Guest Editorial

Onc Genes and Other New Targets for Cancer Chemotherapy*

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Summary. Recent advances in molecular biology have raised the hope that understanding of human cancer might progress rapidly and that improvements in therapy might result (Bishop 1983 a, b; Busch 1962; Busch 1976; Duesberg 1983). With the development of gene cloning, DNA sequence analysis and improved hybridization methods, it became possible to evaluate whether cancer results from alteration in gene dosage, point or multiple mutation of genes, translocations, deletions, insertions, inversions, cis or trans altered promoters, amplification, and a variety of other genetic factors, including enhancer elements that alter rates of readouts of particular mRNA species. “Onc genes” are under intensive study because they offer manageable probes for evaluation of these various possibilities and also because the study of their cellular analogs may further understanding of the molecular biology of normal fetal and malignant cells. Despite the excessive enthusiasm of some proponents of this field and the negativism of its critics (Bishop 1983 a, b; Duesberg 1983), it is clear that analytical tools and new information will be of value in further studies on experimental cancer, regardless of whether cellular oncogenes (c-onc genes) have anything to do with human cancer or not. In the meantime, studies on enzymes, proteins and epitopes involved in growth processes, have opened new avenues for inhibition of human cancer by quantitative reduction of biosynthetic reactions.

Key words: New targets for chemotherapy – Onc genes – Cancer chemotherapy

Introduction

The human cancer problem continues to defy both clinical and scientific experimental approaches. We have much “enthusiasm”, but few facts. The processes involved in the origin of life, evolution, embryogenesis and survival of species all have been suggested to have a bearing on the human cancer problem. The problems are immensely complex. Even such relatively simple events as the production of ribosomes, a fundamental requirement of all protein synthesis, are multifactorial and have only slowly been elucidated (Busch 1976; Ramaley 1980). At present we have only tripping amounts of information on the crucial subject of gene controls even for this system. When one considers the overwhelming array of knowns in our information pool and then recognizes that so much more is unknown about control and growth mechanisms, one becomes humble indeed about major developments in the problem of cancer. Of course, we could be lucky as with bacterial diseases; sudden breakthroughs are possible.

Science has made scintillating advances in many fields and miraculous cures of infectious diseases are commonplace. Accordingly, it is not surprising that in oncology, there has always been the hope that a “quick” cure for cancer could be within our reach if we only could do the right experiment. One great hope was that a cancer was a “virus disease” and sooner or later a proper vaccine would solve this pernicious problem. Now it is clear that most human cancer is not a virus or virus related disease and this has led to much less interest in “vaccinis.”

The current approximately 50 drugs employed by medical oncologists for cancer therapy have limited areas of usefulness but much associated toxicity. Progress in cancer therapy has been slow and difficult but therapeutic advances have been made in Hodgkins disease, lymphomas, testicular cancer and Wilms tumor. These are notable in view of the complexity of the problem. Still, by comparison with treatment modalities for many other human diseases, cancer treatment is quite unsatisfactory.
Frustration has occasionally led to “nondrugs” or even worse, quackery. Because improved cancer drugs have not been forthcoming with rapidity, the National Cancer Institute has set up funding for a number of “drug discovery groups” which may aid in the development of badly needed new ideas and approaches for anticancer drugs. The human cancer problem is complex. There are many caveats (warnings) in cancer research. The first is that the cancer problem is readily divisible into the two parts of experimental cancer and human cancer. It is the human cancer problem that we are trying to solve. The “control” experiments are complex, sometimes emotional and unfavorably hard compared to those of animal cancer. The experimental cancer problem is more tractable but much less meaningful. Here, the experiments are simpler, the controls are readily definable and the experimental results are easily interpreted. Unfortunately, the comparison is like “drunk searching for the quarter under the light.” When asked where he dropped the coin, he remembers he dropped it in a dark corner. However, he is searching under the light because “that is where he can see best.”

The need to specifically study human cancer is apparent. Studies on nucleolar antigens in our laboratory showed that the antibodies which reacted with nucleolar antigens of rat malignant tumors did not react at all with corresponding antigens of the human malignant tumors. Conversely, antibodies to nucleolar antigens of human malignant tumors were not reactive with antigens of rat malignant tumors. These results showed that findings for rodent tumors do not necessarily reflect the human tumor problem.

This problem of validity for human cancer is not limited to fundamental molecular biology. In therapeutic studies, transplantable mouse tumors are highly responsive to many kinds of drugs as are transplantable rat tumors. Lesser degrees of responsiveness are experienced when primary tumor lines are analyzed. Some tumors can be selected for lack of responsiveness. The insensitive tumors are not commonly used in experimental chemotherapy. However, human malignant tumors are primary tumors in each individual. They become complex clonal aggregates with both morphological and biochemical heterogeneity that is manifested as they grow and frequently more so as they metastasize. Simplistic statements are sometimes made with respect to drug design for chemotherapy but in fact, few drugs really have great efficacy. Drugs like 5-fluorouracil once regarded as a “major” therapeutic advance, frequently are found to have only modest activity as therapeutic agents. Recent studies noted the lack of progress in treatment of colon and stomach cancer (White and Schein 1983); unfortunately 5-fluorouracil has little effect on the course of such tumors, despite early suggestions to the contrary.

Studies of “real” human cancer are not trivial. The finding of mutations at position 12 of the P21 protein in the “onc-gene” product of a “mutant” or “transformed” human bladder cancer line (Weinberg 1982; Taparowsky et al. 1982) was heralded as a major breakthrough in the “onc-gene” transformation. However, Feinberg et al. (1983) showed that these sequence alterations were valid only for a few laboratory tumors and the results were not valid for “real cancers” obtained from patients.

It is commonplace that important people make exceptionally broad and overdrawn statements about cancer. Not long ago, an important industrialist stated his conviction that human cancer would be solved with monoclonal antibodies by the end of the 1980's. Miller and Levy (1981, 1982) found that a rare leukemia in an exceptionally fortunate case was susceptible to control and elimination by monoclonal antibodies. Unfortunately, a drop of water does not make a rain and in their subsequent series, the response of most patients has been less favorable; many have not responded at all.

Heterogeneity of Human Cancer. One of the key roadblocks in meaningful studies on human cancer is the biochemical and morphological heterogeneity of the disease. A symposium on heterogeneity of tumor cells (Owens et al. 1982), highlighted a number of experimental and clinical problems arising from this phenomenon. For example, tumors that are initially responsive to treatments such as radiation or various combinations of drugs may lose this susceptibility, proceed to grow and develop and essentially become “resistant” to standard therapeutic procedures. This clinical phenomenon is the major result of proliferation of “resistant clones.” Many forms of cancer are not susceptible to treatment either by drugs or radiation. Instead, they are “resistant” from the very beginning. If they are not amenable to surgery, the patient simply goes on to die.

Experimentally, the “heterogeneity” of human cancers is under detailed study. It is clear that tumors of a given origin differ widely in the cell population as do various types of associated cells. In primary tumors, “supportive” cells include vascular elements, connective tissue, lymphocytes and other non-cancerous cells. The actual population of cancer cells may be small. The cancer cells are divisible into groups of nongrowing (G0) and growing cells which may vary from 5 to 95% of the total cancer cell population. In addition, studies on human cancers reflect both the nontumor cells that are present and the tumor cells. Importantly, the tumor cells may vary in the percent of the population in G0, G1, S, G2, and M phases.