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RESEARCHERS LINK ENZYME TO CANCER DEVELOPMENT

DALLAS — February 28, 1995 — The enzyme telomerase plays an important role in the development of neuroblastoma, one of the most common and often fatal cancers of childhood, say researchers at UT Southwestern Medical Center at Dallas.

Dr. Jerry Shay, professor of cell biology and neuroscience, and research fellow Dr. Mieczyslaw Piatyszek, both with UT Southwestern, and investigators from the Hiroshima University School of Medicine in Japan, published their findings in the March 1995 issue of *Nature Medicine*. Drs. Eiso Hiyama and Keiko Hiyama of Japan came to Shay's laboratory as visiting scientists to study the technique he and his colleagues developed for detecting telomerase activity in tumors. The researchers from Hiroshima University School of Medicine provided 100 tissue samples from Japanese children for the investigators to examine.

Earlier research by Shay and his UT Southwestern colleagues showed that almost all established tumor cell lines and primary tumors have telomerase activity. Telomerase modifies the ends of the chromosomes — called telomeres — and allows cells to reproduce indefinitely. Cancer cells turn telomerase "on" and keep the cells growing long after they should have stopped dividing. This unlimited proliferation of what Shay calls "immortal cells" may contribute to cancer.

"This latest study confirms our initial assumptions about the cellular mechanisms of human cancer," Shay said. "Telomerase expression may be an essential step in the development of neuroblastomas. We detected telomerase activity in 94 of the 100 neuroblastoma cases studied."

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Neuroblastoma is the most common solid tumor in children younger than 5, affecting about one in 7,000 children. Surgical removal of the tumor is often the most effective form of treatment, but chemotherapy and radiation therapy are used in advanced cases. Early diagnosis and treatment of the disease is very important, researchers say.

Shay and his colleagues found that telomerase activity in neuroblastomas develops in two ways.

In the first, telomerase was present in the tumor but was expressed at very low levels. Although tumors were present, they were not likely to progress because the level of telomerase activity was too low and the telomeres continued to shorten, Shay said. "This could help explain the generally good prognosis for these types of infant neuroblastomas. The telomerase is at such a low level that the tumor may regress on its own."

For example, in three of the neuroblastoma cases studied there was no detectable telomerase activity. These were from a type of neuroblastoma tumor in small children that is often reported to regress spontaneously even without surgery or chemotherapy. "What has been a mystery turned out to be a straightforward molecular explanation for the cancer remission in these patients," Shay said. "Now it appears that because these tumor cells cannot express telomerase activity, they develop critically shortened telomeres and die."

In the second type of development, tumors that formed had high telomerase activity. "Those tumors consisted of immortal and potentially highly malignant cells and also had other genetic alterations. Such a combination almost always results in a poor prognosis," Shay said.

Shay and his colleagues are continuing to study other forms of cancer to broaden their understanding of the regulation of telomerase. "We know telomerase is an important component in the development of cancer, but we still don't know much about how it is regulated," he said. "We may find that answer in six months, one year or five years. We don't know. But that is our next focus."

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Another challenge, Shay said, is to develop effective anti-cancer drugs that block telomerase. Since telomerase appears to be vital to the continued proliferation of cancer cells, development of anti-cancer agents based on telomerase inhibition may be highly effective.

Other research collaborators from Hiroshima University School of Medicine were Drs. Takashi Yokoyama and Yuichiro Matsuura.

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