



## News & Trends

# ROSACEA: MOLECULAR INSIGHTS



By Harvey Jay, M.D.

Several recent studies are shedding new light — both literally and figuratively — on biochemical events that may play significant roles in the etiology and pathogenesis of rosacea.

### THE ROLE OF ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (which I will refer to as “AMiPs” to differentiate them from the AMP →ADP→ATP energy transfer adenosine 5’ mono-, di-, or tri-phosphate molecules), such as cathelicidin, appear to be capable of producing changes in skin that resemble those found in rosacea.

In a review of AMiPs, Izadpanah and Gallo discussed the human immune defense, explaining that AMiPs are an important part of “innate immunity,” which is genetically determined and able to respond to the first exposure, and which precedes the “acute inflammatory response” and then the “antigen-specific adaptive immune response.”<sup>1</sup>

Cathelicidins are positively charged AMiPs, which can react with the negatively charged surface of microbes (such as bacteria, viruses and yeast) and destroy these organisms. Cathelicidins are produced by keratinocytes, neutrophils and mast cells. They are found in sweat and saliva; attract neutrophils, mast cells, monocytes and T cells; and increase angiogenesis, keratinocyte proliferation, and synthesis of extracellular matrix. They are activated by serine protease enzymes through cleavage into smaller peptides and a cathelin peptide.

Previous studies by Ong et al<sup>2</sup> showed an increase in AMiPs such as cathelicidin and defensin in psoriatic skin, and a decrease in these same AMiPs in the skin of patients with atopic dermatitis. The authors postulated that “a deficiency in the expression of AMiPs may account for the susceptibility of patients with atopic dermatitis to skin infection with *Staphylococcus aureus*.”

### ROLE OF CATHELICIDIN

New evidence to support cathelicidin’s role in the pathogenesis of rosacea was presented at the 2007 annual American Acne and Rosacea Society by Dr. Richard Gallo and featured as a letter in *Nature Journal* by Kenshi Yamasaki and others, including Dr. Gallo. This research demonstrated in facial rosacea skin an increase in cathelicidin and stratum corneum tryptic enzyme, a protease enzyme which activates cathelicidin. These two changes produce abnormal cathelicidins, which, when injected into mice, produce changes similar to aspects of rosacea. Normal forms of cathelicidin do not produce these rosacea changes when injected into mice.<sup>3,4</sup>

The letter noted that “tetracyclines can indirectly inhibit serine proteases,” and that “preliminary data show that minocycline decreases skin protease activity during treatment.”<sup>4</sup> In his lecture, Dr. Gallo pointed out that topical Vitamin D increases cathelicidin and produces increased inflammation, the opposite effect of minocycline.<sup>3</sup> These researchers discuss the links between “innate immunity” and rosacea, and the potential treatment of rosacea by decreasing the processing or production of AMiPs.<sup>3,4</sup>

### IPL AND LASER TREATMENT

A recent small pilot study<sup>5</sup> involved 10 rosacea patients, five of whom were treated with intense pulsed light (IPL) and five of whom were treated with a pulsed dye laser (PDL). Eight patients had elevated cathelicidin before treatment. Five (three using IPL and two using PDL) of these eight patients had reduced cathelicidin levels after four treatments. Although these results were not statistically significant, this very preliminary work raises an interesting possible explanation for the successful IPL or laser treatment of rosacea redness and symptoms.

### ATP IMPACT

Research featured in the August *Skin & Aging* demonstrated that ATP (adenosine 5’-triphosphate) released by nerves in rosacea could lead to both an increase in vascular dilation after sunlight, emotional stress, or alcohol consumption, and inflammation resulting from the movement of leukocytes into the endothelial cells lining blood vessels.<sup>6</sup> In an earlier article, Seiffert and colleagues<sup>7</sup> showed how “ATP may influence local inflammatory reactions.” ... “That in rosacea, which is characterized histologically by dilated hyperaemic capillaries and a mononuclear inflammatory infiltrate, ATP not only helps to attract leukocytes but also enhances intralésional blood flow.” ... “ATP may be a unifying transmitter in a complex network of inflammatory reactions within the skin.”<sup>7</sup>

### POTENTIAL OF AMiPs

The therapeutic and diagnostic potential for AMiPs are myriad. In the future, AMiP levels may be utilized diagnostically or to monitor a patient’s response to treatment. The abil-

ity to topically deliver these naturally occurring peptides to the skin may ease and thereby accelerate the path from research to clinical application for AMiPs such as cathelicidin. Better understanding the mechanisms for therapeutic success or failure of pulsed or laser light, antibiotics and Vitamin D will help us to develop and refine these treatment modalities. Identifying new AMiPs or potentially “blocking” AMiPs or proteases may, for example, reduce the inflammation and the excessive extracellular substance produced in rhinophyma.

#### JUST THE BEGINNING?

We can be optimistic about utilizing these advances to ameliorate the suffering of our patients with rosacea, atopic dermatitis, and acne. Realistically, however, we are just beginning to understand the complex and intertwined yet redundant and independent mechanisms that can characterize biochemical processes. It is still possible and even probable that increased cathelicidin levels in rosacea may be a result of some other as yet unknown genetic, infectious, or environmentally (eg., sunlight) produced change. Increasing or decreasing cathelicidin levels in response to different medical needs may be offset by undiscovered parallel systems, feedback mechanisms, or new AMiPs or proteases.

Paradoxes abound in science and medicine and until we have a better grasp of the AMiPs and their relevance to immunolog-

ic and physiologic processes, we should proceed with cautious enthusiasm in this promising area. ■

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*Disclosures: Dr. Jay has no conflicts of interest to disclose.*

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## FDA PROPOSES NEW RULE FOR SUNSCREEN PRODUCTS

The U.S. Food and Drug Administration has proposed a new regulation that sets standards for formulating, testing and labeling over-the-counter (OTC) sunscreen drug products with ultraviolet A (UVA) and ultraviolet B (UVB) protection.

#### NEW UVA RATING SYSTEM

The proposal provides a ratings system for UVA sunscreen products on a scale of one to four stars, with one star representing low UVA protection and four stars representing the highest UVA protection available in an OTC sunscreen product.

According to the proposal, products below the one-star threshold would bear a “no UVA protection” marking on the front label near the SPF value.

#### SUNSCREEN EFFECTIVENESS ASSESSMENT

Ratings would be derived from two tests the FDA proposes for assessing the effectiveness of sunscreens in providing protection against UVA light. The first test measures a product’s ability to reduce the amount of UVA radiation that passes through it. The second test measures a product’s ability to prevent tanning. This test is nearly identical to the SPF test used to determine the effectiveness of UVB sunscreen products.

#### SUN WARNING INFORMATION

In addition, a “Warnings” statement in the “Drug Facts” box will be required of all sunscreen product manufacturers. The warning will say: *UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.*

The warning is intended to increase awareness that sunscreens are only one part of a sun protection program.

#### PROPOSED REGULATION AMENDS EXISTING SUNSCREEN RULE

When finalized, the proposed regulation would amend the existing OTC sunscreen rule published in 1999, which established regulations related to UVB light and mandated that OTC UVB sunscreen products be labeled with a SPF. The FDA also is amending its existing 1999 rule to increase the SPF from SPF30+ to SPF50+. Previously, the FDA had recognized SPF values up to 30+. Under the proposed amendment, the range would be SPF2 to SPF50+. SPF50 provides more UVB protection than lower SPF values.

#### OTHER PROPOSED CHANGES

Additionally, the proposed rule: revises the existing SPF (UVB) testing procedures; allows new combinations of active ingredients; and solicits comments on the issue of nanoparticles. ■