Scientists discover new molecular pathway involved in wound-healing and temperature sensation

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Scientists from The Scripps Research Institute have identified a surprising new molecular pathway in skin cells that is involved in wound-healing and sensory communication.

The new study, published in *Nature Communications* on June 28, 2011, shows that in this process skin cells produce nitric oxide, a versatile signaling molecule involved in temperature-sensing and wound-healing. This alternative, oxygen-independent mode of nitric oxide production previously had been thought to occur only outside cells.

"This alternative nitric oxide production process could prove to be crucial in the clinic," said Ardem Patapoutian, a professor at the Dorris Neuroscience Center at Scripps Research and the senior author of the study. "The usual nitric oxide production process requires oxygen, so drugs that target that process might not work when oxygen availability is low after blood supply disruption."

Studying the Biology of Sensation

Patapoutian's lab focuses on the molecular biology of skin-based sensory pathways—pathways that typically start with stimulus-sensing receptors on nerve ends. Such receptors include the TRPV (transient receptor potential vanilloid) class of receptors, which are sensitive to various temperature- and pain-related stimuli. One of these receptors, TRPV3, is

found not only on some nerve cells and nerve ends, but also on outer skin cells known as keratinocytes.

In 2005, Patapoutian's lab reported in the journal Science that TRPV3 seemed to be a heat-sensing receptor; mice bred without it lacked a normal sensitivity to moderately warm stimuli. "That and previous findings made us suspect that TRPV3-expressing keratinocytes are somehow involved in sending thermosensory signals to local nerve ends," said Patapoutian.

In the current study, Patapoutian, his graduate student Takashi Miyamoto, and their colleagues demonstrated that TRPV3 activation leads to the production of nitric oxide in keratinocytes—which suggests that nitric oxide is the carrier of thermosensory signals from skin cells to nearby nerve ends. A simple gas consisting of one atom of nitrogen bound to one atom of oxygen, nitric oxide is one of the more evolutionarily ancient biological signaling molecules, and even plays a role as a neurotransmitter in the brain.

"Nitric oxide was high on our list of possibilities because it is known to be produced in keratinocytes when they are warmed," said Miyamoto, who was first author of the study.

A Surprising Result

Miyamoto applied compounds that are known activators of TRPV3 to cultured mouse keratinocytes, and observed that the cells sharply increased their production of nitric oxide.

"The surprise was that I couldn't find evidence that the nitric oxide was being produced in the normal way, with nitric oxide synthase (NOS) enzymes," he said. The keratinocytes turned out to be producing nitric oxide through a different process, which is known to occur in saliva and

other bodily fluids, but hadn't yet been seen in cells.

This alternative nitric oxide production occurs by the stripping of oxygen atoms from compounds called nitrites, which normally come from dietary sources. When Miyamoto deprived the cultured cells of nitrites, their TRPV3-triggered production of nitric oxide dropped to near zero.

To confirm the role of nitrites in this pathway, Miyamoto compared the mice bred without TRPV3—which don't distinguish two different innocuous warm temperatures—to those with no-nitrite diets. "The behavior of the no-nitrite mice was basically the same as that of the TRPV3-knockout mice," he said. Feeding TRPV3-knockout mice with no-nitrite diets had no additive effect, which again suggested that the two work on the same pathway.

Next, the scientists asked, "If nitric oxide is a messenger that delivers temperature-sense signals from skin cells to nearby nerve ends, then to what nerve-end receptor does it bind?" Miyamoto, Patapoutian, and their colleagues suspected TRPV1, a known pain and temperature sensor on nerve ends, which their lab had shown to be activated by nitric oxide, in a study published in 2009. In the present study, they used a chemical to block the activity of TRPV1 receptors in mice, and observed that the lack of TRPV3 or nitrites no longer made a difference in the animal's behavior—a result consistent with the idea that TRPV1 is the main nerve-end receptor on this thermosensory pathway, acting directly or indirectly.

Hints of Things to Come

Nitric oxide's versatility as a signaling molecule also led the researchers to look for other processes in which the TRPV3-mediated pathway might be involved. "We found evidence that the nitric oxide produced by this pathway makes a partial contribution to wound-healing and also

specifically to the keratinocyte migration that occurs during wound healing," said Miyamoto.

The team now plans to detail the elements of the TRPV3-activated nitric oxide pathway in temperature sensing, and to look for evidence that the same kind of nitrite-dependent pathway is involved in other nitric oxide-producing cells throughout the body.

"The dogma has been that nitric oxide can be produced in cells only with NOS enzymes, but this study hints that nitrite-based nitric oxide production could potentially be just as important," Miyamoto said.

More information: In addition to Patapoutian and Miyamoto, other co-authors of the study, "TRPV3 regulates nitric oxide synthase-independent nitric oxide synthesis in the skin," were Matt J. Petrus and Adrienne E. Dubin, also of the Patapoutian lab at Scripps Research. For more information, see www.nature.com/ncomms/journal/ …/abs/ncomms1371.html

Provided by The Scripps Research Institute

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