Interleukin-17 Levels Low in Skin of Atopic Lesions

KYOOTO, 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 Guttmann-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. Guttmann-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. Guttmann-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 polyacrylamide chain reaction.

According to Dr. Guttmann-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 IL-17 expression in the nonlesional skin of psoriasis patients or normal skin of controls.

► In vitro, IL-23 receptor–bearing Th17 cells and Th17 cells are known to drive the immune response toward Th17 and superinfections, she noted.

► 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 antimicrobial 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 upregulation of the innate defense peptides. Administration of interleukin-17A 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 operates prominently in psoriasis, which is largely absent in lesional skin of atopic dermatitis. This difference is due to major differences in the nature of the epidermal inflammatory dendritic cells and may be associated with work remaining to be done 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 Th17 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. Guttmann-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-17 in atopic dermatitis have on the IL-23/Th17 axis? These elevated IL-17 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. Guttmann-Yassky replied that much recent research has looked at the immunology of these two diseases, and conceded that she and her coworkers have not included measurement of IL-10.