

Interleukin-17 Levels Low in Skin of Atopic Lesions

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KYOTO, JAPAN — The predisposition to recurrent skin infections in atopic dermatitis might be explained by the recent discovery that interleukin-17 is relatively absent in lesional skin, said Dr. Emma Guttman-Yassky.

She and her coinvestigators demonstrated that interleukin-17 (IL-17) selectively induces epidermal keratinocytes to express innate defense proteins, including the antimicrobial peptides lipocalin 2, elafin, human beta-defensin-2, cathelicidin, and psoriasin.

When IL-17 is hypoexpressed in the skin barrier, as she and her colleagues have shown is the case in atopic dermatitis, it means having less of these antimicrobial peptides on-site—and that translates into diminished innate immune defense against microbial invasion, said Dr. Guttman-Yassky of Rockefeller University, New York, at an international investigative dermatology meeting.

"IL-17 is the master regulator of innate defense protein expression in keratinocytes," she said.

Dr. Guttman-Yassky reported on a study

of biopsies obtained from lesional skin of 18 atopic dermatitis patients, both lesional and nonlesional skin of 15 psoriasis patients, and skin from 15 normal controls. Specimens were analyzed by gene microarray analysis, immunohistochemistry, and polymerase chain reaction.

According to Dr. Guttman-Yassky, the key findings included the following:

► Both IL-23 and the IL-23 receptor are highly activated in psoriatic lesions, compared with atopic dermatitis lesions, which in turn feature higher levels than in the nonlesional skin of psoriasis patients or normal skin of controls. IL-23 is known to activate IL-23 receptor-bearing Th17 T cells and induce them to produce IL-17 and IL-22.

► IL-17 is highly upregulated in psoriatic lesions, compared with atopic dermatitis lesions. This is probably in large part why psoriasis is not characterized by recurrent superinfections, she noted.

► Expression of lipocalin 2 and other an-

timicrobial peptides by epidermal keratinocytes is upregulated in psoriatic skin, compared with atopic dermatitis lesions or normal skin.

► Administration of IL-17 to keratinocytes in vitro results in strong up-regulation of the innate defense peptides. Administration of interferon-gamma does not. These observations led the investigators to several hypotheses regarding the nature of some of the key immunologic differences between atopic dermatitis and psoriasis, the two most common inflammatory skin diseases.

One hypothesis is that the IL-23/Th17 axis figures prominently in psoriasis but is largely absent in lesional skin of atopic dermatitis. This difference is due to major differences in the nature of the epidermal and dermal inflammatory dendritic cells involved in the two diseases, and the downstream cytokine environment these dendritic cells create.

The key dendritic cells in psoriasis up-

regulate tumor necrosis factor- α , IL-23, and IL-12, driving T cells toward the Th1 phenotype. In contrast, the inflammatory dendritic cells in atopic dermatitis are more heavily influenced by thymic stromal lymphopoietin, driving T cells toward the Th2 phenotype, Dr. Guttman-Yassky said at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

Audience member Dr. Jon M. Hanifin called the findings intriguing. He posed the question: What effect do the very high levels of IL-10 characteristically present in atopic dermatitis lesions have on the IL-23/Th17 axis? These elevated IL-10 levels constitute a key distinction between atopic dermatitis and psoriasis that has gone almost completely overlooked to date by researchers, said Dr. Hanifin, professor of dermatology at Oregon Health and Science University, Portland.

Dr. Guttman-Yassky replied that much work remains to be done in unravelling the immunologies of these two diseases, and conceded that she and her coworkers have not included measurement of IL-10. ■



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DR. GUTTMAN-YASSKY

Prevalence of Atopic Dermatitis High Among Japanese Adults

KYOTO, JAPAN — Atopic dermatitis is one of the most common skin diseases in Japanese adults, especially those in their 20s and 30s, according to a first-of-its-kind study.

The high prevalence rates found were quite similar to those earlier reported in an Australian study in which, as in the Japanese study, the diagnosis of adult atopic dermatitis was made by experienced dermatologists. Taken together, these two large studies suggest atopic dermatitis in adults is common and underappreciated, according to Dr. Hidehisa Saeki, a dermatologist at the University of Tokyo.

He reported on 2,943 staff members, aged 20-69, at two Japanese medical schools. When they reported for their required annual general health checkup, they were examined by dermatologists who diagnosed atopic dermatitis using Japanese Dermatological Association criteria, which are similar to Hanifin criteria.

This was the first study of adult atopic dermatitis in Japan in which the diagnosis was

based upon clinical examination by dermatologists, Dr. Saeki reported at an international investigative dermatology meeting.

The prevalence of atopic dermatitis was 8% in 1,184 women and 5% in 1,759 men. The disease was classified as mild in 79% of cases, moderate in 17%, severe in 3%, and very

severe—meaning greater than 30% skin area involvement during eruptions—in 1%.

The overall prevalence of atopic dermatitis was 9% among subjects in their 20s, 8% in the 30s, 5% in the 40s, and 3% in participants in their 50s and 60s.

Most affected adults had a history of atopic dermatitis in childhood, Dr. Saeki explained at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for

Investigative Dermatology.

Worldwide, there have been few studies of atopic dermatitis in adults, and mostly they relied upon questionnaire surveys. One of the rare exceptions that employed total body examination and dermatologic diagnosis was conducted by investigators at the University of Melbourne, who reported a 7% prevalence of atopic dermatitis—quite close to the Japanese figure—in 1,457 residents of central Victoria aged 20-94 years (Int. J. Dermatol. 1999;38:901-8).

Dr. Saeki noted that the Australian and Japanese investigators found many shared trends in adult atopic dermatitis: the prevalence in both countries was higher in women, the prevalence declined with age, and roughly 80% of affected individuals had mild disease.

American dermatologists in the audience expressed amazement at the striking cultural difference between the United States and Japan as reflected in the greater than 95% attendance rate for routine annual health checkups in Dr. Saeki's study.

"In my country it seems like nobody comes in," commented an American physician. ■



As with an earlier Australian study, prevalence was higher in women and declined with age.

DR. SAEKI

Oral Vitamin D Increases Cathelicidin in Lesional Skin

KYOTO, JAPAN — Supplementation with oral vitamin D boosted chronically low levels of the antimicrobial peptide cathelicidin in the lesional skin of atopic dermatitis patients in a controlled trial, reported Dr. Tissa R. Hata.

These promising results of an initial 28-patient, 3-week, proof-of-concept study provide the rationale for larger and longer clinical trials testing the hypothesis that oral vitamin D supplementation will reduce the susceptibility of atopic dermatitis patients to recurrent skin infections, added Dr. Hata of the University of California, San Diego, at an international investigative dermatology meeting.

The expression of cathelicidin is abnormally low in the lesional skin of atopic dermatitis patients, she said. It is also known, based upon in vitro studies, that toll-like receptor stimulation of human macrophages induces expression of the vitamin D receptor as well as an enzyme, CYP27B1, which converts 25-hydroxycholecalciferol into immunologically active 1,25-dihydroxycholecalciferol, which then induces expression of cathelicidin in myeloid dendritic cells and keratinocytes. Dr. Hata and coworkers decided to see if this was also true in vivo.

She reported on 14 atopic dermatitis patients and 14 healthy controls who took 4,000 IU of oral vitamin D daily for 21 days.

Two-millimeter punch biopsies were obtained before and after treatment.

After 3 weeks of vitamin D supplementation, cathelicidin expression in the lesional skin of atopic dermatitis patients increased significantly from a median baseline 2.7 relative copy units to 21.8 relative copy units.

Supplementation with oral vitamin D appeared to boost cathelicidin production in atopic lesional skin only. There was no significant change in cathelicidin levels in the control subjects' skin, nor in the nonlesional skin of atopic dermatitis patients, Dr. Hata noted at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

Her study builds upon the work of Dr. Robert L. Modlin and coworkers at the University of California, Los Angeles, who 2 years ago in a landmark study elucidated the physiologic mechanism for vitamin D's antimicrobial and immunologic effects.

The UCLA study (Science 2006;311:1770-3) triggered ongoing intense worldwide dermatologic research into the role of vitamin D in various inflammatory skin diseases. It also helped turn the role of vitamin D deficiency in a variety of diseases into a hot topic among the general public. ■