

Gene Called Link Between Life Span and Cancers

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By NICHOLAS WADE

Biologists have uncovered a deep link between life span and cancer in the form of a gene that switches off stem cells as a person ages. The critical gene, well known for its role in suppressing tumors, seems to mediate a profound balance between life and death. It weighs the generation of new replacement cells, required for continued life, against the risk of death from cancer, which is the inevitable outcome of letting cells divide.

To offset the increasing risk of cancer as a person ages, the gene gradually reduces the ability of stem cells to proliferate. The new finding, reported by three groups of researchers online yesterday in *Nature*, was made in a special breed of mice that lack the pivotal gene, but is thought likely to apply to people, as well.

The finding suggests that many degenerative diseases of aging are caused by an active shutting down of the stem cells that renew the body's various tissues and are not just a passive disintegration of tissues under daily wear and tear. "I don't think aging is a random process — it's a program, an anticancer program," said Dr. Norman E. Sharpless of the University of North Carolina, senior author of one of the three reports.

The other senior authors are Drs. Sean J. Morrison of the University of Michigan and David T. Scadden of the Harvard Medical School. The full implications are far from clear, but the finding that the cells are switched off with age does not seem too encouraging for researchers who hope to use a patient's own adult stem cells to treat disease. That result may undercut opponents of research on human embryonic stem cells who argue that adult stem cells are enough to build new tissue.

Dr. Sharpless said his finding showed the need to pursue both types of research. The gene in the finding has the unmemorable name of p16-Ink4a. It plays a central role in the body's defenses against cancer, and it produces two quite different proteins that interact with the two principal systems for deciding whether a cell will be allowed to divide.

One of the proteins had also been noted to increase substantially with age. The cells of a 70-year-old produce 10 times as much of the Ink4 protein as those of a 20-year-old, Dr. Sharpless said. To help understand that Dr. Sharpless genetically engineered a mouse strain with the gene knocked out. He set out to see whether losing the gene would affect the blood-making stem cells. Learning that Dr. Morrison was interested in that with brain cells and Dr. Scadden with the insulin-making cells of the pancreas, he shared his mice with them.

The teams agreed to publish their findings together, a departure from usual researchers' competitiveness. All three teams report essentially the same results, that in each type of tissue the cells have extra ability to proliferate when the Ink4 protein can no longer be made. At the same time, the Ink-less mice are highly prone to cancer, which they start to develop as early as 1 year of age. The researchers assume, but have not yet proved, that the increasing amounts of Ink4 as a person ages will thrust the stem cells into senescence, meaning that they can never divide again. The evolutionary purpose is evidently to avert the risk that a damaged stem cell might evade controls and proliferate into a tumor.

One implication is that therapists who hope to increase longevity have to tackle a system that may be hard to cheat. An intervention that reduces Ink4 production to prevent the age-related decline of stem cells will also increase the risk of cancer.

"There is no free lunch," Dr. Sharpless said. "We are all doomed." He quickly modified that by noting that a calorically restricted diet is one intervention that is known to increase life span and reduce cancer, at least in laboratory mice. The reason, he said, is probably because such diets reduce cell division, the prime source of cancer risk.

For cell therapists, the dual activity of Ink4 may be "a hard box to get out of," he said, unless they use cells that are somehow much younger than the patient. Dr. Scadden, however, said he hoped that there would turn out to be some sloppiness in the Ink4 gene's balancing trick, allowing it to be switched off temporarily with yet-to-be invented drugs in a way that would promote stem cell proliferation without greatly increasing the risk of cancer. "There is clearly a dark side to the finding, but whether or not we can exploit it, that's the challenge," he said.

Some proposals for stem cell therapy with adult stem cells envisage taking a patient's stem cells, making them divide in the laboratory and putting them back in the patient to build new tissue. "The notion that adult stem cells are infinite in proliferative capacity is seriously undermined by this work," Dr. Sharpless said. Dr. Morrison said it had long been known that older patients did not do as well in bone marrow transplants as younger ones, and the new finding might explain why.

"I don't think any of these findings dims the promise of stem cell research at all," he said, because the greater robustness of younger people's cells was already well known. The researchers said they did not yet know what stimulus makes cells increase their production of the Ink4 protein as a person grows older. Their suspicion is that the usual factors implicated in aging like mutation and oxidative damage to tissues would turn out to have a role in making cells produce more Ink4.

Dr. Ronald A. DePinho, an expert on cellular aging and a co-author of Dr. Scadden's report, said the new finding, in showing how the renewal capacity of stem cells was governed, might enable drugs to be made that would improve cell transplants.

Dr. Scott Lowe, a cancer gene expert at the Cold Spring Harbor Laboratory on Long Island who was not involved in the three papers, said the results were interesting because they linked to aging a gene of central importance in cancer.

Press releases by the University of North Carolina School of Medicine and the University of Michigan attributed the advance to all three teams equally. But the press release issued by the Harvard Stem Cell Institute, where Dr. Scadden has an appointment, described him as the leader of the multi-institutional team, with the other two teams confirming his work. Dr. Scadden made no such claim in an interview, and acknowledged Dr. Sharpless's generosity in lending his mice.

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