Plenary Symposium

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The implications of the human genome sequence for cancer research

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The human genome project is providing a catalogue of all 30,000-40,000 human genes and their precise positions along the chromosome. This fundamental information provides the basis for identifying the genetic and epigenetic changes which underlie the somatic evolution of cancers. This information in turn provides the basis for exploring the functional implications of these genetic changes and their interactions.The use of high density microarrays of gene sequences further enables the detection of different patterns of gene expression related to different evolutionary sequences of cancer.

A great deal of progress has been made in elucidating these critical genetic steps in the development of cancers, especially using colorectal cancer as a model. These advances provide enormous opportunities for new approaches to the prevention, early detection and treatment of cancer.

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Rules governing the creation of human tumor cells

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Unlike rodent cells, which are readily transformed from a normal growth phenotype to a malignant phenotype through the introduction of defined genes, human cells have proven refractory to such transformation. Recently, following the cloning of the hTERT gene, which encodes the catalytic subunit of the telomerase holoenzyme, this transformation has indeed succeeded. To date, we have transformed normal human fibroblasts, kidney cells, and epithelial cells from the breast, lung and prostate to anchorage-independent and tumorigenic phenotypes. This illustrates substantial biological differences between rodent and human cells in the mechanisms governing their proliferation.

The combination of genes introduced into these cells - hTERT, ras and the SV40 LT oncogene - results in human tumor cells that are highly angiogenic. Such cells are not, however, metastatic, suggesting that additional genetic alterations are required to elicit that final phenotype of tumor progression. These transformations indicate that the rules governing malignant progression seem to be similar in a variety of human cell types. Moreover, it will be possible shortly to define the total number of growth-regulating pathways that are required in order to transform a normal human cell into a tumor cell. We imagined that minimally four such pathways are required: the mitogenic signaling pathway governed by the Ras protein, hTERT, and the p53 and pRb tumor suppressor pathways disrupted by the LT oncoprotein. Recently, however, we have acquired evidence that a fifth change is needed - that involving the small t oncoprotein which is also encoded by the SV40 early region used in our initial transformation experiments. Here the evidence indicates that the ability of sT to inhibit protein phosphatase 2A (PP2A) may be critical to successful transformation.

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Emerging infections and cancer

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During the past 30 years a steadily increasing number of specific infections has been linked to various forms of human cancers. Besides parasitic (*Schistosoma, Opisthorchis, Clonorchis*) and bacterial infections (*Helicobacter pylori*), members of different virus families (*Herpesviridae, Papillomaviridae, Hepadnaviridae, Flaviviridae, Retroviridae*) account for the majority of infection-linked human cancers. Presently 15-20% of the global cancer burden can be attributed to an infectious etiology. In recent years the number of novel virus types infecting humans increased remarkably. This accounts particularly for members of the *papillomavirus* family, but also for a very recently discovered virus family, the *circino-* or *TT viruses*. Whereas the former seem to be generally able to stimulate host cell proliferation, cell growth-influencing properties of the latter remain to be determined. Searches for viruses in human tumors frequently result in virus-specific clones whose significance is difficult to determine and often remains controversial. The discussion will focus on some recent isolates of Papilloma-, Herpes-, Circino-, and Polyoma-type viruses and their possible significance for specific cancers.

The identification of infectious agents as causative factors in carcinogenesis permits new approaches to cancer prevention, but also to early detection and cancer therapy. Clinical trials are presently underway to explore these opportunities.

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Will clinical oncology really change?

Abstract not received.