Perspective

A Turning Point in Cancer Research: Sequencing the Human Genome

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ONE OF THE GOALS OF CANCER RESEARCH IS TO ASCERTAIN the mechanisms of cancer. Efforts in this direction have been made by using model systems of limited complexity, such as cancer cells in vitro and oncogenic viruses. The use of cell cultures avoided the complexity of the whole animal but not the complexity of the animal genome. The use of oncogenic viruses seemed to circumvent this complexity by replacing it with the extraordinary simplicity of the viral genome. This simplicity made the study of viruses very productive. The persistence of the transformed state in a cell clone could be explained by the persistence of the viral genome in cells (*1*); genetic and molecular results showed that transformation is the consequence of the expression of one or a few viral genes. Finally, the viral transforming genes, or "oncogenes," and the proteins they specify were identified. The crowning development was the demonstration that in retroviruses the oncogenes are picked up from the cellular genome during the viruses' most recent history (*2*). As a result of these studies, cancer seemed to be locked to the expression of some viral gene; the possibility of a "hit-and-run" mechanism, in which the virus alters the cell and then vanishes, seemed excluded. Two types of oncogenes were identified: some which immortalize cells, and others which make them tumorigenic (*3*). In most cases oncogenes of both types are needed to cause a continuously growing tumor.

Subsequent work, however, blurred the distinction between immortalizing and transforming oncogenes by showing that their effects differ in primary cultures or permanent lines and in cells of different species (*4*). These findings suggested that the state of the cellular genes is important for the effect of oncogenes, in agreement with the great differences in cancer incidence and in the effects of chemical or viral carcinogens in different species.

These studies dealt with the initial cancer events. But natural cancers evolve slowly toward malignancy through many definable stages in a process called "progression" (*5*), which is the least understood but probably the most crucial phase in the generation of malignancy. Progression generates the marked heterogeneity of cancers (*6*) and their many chromosomal abnormalities (*7*); it must be differentiated from the initial action of oncogenes (*8*). Progression is observed in cells transformed by viruses. This is the case, for instance, of bursal lymphomas induced by avian leukosis viruses (*9*), of viral T-cell lymphomas in mice (*10*), and of leukemogenesis by Friend leukemia virus in cultures of mouse bone marrow cells (*11*). Stepwise transformation is observed also with DNA viruses (*12*). Fibroblastic cells from a variety of organs of a transgenic mouse containing *myc* and simian virus 40 (SV40) sequences, although expressing SV40 T antigen, were normal but became gradually transformed upon cultivation (*13*). In all these cases cellular changes occurring during culture growth determined full transformation. The "hit-and-run" hypothesis of viral transformation must be reconsidered.

A clue as to what these changes are is obtained by examining the heterogeneity of chemically induced rat mammary carcinomas with respect to several well-characterized markers. The expression of the markers is altered in different ways in different parts of the same cancer; the alterations seem to be clonal, being uniform in small parts of a tumor but different in adjacent parts (*14*). The closeness of the parts makes it unlikely that the differences are due to the environment; it is more likely that they are caused by structural changes of the genes, as is also suggested by the chromosomal rearrangements observed in cancers (*15*) and by the finding that each chemically or radiation-induced mouse sarcoma expresses a different class I major histocompatibility antigen, probably produced through gene rearrangement (*16*).

A major gap in our understanding of cancer is how the activity of an oncogene is related to the events of progression. But the first task is to ascertain whether the DNA of an advanced cancer is as heterogeneous as the phenotype of its cells. If it is so, a new field of cancer research opens up, possibly leading to the discovery of the genes whose activity or inactivity is responsible for infiltration and metastasis.

We are at a turning point in the study of tumor virology and cancer in general. If we wish to learn more about cancer, we must now concentrate on the cellular genome. We are back to where cancer research started, but the situation is drastically different because we have new knowledge and crucial tools, such as DNA cloning. We have two options: either to try to discover the genes important in malignancy by a piecemeal approach, or to sequence the whole genome of a selected animal species. The former approach seems less formidable, but it will still require a vast investment of research, especially if the important genes differ in cancers of different organs and if they encode regulatory proteins. A major difficulty for conventional approaches is the heterogeneity of tumors and the lack of cultures representative of the various cell types present in a cancer. I think that it will be far more useful to begin by sequencing the cellular genome. The sequence will make it possible to prepare probes for all the genes and to classify them for their expression in various cell types at the level of individual cells by means of cytological hybridization. The classification of the genes will facilitate the identification of those involved in progression.

In which species should this effort be made? If we wish to understand human cancer, it should be made in humans because the genetic control of cancer seems to be different in different species. Research on human cancer would receive a major boost from the detailed knowledge of DNA. Humans would become the preferred experimental species for cancer research with cells in culture or in immunodeficient mice. Because cancer could be defined in molecular terms, the agents capable of inducing cancer in humans could be identified by the combination of in vitro and epidemiological studies. Knowledge of the genes involved in progression would open new therapeutic approaches, which might lead to a general cancer cure if progression has common features in all cancers.

Knowledge of the genome and availability of probes for any gene would also be crucial for progress in human physiology and pathology outside cancer; for instance, for learning about the regulation of individual genes in various cell types. Many fields of

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research, such as the study of development and of the organization of the nervous system, would benefit. The identification and diagnosis of hereditary diseases or of hereditary propensity to disease would be greatly facilitated. The knowledge would rapidly reflect on therapeutic applications in many fields.

An effort of this kind could not be undertaken by any single group: it would have to be a national effort. Its significance would be comparable to that of the effort that led to the conquest of space, and it should be carried out with the same spirit. Even more appealing would be to make it an international undertaking, because the sequence of the human DNA is the reality of our species, and everything that happens in the world depends on those sequences.

Many practical and technical problems would have to be solved. A considerable improvement in the technology would be needed in order to shorten the time required. Increasing by 50-fold the present rate of sequencing would make it possible to complete the main task in perhaps 5 years with adequate manpower.

In one generation we have come a long way in our efforts to understand cancer. The next generation can look forward to exciting new tasks that may lead to a completion of our knowledge about cancer, closing one of the most challenging chapters in biological research.

REFERENCES AND NOTES

1. J. Sambrook, H. Westphal, P. Srinivasan, R. Dulbecco, *Proc. Natl. Acad. Sci. U.S.A.* **60**, 1288 (1968); H. Varmus and R. Swanstrom, in *RNA Tumor Viruses*, R. Weiss, N. Teich, H. Varmus, J. Coffin, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1982), p. 369; J. E. Robinson and G. Miller, in *The Herpesviruses*, B. Roisman, Ed. (Plenum, New York, 1982), vol. 1, pp. 151; H. Pfister, *Rev. Physiol. Biochem. Pharmacol.* **99**, 111 (1984).
2. J. M. Bishop, *Annu. Rev. Biochem.* **52**, 301 (1983).
3. M. Rassoulzadegan, A. Cowie, A. Carr, N. Glaichenhous, R. Kamen, F. Cuzin, *Nature (London)* **300**, 713 (1982); H. Land, L. F. Parada, R. A. Weinberg, *ibid.* **304**, 596 (1983).
4. D. A. Spandidos and N. M. Wilkie, *ibid.* **310**, 465 (1984); L. Bouchard, C. Gelinas, C. Asselin, M. Bastin, *Virology* **135**, 53 (1984).
5. L. Foulds, *J. Chron. Dis.* **8**, 2 (1958).
6. G. H. Heppner, *Cancer Res.* **44**, 2259 (1984); H. Rubin, *ibid.* **45**, 2935 (1985).
7. S. R. Wolman, *Cancer Metast. Rev.* **2**, 257 (1983).
8. P. H. Duesberg, *Science* **228**, 669 (1985).
9. T. W. Baba and E. H. Humphries, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 213 (1985); D. Westaway, G. Payne, H. E. Varmus, *ibid.* **81**, 843 (1984).
10. M. Haas, A. Altman, E. Rothenberg, M. H. Bogart, O. W. Jones, *ibid.*, p. 1742.
11. J. M. Heard, S. Fichelson, B. Sola, M. A. Martial, B. Varet, J. P. Levy, *Mol. Cell. Biol.* **4**, 216 (1984).
12. B. J. Hargis and S. Malkiel, *J. Natl. Cancer Inst.* **63**, 861 (1981); J. Abramczuk, in *Manipulation and Expression of Genes in Eukaryotes*, P. Nagley *et al.*, Eds. (Academic Press, New York, 1983), p. 355; M. Vogt and R. Dulbecco, *Cold Spring Harbor Symp. Quant. Biol.* **27**, 367 (1962).
13. J. A. Small, D. G. Blair, S. D. Showalter, G. A. Scangos, *Mol. Cell. Biol.* **5**, 642 (1985).
14. R. Dulbecco, B. Armstrong, R. Allen, M. Bowman, in preparation.
15. P. C. Nowell, *Science* **194**, 23 (1976).
16. C. Philipps *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 5140 (1985).