Factors in rosacea pathogenesis clearer

JOHN JESITUS | SENIOR STAFF CORRESPONDENT

FOR EVERY ROSACEA-RELATED question that research answers, according to experts who spoke at recent meetings in Monterey and Newport Beach, Calif., several unsolved issues remain. However, they agree that reducing rosacea symptoms begins with teaching patients to avoid triggers.

QUICK READ

Keeping abreast of findings regarding the immunological, neurological and vascular roots of rosacea helps dermatologists target treatments accordingly, experts say.

MANY MOVING PARTS

The difficulties in understanding rosacea stem from its multiple forms (erythematotelangiectatic/ETT, papulopustular/PP, phymatous and ocular) and potential mechanisms (vascular, innate immune, neurological and diet), says Guy F. Webster, M.D. He is a Hockessin, Del.-based dermatologist and past president of the American Acne & Rosacea Society (AARS).

Nevertheless, says AARS president-elect Julie C. Harper, M.D., "It's important that dermatologists have some understanding of what we're learning about the pathogenesis of rosacea. We must know where in that pathway our treatments potentially work." She is a Birmingham, Ala -based dermatologist in private practice who is affiliated with the University of Alabama at Birmingham.

Conceptually, Dr. Webster advanced two potential models for rosacea pathogenesis, the first involving multiple, perhaps equally culpable, cofactors such as histamine, cathelicidins and the innate immune system. "If any of them are out of balance, that can get the rosacea gears turning."

Dr. Harper says, "We believe that some of the normal innate immune pathways are working overtime in people with rosacea. There's too much toll-like receptor (TLR)-2 activity, cathelicidin activity and kallikrein 5, which turns the inactive form of cathelicidin into LL37, the antimicrobial peptide at work in rosacea."[1] Mouse models and *ex vivo* human skin studies have shown that LL37 increases skin symptoms such as erythema and telangectasias, she says.

Within the innate immune system, mast cells may represent a promising target. Dr. Webster explains, "Mast cells communicate with nerves. And one of the things we know for sure about rosacea is that the nerves trigger blood vessel functions including vasodilation and constriction. The mast cell may well be at the heart of rosacea — if one can calm it down, rosacea also may calm down, in theory."

Alternatively, he says, "One might say that there is one prime driver – I'd conjecture that it may be a neurological stimulus — and all the other factors are epiphenomena."

Triggers such as heat, stress and spices stimulate the transient receptor potential vanilloid (TRPV 1 through 4) and transient receptor potential ankyrin (TRPA) channels.[1] These receptors play a role in inflammation and innate immunity, Dr. Harper says. Along with cardiovascular disease, recent research suggests epidemiologic links between rosacea and Parkinson's disease[2], glioma[3] and autoimmune diseases[4]. While epidemiologic associations do not establish causality, she said, researchers began investigating in these directions because these illnesses share common inflammatory pathways.

Clinically, said Dr. Harper, "We see flushing, stinging, and papules and pustules. We also know what the triggers are – our patients tell us what makes their rosacea worse. It's different for different people. But the most common one is usually ultraviolet light."

Edible triggers such as chocolate, cheese and red wine share a common feature: fermentation, Dr. Webster says. This process can deaminate histidine, creating histamine, which has many vasoactive properties, such as inducing blush and itch, he says. "Nobody has shown that histamine in food turns on rosacea." The concept may have merit, he says, though presently it remains conjecture.

Conversely, Dr. Webster says, some forms of niacin may dilate blood vessels. If a rosacea-prone person takes niacin that's released all at once (versus delayed-release), he explains, the person gets a hot flash — which can set off rosacea — when it's absorbed.

Pathological subtleties aside, says Dr. Harper, patient education remains crucial. "We can write all these prescriptions, but it is still very important that we educate our patients about rosacea triggers." Complete avoidance is rarely possible. "But if we can lessen exposure to those triggers, we have the ability potentially to lessen the impact of innate immunity and the neurological dysregulation."

UNFINISHED BUSINESS

The impact of other potential pathogens remains unsettled. For example, says Dr. Webster, European physicians accept completely that the *Demodex folliculorum* mite is the root of rosacea. "If you ask me, or many American dermatologists, it's less decided." Although *D. folliculorum* levels are elevated in rosacea, he explains, people can have heavy *D. folliculorum* colonization, but no rosacea, and vice versa. The fact that Demodex levels are highest in ETT rosacea counters the assumption that mites attack the hair follicles, causing inflammation and pimple formation, he adds.

"The issue is confounded by the fact that the anti-mite drug Soolantra (topical ivermectin, Galderma) works well in rosacea. But no one has fulfilled Koch's postulates:[5] by showing that killing the

FACTORS see page 42

"We can write all these prescriptions, but it is still very important that we educate our patients about rosacea triggers."

Julie C. Harper, M.D.
Birmingham, Ala.

Demodex improves rosacea; that Soolantra lowers Demodex levels; and that patients who resist Soolantra have Demodex levels that don't decrease with treatment." One cannot assume that topical ivermectin works in rosacea by killing Demodex, he says, because antibiotics such as doxycycline work in rosacea through many non-antibiotic effects. Topical ivermectin also has anti-inflammatory activity, he notes.

Also unclear, he says, is the contribution of *Bacillus oleronius*. This bacterium has been found to have antigens (chaperonin GroEL and aconitate hydratase) that excited the lymphocytes of patients with rosacea, but not in normal subjects.[6]

"It sounds like something's going on there. Also, the immune response to *B. oleronius* was found to be especially elevated in ocular rosacea. But we don't know that the antigens in this bug are unique to this bug. Much remains to be worked out. It's a stretch to conclude that the bug isolated from one mite of 40 studied is relevant. I'd be more convinced if these antigens are in *Propionibacterium acnes* or some known skin resident" that causes disease.

Answers to the above conundra may come slowly, Dr. Webster cautions. With few dermatologists directly researching rosacea mechanisms, he says, insights regarding rosacea frequently emerge from other research, often in neuroimmunology.

Dr. Harper adds, "We must give Richard Gallo, M.D., Ph.D., a lot of credit. He's done much of the research in rosacea." He is professor and chief of dermatology at the University of California, San Diego.

"The mast cell may well be at the heart of rosacea – if one can calm it down, rosacea also may calm down, in theory."

Guy F. Webster, M.D.
Hockessin, Del.

Annually, the AARS offers grants to spur research in rosacea and acne. Dr. Harper says, "We have multiple grants that will be available in 2017. We would love to have any dermatologist or other researcher interested in furthering the understanding of rosacea apply." **DT**

Disclosures: Dr. Webster has been a consultant, researcher and/or advisor for Allergan, Dermira, Galderma, Valeant, Sienna, BiopharmX, Sol-Gel, Foamix, Almirall, Cutanea and Sun Pharmaceutical Industries Ltd. Dr. Harper has been a consultant, researcher and/or advisor for Allergan, Bayer, Galderma and Promius Pharma. This article is based on presentations given by Dr. Webster at the Coastal Dermatology Symposium, Monterey, Calif., and by Dr. Harper at the Skin Disease Education Foundation (SDEF)'s 12th Annual Women's & Pediatric Dermatology Symposium, Newport Beach, Calif.

References

1. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: Part I. Introduction, categorization, histology, pathogenesis, and risk factors. *J Am Acad Dermatol.* 2015;72(5):749-58.
2. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Exploring the association between rosacea and Parkinson disease: a Danish nationwide cohort study. *JAMA Neurol.* 2016;73(5):529-34.
3. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Association of rosacea with risk for glioma in a Danish nationwide cohort study. *JAMA Dermatol.* 2016;152(5):541-5.
4. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Clustering of autoimmune diseases in patients with rosacea. *J Am Acad Dermatol.* 2016;74(4):667-72.e1.
5. MedicineNet.com. Definition of Koch's postulates. http://www.medicinenet.com/script/main/art.asp?articlekey=7105. Updated May 13, 2016. Accessed October 20, 2016.
6. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol.* 2007;157(3):474-81.