Mice with skin condition help scientists understand tumor growth

6 July 2009

Cancerous tumors sometimes form at the site of chronic wounds or injury, but the reason why is not entirely clear. Now researchers at Washington University School of Medicine in St. Louis have engineered mice with a persistent wound-like skin condition, and the mice are helping them understand the tumor-promoting effects of long-standing wounds and injuries.

"The chronic skin condition in the mice led to the growth of skin tumors," says Raphael Kopan, Ph.D., professor of developmental biology and of dermatology. "And what we learned from this process fit very well with the emerging realization that a tumor's surroundings play a critical role in its development."

Past clinical evidence has linked chronic skin wounds such as leg ulcers to an increased risk of skin cancer, and some scientists have suggested that chronic injury can predispose various organs to cancer.

In this study, published in the July 7 issue of *Cancer Cell,* the researchers found that the chronic skin condition led to secretion of molecules that activated dermal cells, increased the number of blood vessels and increased local inflammation, reinforcing the idea that wound repair mechanisms and inflammation are important agents in promoting cancer.
The skin condition was engineered in the mice by inactivating a gene called Notch1 in patches of skin cells, leaving the rest of the skin intact. Notch1 is a master controller for normal skin development and was thought to suppress tumor growth in skin cells in which it resides.

Without Notch1, patches of the mice's skin developed abnormally and became thickened and inflamed. As the mice aged, benign tumors called papillomas formed. About 10 percent of these tumors spontaneously progressed to basal cell carcinoma, the most common type of skin cancer in people.

Importantly, further analysis showed that skin tumors had originated from both mutant and normal skin cells. Because normal cells contain active Notch1, they were not expected to form tumors, and that was an important clue that factors other than the missing Notch1 were responsible for tumor formation in skin.

"Loss of Notch1 signaling in the mutant skin cells generated a wound-like environment in which both the mutant and normal skin cells became prone to cancer," Kopan says.

The research team showed that the mutant skin patches encouraged the growth of tiny blood vessels and production of growth factors that when expressed transiently help repair skin damage. The persistent expression of these factors provided cells with nutrients and proliferation signals that promoted tumor formation, Kopan says. Numerous immune cells secreting additional factors infiltrated the abnormal skin patches and adjacent cells, contributing to inflammation.

Recently, drugs that lower Notch1 activity have been used to manage Alzheimer's disease and to treat some forms of cancer - because paradoxically Notch1 can be a tumor promoter in tissues other than skin. Kopan says that his study shows that skin is very sensitive to reduction of Notch1 activity. The long-term use of such medications and others that compromise skin integrity could contribute to an increased likelihood of skin cancer, he says.

"The study suggests that as researchers develop drugs, they should be mindful of their potential effect on the skin, particularly those that cause chronic damage to skin integrity," Kopan says. "Studies like ours help define the range of possible complications in drug design and help tailor therapies to avoid them."

The researchers also plan to use Notch-deficient mice to provide a system in which to identify molecules and cellular interactions responsible for the oncogenic effect of chronic wounds. Based on such analyses, new drug targets might be identified to develop therapies for cancers of the skin and perhaps other organs.

"It's very reasonable to assume that chronic wounds in a variety of tissues have similar characteristics," Kopan says. "The skin of these mice is easy to monitor and will give us the ability to further analyze tumor promotion and find answers that might apply to any chronic wound."

Source: Washington University School of Medicine (news : web)