SOUTHWESTERN NEWS

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Gene therapy reduces skin cancer to sunburn in mouse model

DALLAS – Dec. 10, 2004 – Researchers at UT Southwestern Medical Center at Dallas have successfully tested the first gene therapy for skin cancer, using a mouse model for the disease xeroderma pigmentosum, or XP.

Their results, available online and to be published in an upcoming issue of the *Proceedings of the National Academy of Sciences*, show promise for similar gene therapy to be pursued in children suffering from this rare disorder.

XP is a debilitating disease in which patients must avoid the sun and all other sources of ultraviolet (UV) light. Exposure to UV light increases the risk for all cancers, but exposed skin is most prone to the disease. With a 10,000-fold increase in cancer risk, many XP sufferers eventually succumb to tumors at an early age.

Mice with mutations in the gene *Xpa* suffer from XP and develop cancerous lesions on their skin within three weeks after UV light exposure. Dr. Errol Friedberg, professor and chair of pathology at UT Southwestern, in collaboration with Dr. Carlos F.M. Menck of the Institutes of Biomedical Sciences in Sao Paulo, Brazil injected the normal gene into mice suffering from XP. After treatment with the normal gene, the mice were free from disease.

"Gene therapy for XP has the potential to completely prevent cancer in a group of patients who otherwise may suffer no other ill effects from their genetic defect," Dr. Friedberg said.

When the body is exposed to UV light, the DNA in dividing cells can become damaged. Normally, the body enlists a group of proteins whose job it is to repair the sites of UV-induced damage. But in children with XP, mistakes in DNA caused by UV light cannot be fixed because of mutations in the genes for the repair proteins. DNA damage goes uncorrected, and as cells divide they accumulate numerous mutations. When these mutations occur in genes that normally suppress cancer, cells develop abnormally and cancer ensues.

A mutation in any one of seven human genes involved in DNA repair is sufficient to cause XP. One of these genes is *XPA*. Humans with mutations in *XPA* are one the largest groups of XP patients.

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In their gene therapy study, Dr. Friedberg and colleagues injected the normal version of mouse *Xpa* into the mutant mice, using a disabled virus that infects multiple cells. They then exposed the mice to UV light for a few hours over several days. Five months after the last exposure – long after *Xpa* mutant mice would normally develop skin lesions – the treated mice merely had sunburn.

The skin cells surrounding the site of the injection in the treated *Xpa* mutant mice were nearly identical to those of normal animals, indicating that the DNA repair mechanism had been restored by the addition of the normal *Xpa* gene, Dr. Friedberg said.

Dr. Friedberg said he believes that with some technical refinement, this gene therapy technique may soon be applicable to all the mutations that cause XP in humans.

"XP is a disease that lends itself well to gene therapy, for a variety of reasons," Dr. Friedberg said. "Most importantly, skin cells are highly accessible for introducing foreign genes. Also, infection of the skin with a virus carrying the gene of interest, as we did with the mice, allows for many, many cells to receive the appropriate gene. Once some of the existing technical limitations are solved these studies can hopefully be extended to trials with human XP patients."

Other UT Southwestern contributors to this research are Maria Carolina N. Marchetto, visiting student and lead author, and Dr. Dennis Burns, professor of pathology. Dr. Allyson R. Muotri of the Salk Institute also contributed to the study.

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