Skin defects set off alarm with widespread and potentially harmful effects

May 28 2008

When patches of red, flaky and itchy skin on newborn mice led rapidly to their deaths, researchers at Washington University School of Medicine in St. Louis looked for the reason why. What they found was a molecular alarm system that serves as a sentinel to monitor the integrity of skin — the body's essential protective barrier. The fatal effects of raising this alarm in the lab mice suggests generally that certain kinds of impairments to the skin's structure can potentially trigger harmful effects in other areas of the body, according to the researchers.

The study was published May 27, 2008, in *PLoS Biology* (a Public Library of Science journal). The research team found that the mice's irritated skin produced an alarm signal in the form of a natural inflammatory substance called TSLP (thymic stromal lymphopoietin), which launched a massive overproduction of white blood cells and ultimately killed the mice.

In people, TSLP has been shown previously to be involved in atopic dermatitis and in asthma. The mice's skin problems closely resembled atopic dermatitis, a chronic skin irritation experienced by up to a fifth of children in industrialized countries.

"Both the lung and the skin are barrier organs whose job is to keep what's inside in and what's outside out," says Raphael Kopan, Ph.D., professor of developmental biology and of medicine in the Division of Dermatology. "Under normal circumstances, TSLP serves as an alarm to call in the immune system to heal breaches in these barrier organs.

Healing turns the alarm off and sets everything back to normal."

Kopan notes that TSLP could be part of the reason that children that have atopic dermatitis also go on to have a high incidence of asthma. "It's possible that once this molecule gets into the system other organs such as the lungs go on guard and become more susceptible to problems such as asthma," he says.

The experimental mice were engineered so that they had skin patches that were missing one or more genes that help insure normal cell growth and differentiation during skin's continual process of renewal and during wound healing. The research team found that TSLP was produced only in the defective areas of skin, and then entered the bloodstream, reaching concentrations 5,000 times above normal.

Careful scientific detective work by M.D./Ph.D. student Shadmehr Demehri uncovered the connection between the skin defects and the fatal immune disorder in the mice. "When I joined the lab, the team had developed genetically engineered mice with structural skin defects, but they didn't have any idea why they were dying," Demehri says. "I started looking for the cause, and one of the first things I noticed was the high white blood cell counts."

A lengthy process of elimination eventually revealed that the fatal immune response was a reaction to a factor released by the defective skin patches. The researchers found that the factor was TSLP. Because the mice's skin problems stemmed from genetic abnormalities, the skin couldn't return to normal, and the TSLP alarm signal couldn't be turned off. High levels of TSLP activated an immune response that produced extreme numbers of B-cells, a kind of white blood cell that makes antibodies to destroy pathogens.

The researchers uncovered the skin's alarm system while studying a

different molecule — Notch, an important component of a cellular communication system present in most multicellular organisms. Notch signaling ensures that skin cells grow and differentiate appropriately.

One by one, the team stopped the activity of the eight Notch genes active in mouse skin and found that each time a gene was taken out, skin problems increased. Mice with skin patches missing all eight genes died of B-cell lymphoproliferative disorder within 30 days. Their white blood cell counts were 40 to 80 times above normal.

Interestingly, further experiments revealed that the absence of Notch was not the direct cause of the rise in TSLP in the mice. When the team discovered that another type of mouse with a different genetic skin defect also had high levels of TSLP, they realized that there must be some as yet unidentified molecular mechanism in skin that senses defects in the integrity of the tissue and sets off the TSLP alarm. That sensor mechanism is the next target of their research investigations.

"We feel the sensor could play two roles," Kopan says. "On the one hand it's very critical because it would alert the body to breaches in its barrier organs such as skin and the lungs. On the other hand, if something goes wrong and the alarm can't be turned off, it could be dangerous."

Kopan says that this system is an excellent example of the way processes in the body are integrated. "When something on one part of the body is acting improperly, the entire system becomes aware of it," he says.

Source: Washington University in St. Louis

potentially.html