility to cancer are other syndromes in which hereditary defects in DNA repair are associated with an increased incidence of cancers. Ataxia telangiectasia is an hereditary disease in which the cells of patients...
are unusually sensitive to x-ray, reflecting a defect in the repair of DNA damaged by ionizing radiation.\textsuperscript{21} The genetically determined defect in ataxia telangiectasia is distinguishable from that of xeroderma pigmentosum. In both instances, they provide examples of an interaction between genetic and environmental factors that can lead to cancer. The role of genetic factors in increased susceptibility to cancer is undoubtedly quite complex. As noted above, the hereditary defect in DNA repair associated with xeroderma pigmentosum, detectable in different cells of the body, causes a marked increase in the incidence of skin cancer only, while in other hereditary diseases, as for example, Bloom’s syndrome or Gardner’s syndrome, the genetic factor appears to increase the incidence of many common forms of cancer in these patients.

It seems probable that at least in certain instances, susceptibility to chemical carcinogens may also be determined, in part, by genetic traits. For example, the genetic trait expressed as low activity of the enzyme, aryl hydrocarbon hydroxylase, may confer some protection from the carcinogenic effects of cigarette smoke and a lower rate of lung cancer than predicted from smoking habits.\textsuperscript{22,23} Other studies have disputed the conclusion that susceptibility to lung cancer induced by cigarette smoking results from genetically determined inducibility of this enzyme, so that this remains an open question.\textsuperscript{24,25}

CHROMOSOMAL REARRANGEMENTS AND CANCER

Another line of evidence that indicates a role for genetic factors in carcinogenesis derives from cytogenetic studies. There are approximately 20 neoplastic disorders that exhibit consistent chromosomal defects. The chromosomal defect is most often manifest as a reciprocal translocation in which one chromosome remains constant and breaks at a specific site (the donor chromosome), while the receptor chromosome and its break point vary.\textsuperscript{26} The existence of specific chromosomal rearrangements associated with cancer was first suggested by the discovery of the Philadelphia chromosome in chronic myelogenous leukemia.\textsuperscript{27} The Philadelphia chromosome is generally the product of a translocation of part of chromosome 22 to another chromosome, usually chromosome 9, but in a small percentage of cases, other chromosomes.\textsuperscript{28} The fact that the recipient chromosome can vary suggests that there is a critical site in chromosome 22 whose function may be disrupted by this translocation and could conceivably be a factor in the development of cancer. One cannot conclude from cytogenetic observations that the alterations in chromosomal structure precede the development of cancer and are causative. The molecular mechanism involved in translocation is only beginning to be understood,\textsuperscript{29,30} and its role in the etiology of neoplasms remains speculative.\textsuperscript{8,31}

GENETIC FACTORS AND THE PROCESS OF CARCINOGENESIS

Over the past 2 or 3 yr, remarkable progress has been made in understanding how certain genetic factors can lead to the transformation of normal cells to malignant ones. Studies with tumor viruses indicate that so-called viral oncogenes can lead to the production of a protein that can account for a number of the changes associated with transformation of cells.\textsuperscript{32,33,35} Recent work suggests that the transforming proteins may be enzymes with protein kinase activity, that is, enzymes that catalyze the transfer of phosphate groups from adenosine triphosphate to protein acceptors.\textsuperscript{34,35} More than one protein can act as an acceptor for most protein kinases, and thus, in theory at least, the transforming protein could alter the function of a variety of normal proteins. Particularly intriguing are recent findings, such as those reported by Racker and his coworkers,\textsuperscript{36} indicating that the sodium “pump” in Erhlich ascites tumor cells is very inefficient, pumping little sodium in comparison to the amount of ATP hydrolyzed. The low efficiency of this sodium “pump” is caused by the abnormal function of the enzyme, Na‘K‘-ATPase, because of the phosphorylation of a subunit of the enzyme by an endogenous protein kinase. Racker and his coworkers have identified a protein kinase in the tumor cells that puts the phosphate on the subunit of the “pump” enzyme, Na‘K‘-ATPase. These findings suggest a way in which the oncogene product, the protein kinase, might contribute to the neoplastic transformation of the cell by altering the action of the enzyme such that it leads to abnormalities in the cellular metabolism. Particularly intriguing is the observation that normal cellular protein constituents are substrates for the viral protein kinase.

Studies on viral oncogenesis are providing the most precise information with respect to the nature of gene alterations that can cause neoplastic transformation in cells. For example, in the case of Rous sarcoma virus, only one gene appears to be required to cause cancer—the SRC oncogene.\textsuperscript{37} Analysis of other viral systems are providing evidence that activation of a cellular oncogene may be an initiating event in neoplastic transformation by both viral and nonviral agents.\textsuperscript{38} As indicated above, ionizing radiation and many chemical carcinogens are potent mutagens. It has been suggested that such agents might induce increased expression of a cellular oncogene by altering regulatory sequences and/or causing translocations.
that join oncogenic coding sequences to transcriptionally active elements in the genome. Different types of cancers may then reflect a particular cellular oncogene which is activated and the particular type of cell in which activation occurs.

It is important to emphasize that there is no established example of a human tumor caused by a virus. Epstein-Barr virus in Burkitt’s lymphoma and nasopharyngeal carcinoma, and hepatitis-B virus in primary hepatocellular carcinoma, are examples of possible virus-associated human neoplasms. Viruses do not appear to be involved in the vast majority of human cancers.

DETECTION OF CANCER GENOTYPE

As evidence for genetic factors that increase risk for cancer accumulates, we are challenged to develop ways to detect which individuals carry “cancer gene(s).” There is a need for recognizing specific markers for the genotype that places the individual at risk.

REFERENCES

25. Paigen B, Minowada J, Gurto HL, Paigen K, Parker NB,


30. Max EE, Seidman JG, Leder P: Sequences of five potential recombination sites encoded close to an immunoglobulin \( \kappa \) constant gene. Proc Natl Acad Sci USA 76:3450–3454, 1979


