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Skin must develop tolerance to 'good' bacteria early in life, says new study

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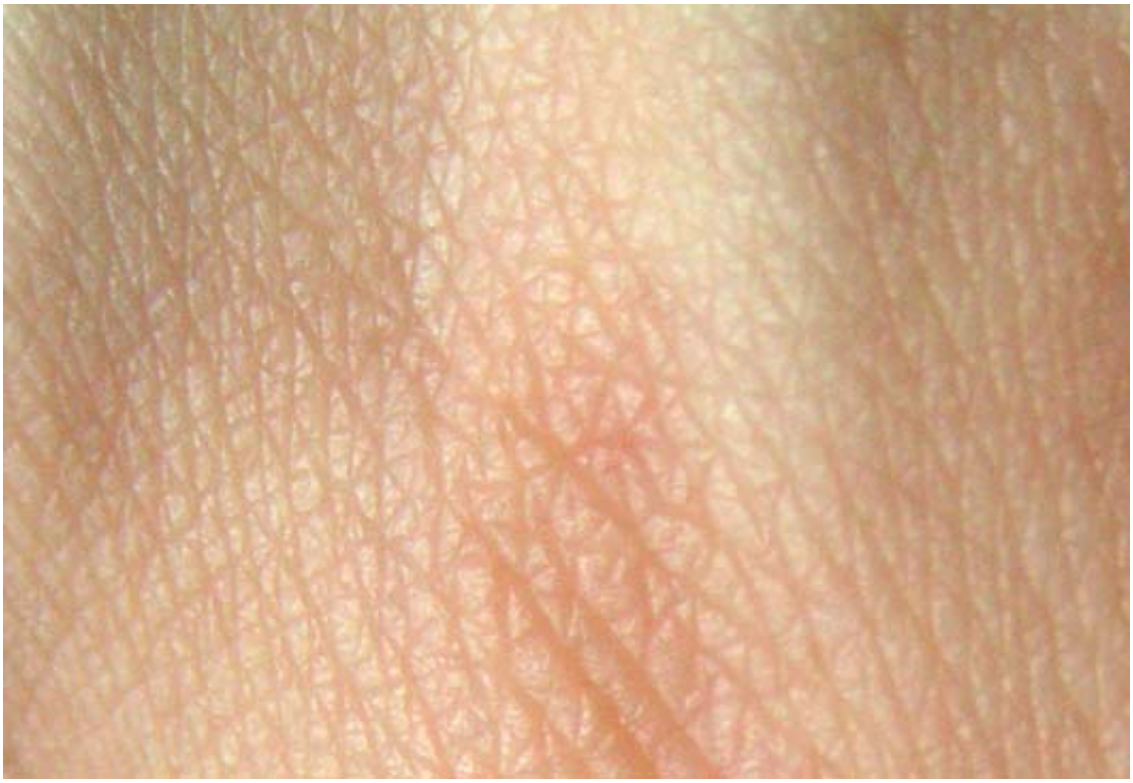

Human skin structure. Credit: Wikipedia

A wave of specialized immune cells entering the skin in early life may induce tolerance to the hundreds of species of so-called friendly bacteria that live on the surface of the body, according to a new study led by scientists from UC San Francisco.

In addition to offering a new view of the shaping of the skin microbiome – the term for communities of microbes that reside in or on different parts of the body – the new research may shed light on the development of chronic inflammatory skin conditions.

"There's an early developmental window during which you can be exposed to bacteria and they're seen as friendly – the immune system incorporates them and says, 'Yes this is good, this is 'self,' and it will not mount an immune response," said Michael D. Rosenblum, MD, PhD, assistant professor of dermatology at UCSF and senior author of a new paper on the research. "But if you introduce the same bacteria for the first time later in life, the response is completely different. The immune system says, 'This is bad, and we need to get rid of it.'"

An estimated one trillion "commensal" bacteria from about 1,000 species live on the human skin and have been shown in recent studies to provide benefits for our health. But little is known about how or why the immune system tolerates the presence of these microbes, which in some circumstances – in immunosuppressed patients, for example – can cause serious infections.

As reported in the Nov. 17, 2015, issue of *Immunity*, a UCSF team led by Tiffany C. Scharschmidt, MD, assistant professor of dermatology, genetically engineered the most common of these skin bacteria, Staphylococcus epidermidis, to carry a "model antigen" called 2W. The 2W antigen was devised by co-author James Moon, PhD, of Harvard Medical School and Marc K. Jenkins, PhD, of the University of Minnesota. Using this technique, the researchers could precisely monitor the specific immune response to the modified bacterium, which they dubbed Epi-2W.

"Before this study, nobody had ever successfully modified a commensal skin microbe to enable an anti-commensal immune response to be

precisely analyzed," Rosenblum said. "Epi-2W should be a great research tool for understanding the skin microbiome, because 'Staph epi' is the quintessential human commensal skin microbe."

In experiments described in the new paper, Epi-2W was first placed on the skin of adult mice and allowed to colonize the skin surface. Then, three to four weeks later, the skin of these mice was very mildly abraded by applying and removing a piece of tape, and Epi-2W was applied again in a bacterial "challenge." In these mice, the Epi-2W challenge caused inflammation in the abraded skin, indicating that the earlier application of Epi-2W in adulthood had not allowed the mice to develop tolerance to the bacterium.

But if Epi-2W was applied to the skin of seven-day-old mice, the mice did not exhibit an inflammatory response to mild abrasions followed by an application of Epi-2W when they reached adulthood.

"If we colonized the mice with Epi-2W bacteria in adulthood, it was almost like immunizing them – they mounted a strong immune response ," Rosenblum said. "But if we introduced the bacteria to the mice in the first 13 days of life they didn't respond to it at all in adulthood. They were totally tolerant of the bacteria."

The researchers write that the tolerance to Epi-2W seen in mice exposed as newborns was accompanied by "an abrupt accumulation" of activated immune cells known as T regulatory cells (Tregs, pronounced "tee-regs") in the skin, including a subpopulation of Tregs that specifically recognized Epi-2W. This Treg wave peaked about 13 days after birth. Rosenblum and colleagues believe that similar mechanisms are at work in human skin and are now designing experiments to find out.

"We think that bacteria have to be present on your skin during an early developmental window for you to develop tolerance. So when you

encounter new microbes for the first time later in life, you may develop low-level inflammation in your skin as a reaction," Rosenblum said. "When we give small infants antibiotics we're killing certain species, and we may be limiting the species to which they're tolerant, which may lead to chronic inflammation later in life."

Provided by University of California, San Francisco