Researchers Debate Clinical Role of Telomerase

At a recent international meeting on the enzyme telomerase, scientists for the first time evaluated its use in the clinic for the early detection of cancer.

Even though most of the data presented at the 2-day workshop, sponsored by the National Cancer Institute, were preliminary, there was general agreement that telomerase — present in almost all primary human tumors — shows promise as a biomarker for early stage cancers. In addition, researchers agreed this enzyme could aid in sorting out aggressive from benign tumors.

The workshop, titled "Telomerase Activity and the Early Detection of Cancer," was organized by Sudhir Srivastava, Ph.D., program director of the Early Detection Branch of NCI.

Predicting Outcome

Jerry W. Shay, Ph.D., of the University of Texas Southwestern Medical Center, Dallas, co-chairman of the conference, said that scientists are just beginning to evaluate the role of telomerase, but "everyone agrees that this is an exciting and rapidly expanding field that warrants additional studies."

He added that there is general consensus that using telomerase for early diagnosis in lung and breast cancers should be investigated in more detail, and that telomerase may play a role in predicting disease outcome for certain leukemias, meningiomas, late stage neuroblastomas, and perhaps colon and gastric cancers."

Telomerase is an enzyme that maintains telomeres, the protein-DNA caps covering the ends of chromosomes. Chromosomes lacking telomeres are known to undergo fusions, rearrangements, and translocations; are degraded by cellular enzymes; and eventually become lost as the cell divides. Telomeres, then, protect chromosomal DNA from these instabilities.

When telomerase is absent from a cell, telomeres get shorter with each cell division because a small bit of DNA on the chromosome ends is lost. Because most cells have no telomerase activity, their telomeres shorten with age, and eventually they stop dividing and exit the cell cycle altogether. Telomere shortening is thought to be a cellular sign of aging. Spermatogonial and ovary cells (germ cells) are an exception. Their chromosome ends are maintained by a high level of telomerase and do not shorten over time.

Shortly after the development of a sensitive assay for telomerase in 1994, a study reported in Science showed a dramatic correlation between cancer and telomerase. Investigators found high levels of telomerase activity in 90 of 101 distinct tumors representing 12 cancer types and in 98 of 100 independent immortalized cell lines. In contrast, the enzyme was not detected in benign tumors, somatic (non-germline) tissues, and mortal cell lines. These results suggest that telomerase may be necessary for a cell to become immortal.

Questions to Answer

To date, telomerase has been detected in more than 20 different types of cancers and in over 85% of all tumors tested. But in order to assess its clinical utility, certain questions need to be answered: Can the enzyme be detected in early stage disease? Are certain types of cancers particularly amenable to predicting disease outcome using measurement of telomerase activity? Can the absence of telomerase serve as a good marker of whether chemotherapy or chemoprevention worked?

To address these questions, 20 scientists looked for the presence of telomerase in a variety of tumors, from early to late stage, as well as in blood, urine, and colonic washings from cancer patients, and presented their findings to the group.

To see if the enzyme might be useful for early detection of cancer, the husband-and-wife team Keiko Hiyama, M.D., and Eiso Hiyama, M.D., of the Hiroshima University School of Medicine, Japan, analyzed telomerase activity in a variety of lung and breast cancers. K. Hiyama detected the enzyme in each of 30 tumors representing...
all stages of small-cell lung cancer, and E. Hiyama reported finding telomerase in fine-needle-aspirated breast samples from 100% of malignant tumors and in only 4% of normal adjacent tissue.

However, there were some important caveats and inconsistencies. Surprisingly, E. Hiyama found weak telomerase activity in 45% (9/20) of breast fibroadenomas, a noncancerous condition. In addition, using a method to enhance the detection of telomerase, he found that certain normal tissues, such as the spleen, bone marrow, and lower intestinal crypts, had low but detectable activity.

So, although he supports further exploration of telomerase as a diagnostic marker, Hiyama cautioned physicians to pay “careful attention to distinguish between the weak telomerase activity of normal tissues and the activity of cells progressing to cancer.”

**Hope for Diagnosis**

David Tarin, D.M., a pathologist from the University of Oxford, England, whose job is to predict clinical outcome from patient tissue, hopes that telomerase might be useful for screening clinical samples— in his case oral rinses from patients with head and neck squamous cell (HNSC) cancers. Sidransky found telomerase in oral rinses from all the HNSC patients examined so far and in about 10% of the control patients, and, although he is optimistic about its clinical utility, he believes that clinical decisions will probably not be made on the basis of a single test.

Several investigators reported preliminary data showing a correlation between the level of telomerase and disease severity. Junka Ohyashiki, M.D., from Tokyo Medical College, looking at telomerase activity in peripheral blood mononuclear cells of patients with acute myeloid leukemia, found levels of telomerase decreased sixfold during remission and rose to the original level during relapse. Another investigator, Wei Zhang, Ph.D., of the University of Texas M. D. Anderson Cancer Center in Houston, reported very high telomerase activity in acute myeloid leukemia patients who are resistant to therapy.

Likewise, Silvia Bacchetti, professor of pathology at McMaster University Medical Center in Hamilton, Ont., Canada, found that, in patients with chronic and acute leukemias, those with more serious disease had higher levels of telomerase. She cautioned that careful quantitation of the enzyme would be necessary for predicting clinical outcome in these leukemias, since normal leukocytes (from bone marrow, peripheral blood, and cord blood) contain low levels of telomerase.

These results seem to mirror findings that appeared in the March 1995 issue of Nature Medicine, reporting levels of telomerase activity in neuroblastomas, the most common solid tumor in children younger than 5 years of age. Neuroblastomas with high telomerase activity were associated with unfavorable prognosis, those with low levels of the enzyme had a favorable prognosis, and a late stage neuroblastoma, lacking telomerase, regressed.

The data from the conference likely to have the most immediate clinical benefit are from the meningioma studies presented by Lauren Langford, M.D., of M. D. Anderson. Meningiomas, a specific kind of brain tumor, are frequently found in a location that makes both removal and diagnosis difficult. There is also no reliable method of predicting biological aggressiveness from appearance. Of the 52 biopsy samples analyzed, Langford found telomerase present in 100% of
Prostatic Intraepithelial Neoplasia: Will It Help Doctors Pinpoint Early Prostate Cancer?

The rising incidence of prostate cancer and the widespread use of prostatespecific antigen in screening have led clinicians to push for better and more accurate diagnostic tools. One of many unsolved puzzles is a putative pre-cancerous lesion known as PIN (prostatic intraepithelial neoplasia). The nature of these lesions and whether they are precursors for invasive cancer are hotly debated.

A seemingly similar, and better studied lesion, cervical intraepithelial neoplasm or CIN, is found in nearly 600,000 women screened for cervical cancer each year. While advanced cases of CIN usually persist or progress to true cervical cancer, some regress on their own. The average progression from CIN to cervical cancer takes 10 to 15 years, but a small subset may progress to cancer in a matter of months. Earlier stages of CIN often, but not always, regress with no treatment.

At a recent workshop on PIN, the dearth of knowledge about PIN, as compared to CIN and other confirmed pre-cancerous lesions, became apparent. The debate ranged from how to use a diagnosis of PIN in determining patient follow-up and treatment to whether PIN is a valid pathologic diagnosis at all.

Worthless?

One expert at the workshop called a diagnosis of PIN “absolutely worthless,” while other opinions ran the gamut from skepticism to a faith that PIN will be usable for earlier and more effective interventions in prostate cancer in the future.

Experts distinguish between high-grade and low-grade PIN, and some have argued that as a diagnostic tool only high-grade PIN is useful. A number of workshop participants concurred with one researcher who said, “I happen to believe [high-grade] PIN goes to cancer.”

“There are more questions [about PIN] than answers,” according to the workshop presentation of Harry Burke, M.D., Ph.D., assistant professor of medicine at New York Medical College in Valhalla. PIN and prostate cancer could co-occur by chance, he observed. “Or, some X factor causes both. Or PIN is a necessary but not sufficient cause of prostate cancer. Or PIN may give rise to different kinds of prostate cancer. The evidence does not exist to rule [any of these possibilities] in or out.”

According to Lance Liotta, M.D., Ph.D., of the National Cancer Institute, the next research frontier is an analysis of what genetic changes occur between PIN and invasive cancer — a step that would yield a lot of valuable informa-