[LITERATURE REVIEW]

Advances in Understanding and Managing Rosacea: Part 1

Connecting the Dots Between Pathophysiological Mechanisms and Common Clinical Features of Rosacea with Emphasis on Vascular Changes and Facial Erythema

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ABSTRACT

Rosacea is a common inflammatory facial dermatoses affecting primarily adults with fair skin, although all skin types may be affected. The diagnostic term "rosacea" reflects a spectrum of clinical features with the more common presentations characterized by increased blood flow and vasodilation during disease flares, which accentuate central facial erythema. Inflammatory lesions, usually papules and/or pustules are present in some cases. Variations in magnitude of the associated features of rosacea are noted clinically. Over time, other clinical features emerge or may be further accentuated, such as diffuse facial erythema and telangiectasias, as fixed changes in cutaneous vasculature occur. These later findings account for persistent diffuse facial erythema usually accentuated centrally on the inner cheeks, chin, nose, and/or medial forehead. Some patients may also develop phymatous changes and/or have concurrent ocular rosacea. Augmented innate immune response to certain triggers (often exogenous) and neurovascular/neuroimmune dysregulation appear to be involved early in the pathophysiological sequence of cutaneous rosacea and appear to signal other downstream inflammatory or physiochemical cascades that contribute to the pathogenesis of the disorder. In this article, Part 1 of a two-part series, emphasis is placed upon the correlation of clinical features and underlying pathophysiological changes in the more common presentations of rosacea encountered by the clinician. The importance of this information is that some of these pathogenic mechanisms are modulated by available therapies, and others remain as targets for the development of new therapeutic agents or modalities. (*J Clin Aesthet Dermatol.* 2012;5(3):16–25.)

"Rosacea is an odd disorder which seems to defy understanding and the aim is…to see whether we can identify any central unifying theme that can explain the pathogenesis and/or major signs of the disease."

"… it is quite possible (some might say 'quite likely') that what we understand by the term 'rosacea' is in fact a collection of several disease entities all manifesting the same set of physical signs—a final common pathway—but at least we should all agree on these physical signs."[1]

The preceding statements were published as recently as 2007 by Dr. Ronald Marks, a dermatologist who has dedicated much of his career to the subject of rosacea. Together, they clearly emphasize our limited ability over many years to scientifically and rationally classify the clinical presentations of the common facial disorder that we term "rosacea." These statements also reflect our relative lack of knowledge and understanding of the underlying pathophysiological mechanisms that correlate with the clinical features we encounter in individual cases, and how

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the therapies we utilize modulate the underlying pathways and cascades that induce specific clinical features of rosacea.[1] However, over the past decade, many advances have been made regarding our understanding of rosacea. Practical advances include how clinical subsets are defined, the terminology used to describe patterns of presentation, and the correlation of clinical features with treatment selection. In addition, data from several research studies that have evaluated the basic science aspects of rosacea collectively provide better explanations for at least some of the clinical features we observe in affected patients and/or modes of action of the therapeutic agents we employ in the management of rosacea.[2–17] In addition to learning more about rosacea and the therapies used for treatment, the myriad of basic science and clinical research studies evaluating many aspects of rosacea are providing insights into several other subject areas related to pathophysiological mechanisms that are clinically relevant. Included among these are distinct pathways of inflammation, the role of epidermal proteases and their multiple effects in skin, the contribution of cutaneous antioxidant systems, innate immune response and receptor patterns in normal and diseased skin, the influence of antimicrobial peptide (AMP) balance and regulation on pathophysiology in different disease states, the impact of neurogenic factors on immunological responses and vasoregulation, and the role of chemical mediators (i.e., cytokines, chemokines) in disease activation and progression. Other mechanisms relevant to rosacea include the impact of stratum corneum (SC) permeability barrier impairment on pathophysiology, visible skin changes, symptomatology, and tolerability; alterations of cutaneous vasculature in rosacea versus other skin disorders; and types of vascular receptors in skin and how they can be modulated. Taken together, all of these subject areas appear to be clinically relevant, correlating with why patients present with specific clinical features, including both signs and symptoms, and why individual therapies may or may not be effective for certain disease manifestations.

This two-part article reviews many of the challenges in defining and assessing the various clinical presentations of rosacea. Although multiple subtypes of rosacea will be referred to based on the conventional standard classification that is commonly used, major emphasis will be placed on the two most common cutaneous subtypes seen in clinical practice—erythematotelangiectatic rosacea (ETR), also referred to as subtype 1, and papulo-pustular rosacea (PPR), also referred to as subtype 2. Among the areas discussed in Parts 1 and 2 of this article are perspectives on clinical manifestations that are commonly encountered by clinicians at initial and follow-up visits, current information on pathophysiology of rosacea with links to clinical relevance, a thorough review of diffuse and persistent facial erythema as a major fundamental component of the common clinical presentations of rosacea (Figure 1), an overview of cutaneous vasculature and adrenoreceptors involved in blood flow modulation, and a discussion of causative mechanisms of erythema and how different therapies can modify some of these mechanisms. Also discussed are the clinical importance of naturally progressing from diagnostic subtyping to defining the clinical features present in a given patient at any point in time; approaches to selecting, adjusting, or combining various therapeutic options to manage specific clinical findings and presentations; and an overview of the management of rosacea with emphasis on medical therapies, including emerging topical options for diffuse and persistent facial erythema.

Part 1 provides a thorough update of underlying pathophysiological mechanisms and their correlation with common clinical features and presentations of rosacea (such as in PPR and ETR). The rationale behind "thinking beyond the rosacea subtype" and focusing on manifestations present in the individual patient is discussed. Also, the development and fundamental relevance of diffuse and persistent facial erythema as the core finding in almost all cases of cutaneous rosacea is emphasized and explained.

SUBTYPING: A STEP IN THE RIGHT DIRECTION IN CLINICAL DIFFERENTIATION OF PATTERNS OF ROSACEA

The first major advance in bridging the overall understanding of rosacea and the differentiation of its clinical presentations among researchers and clinicians was a sentinel article published in 2002 on the standardized classification of rosacea.[16] This article focused on the diagnosis of rosacea with differentiation based primarily on clinical patterns and described basic primary and secondary diagnostic criteria. A second article published in 2004 by the same panel of authors outlined a standardized grading system for rosacea designed to aid in the assessment of disease severity.[17] However, it was the article on standard classification, despite some recognized limitations, that brought into focus the specific terms and definitions that could be applied in clinical and research settings to more accurately place patients with rosacea into a diagnostic category, referred to as a subtype. The description of each subtype was based on visible clinical features and symptom tendencies that are generally characteristic of that subtype. For the first time, when a clinician or researcher was discussing rosacea, they could have all listeners be "in the same ballpark" with them simply by referring to a specific rosacea subtype.

It took approximately 3 to 5 years for the concepts and definitions expressed in the aforementioned standard classification article to gain progressive exposure in the United States and elsewhere around the world. Over time, use of the definitions of rosacea described in this article have become adopted by most into the mainstream of dermatology, the end result being that all those involved were redirected to speak the same language using the same agreed-upon terminology. Now, academic, community, and research-oriented dermatologists address specific subtypes of rosacea in publications, at the podium, and in interpersonal conversations using the same diagnostic terms when referring to individual clinical presentations. Thus, subtyping of rosacea from a clinical perspective proved to be a major step in the right direction.

UPDATE ON PATHOPHYSIOLOGICAL MECHANISMS CORRELATING WITH ROSACEA SUBTYPES AND CLINICAL FEATURES

This section provides an in-depth update reviewing current knowledge on pathophysiological mechanisms that correlate with classical rosacea subtypes and/or specific clinical features associated with different presentations of rosacea. Some information is directly pertinent with clear clinical relevance, while other findings may suggest clinical relevance or provide potential support of clinical observations. Nevertheless, both diagnosis and treatment are enhanced when their scientific basis is more clearly understood.

More recently, newer research findings using characterization of gene array profiles, polymerase chain reaction (PCR) analysis, molecular and morphometric determinations, and immunohistochemical testing techniques have noted some differentiating features among specific rosacea subtypes.[10] Thus far, based on publications to date, all of the defined major subtypes of rosacea differ in their gene array profiles when compared with healthy skin and to each other, although there is some overlap between the major cutaneous rosacea subtypes (ETR [subtype 1], PPR [subtype2], phymatous [subtype 3]).[10,16]

Augmented innate immune response. In rosacea patients with facial erythema without inflammatory papules or pustules (ETR subtype), marked upregulation of proinflammatory and vasoregulatory genes are present, including early on in the disorder, with a predominantly perivascular inflammatory infiltrate composed of lymphocytes (mostly CD4+ T cells; Th1 pattern), macrophages, and mast cells also documented.[10] Importantly, these studies demonstrated no enhancement of Langerhans cells, natural killer cells, or eosinophils. This pattern of inflammatory cell infiltration suggests early involvement of innate immune response in ETR and PPR; although adaptive immune response is also activated in ETR, its magnitude of activation appears to be less than in PPR.[10]

In patients with PPR, upregulation of both innate and adaptive immune response genes has been documented, including for cathelicidin (hCAP18), a major AMP found in human keratinocytes that is physiologically responsible for innate antibacterial defense.[10] This gene profile data obtained from PPR-affected facial skin is supportive of other research performed in both murine and human skin.[7–10,18] Data from these other studies have confirmed expression of abnormally high epidermal levels of both cathelicidin and the predominant serine protease (SP) enzyme involved in cathelicidin processing, kallikrein-5 (KLK-5), in patients with PPR as compared with matched normal skin controls.[7–9,11,18] To add, the expression of Toll-like receptor 2 (TLR2), a pattern recognition receptor ("alarmin") that serves as a first line of innate immune defense, is increased in PPR, with TLR2 also shown to increase the expression of KLK-5 in human epidermal keratinocytes.[7–9,11,18] The importance of this research data is that the peptide forms produced by overexpressed cathelicidin metabolism and aberrant serine protease activity that are operative in PPR (i.e., long form of LL-37) promote chemoattraction of inflammatory cells (neutrophils, monocytes, T cells), angiogenesis, and altered expression of components of the extracellular matrix in some research models.[3–5,7–9,11,18–21] Importantly, some therapeutic agents (e.g., tetracyclines) used to treat primarily PPR and ocular rosacea (subtype 4) demonstrate the ability to modulate some of the components and steps of these pathways (reviewed later in this article).[3–5,7–9,22]

In addition to augmented cathelicidin and KLK-5 activities, marked expression of interleukin-8 messenger RNA (IL-8 mRNA) has been demonstrated in PPR. This finding is clinically relevant as the primary role of IL-8 as a cytokine "messenger" is chemoattraction of neutrophils, along with its supportive involvement in other processes, such as angiogenesis.[10] In patients with PPR, neutrophil chemotaxis can be promoted by both cathelicidin-derived peptides (such as the long form of LL-37) and IL-8, with

both factors potentially contributing to the formation of inflammatory lesions in PPR.[7,10,18,19]

Underlying sources of changes in cutaneous vasculature. Dilation of cutaneous vasculature and lymphatics have been reported in rosacea, with some studies demonstrating an increase in cutaneous blood flow in affected skin and more recent data confirming vascular and lymphatic dilation in both ETR and PPR by morphometric analysis, immunohistochemical testing, gene array profiling, and real time-PCR studies.[2,8,10,14,23–25] Enlargement of vasculature, hyperpermeability, and fluid extravasation are hallmarks of tissue inflammation, with angiogenesis, lymphangiogenesis, vascular endothelial growth factor (VEGF)-A, and other markers for blood vessels (CD31) and lymphatics (D2-40) shown to be increased in rosacea.[8,10,18,23,25] In addition, the cathelicidin-derived peptide LL-37, which has been shown to be increased in PPR-affected facial skin, exhibits potent angiogenic activity and can induce alterations in endothelial cells via multiple signaling pathways.[18] These include promotion of angiogenesis with neovascularization mediated by interaction with endothelial cell receptors, receptor transactivation with downstream signaling in epithelium, and receptor-mediated induction of VEGF in keratinocytes, all based on studies in various research models.[18,20,26–28] Thus, the cathelicidin-derived peptide forms produced in PPR, especially LL-37, may serve as a common denominator for multiple pathophysiological processes involving both inflammatory effects and vascular changes, both of which appear to correlate with some of the observed clinical features in rosacea (Table 1). Of further interest is the finding that cathelicidin AMP has been shown to be upregulated in ETR, PPR, and phymatous rosacea.[13]

Changes in cutaneous blood flow. In addition to findings related to vascular and lymphatic dilation in ETR and PPR and changes in vascular integrity and function secondary to acute and chronic inflammation, a significant increase in mean cutaneous blood flow has been demonstrated in affected facial skin as compared to nonaffected facial skin in patients with PPR using laser Doppler perfusion imaging (P=0.02) (Table 1).[24] In the same study, a similar differentiation in mean cutaneous blood flow was noted in facial skin of patients with ETR; however, the difference between affected and nonaffected skin sites did not reach statistical significance. It is interesting to note that mean cutaneous blood flow results in PPR-affected facial skin and ETR-affected facial skin were higher than in facial skin of normal controls, although the differences between each rosacea-affected group and the control group did not reach statistical significance.[24]

Table 1. Vascular Changes in Rosacea

Unification of Innate Immune Dysregulation and Increased Vascularity

- **Alterations of vascular response and blood flow[1-7]**
  - Easier + more prolonged flushing response (to heat)[1,2]
  - Oral-thermal flushing[2]
  - Altered blood flow[1,3-7]
    - Decreased venous blood flow from periphery (facial skin) to core (brain) in response to heating[7]
    - **Increased blood flow in affected skin > nonaffected skin[6]**
      - Greater difference with inflammatory lesions
- **Physiochemical stimulation of vasodilation and/or angiogenesis[8-12]**
  - Increase in VGEF in rosacea (nonphymatous skin) and via stimulation by UV exposure[8,9]
  - Endothelial nitric oxide (eNO) → Vasodilation[8,10]
  - Cathelicidins → Derived peptides (ie. LL-37+) → Angiogenesis/Neovascularization[11,12]
    - **Potential role in increased vascularity in rosacea through cathelicidin-induced endothelial changes**
      - **Downstream receptor simulation (FPRL1* and EGFR**-induced increases in VGEF)**
- **Progressive chronic vasodilation and angiogenesis underscore the development of persistent erythema due to fixed changes in vasculature (larger cutaneous vessels, dilated cutaneous vessels, telangiectasias)[13]**

1 Crawford et al. J Am Acad Dermatol 2004;51:327-41. 2 Wilkin J Invest Dermatol 1988;19:309-13 3 Buechner Dermatology 2005;210:100-08. 4 Wilkin Arch Dermatol 1994;30:359-62. 5 Sibenge et al. J Am Acad Dermatol 1992;26:590-93. 6 Guzman-Sanchez et al. J Am Acad Dermatol 2007;57:800-5. 7 Brienel et al. Arch Dermatol Res 1989;281:66-72. 8 McAleer et al G Ital Dermatol Venereol 2009;144:663-71. 9 Gomaa et al. J Cutan Pathol 2007;34:748-53. 10 Korting et al Skin Pharmacol Physiol 2009;22:287-94. 11 Yamasaki et al J Dermatol Sci 2009;55:77-81. 12 Aroni et al Arch Dermatol Res2008;300:125-131. 13 Rosina et al J Am Acad Dermatol 2006;54:100-104

+ Long-form of LL-37 produced in rosacea with greater effects on vasculature than in healthy skin

* FPRL1 = formyl peptide receptor-like-1 / EGFR = epidermal growth factor receptor

Altered vascular response. The heightened vasodilatory response of facial skin to a variety of stimuli (i.e., ambient heat exposure, food or drink of hot temperature [oral-thermal flushing], exercise, ingested vasodilator medications, spicy foods, alcohol ingestion) is characteristic of many patients with PPR and ETR (Table 1).[2,10,16,24,29] This augmented vascular responsiveness has generally been considered to be primarily neurogenic in origin, with more recent studies providing further support of this concept.[2,10,13,16,24,29]

The recognition of neurogenic inflammation associated with neuropeptide release from sensory nerve endings as a cause of localized hyperemia, edema, erythema, and recruitment of neutrophils, and neuropeptide-induced release of mast cell mediators that contribute to inflammation and symptomatology (i.e., burning sensation, pruritus) has resulted in a more detailed evaluation of the potential correlation between neurogenic mechanisms and the pathogenesis of rosacea.[10,13,30,31]

Evaluation of neurovascular and neuroimmune changes in different clinical presentations of rosacea using quantitative real-time PCR and immunohistochemistry supports the major presence of vasodilation of blood vessels and lymphatics in ETR, PPR, and phymatous rosacea, demonstrates the upregulation of genes involved in vasodilation, and supports the observation that blood vessels in rosacea retain their ability to respond to vasoactive stimuli.[2,13] These studies further demonstrate

that dysregulation of neural-associated mediators and receptors plays an important role in the pathophysiology of rosacea, including early in its course of development.[13] Neurogenic inflammation caused by the pathophysiological consequences of aberrant neurovascular and neuroimmune communication promotes marked vasodilation in ETR, PPR, and phymatous rosacea, and contributes to fibrosis in some patients with chronic inflammation and phymatous changes.[10,13] Supportive observations from these analyses include colocalization of facial sensory nerves, blood vessels, and mast cells; slightly increased numbers of myelinated nerves (pain transmission) in ETR-affected facial skin compared with healthy skin; increased density of mast cells in ETR, PPR, and phymatous rosacea; upregulation of target receptors for mediators released from mast cells or sensory nerves; enhancement of several vasoactive neuropeptides linked to vasodilation, plasma extravasation, and mast cell degranulation; and inflammation-associated endothelial cell responses.[13] Ultimately, neuroimmune and neurovascular effects appear to be major pathophysiological factors that are operative in ETR, PPR, and phymatous rosacea, including early in the disease course. It is conceivable that augmented innate immune response and neurogenic inflammation utilize "crosstalk" mechanisms and work in concert at time points both early and later in the course of rosacea to elicit many of the common clinical features of ETR, PPR, and, in some cases, phymatous rosacea.

Physical ("fixed") changes in cutaneous vasculature. Interestingly, videocapillaroscopic evaluation of facial cheek skin in ETR (n=30 patients) demonstrated physical changes in cutaneous vasculature that correlate with clinical observation by both clinicians and affected patients (Table 1).[14] Markedly larger vessel diameter, more prominent telangiectasias, neoangiogenesis, and larger capillary nets (polygons) were noted in those with ETR as compared with healthy patients (n=30) and patients with seborrheic dermatitis (n=30).[14] Collectively, these vascular-related findings support the visibly apparent diffuse and persistent facial erythema and telangiectasias that are very consistent clinical features of both ETR and PPR.[2,10,14,16,17] It is important to note that the development of diffuse facial erythema, persistent facial erythema, and telangiectasias associated with rosacea occur independent of whether inflammatory lesions are ever present as a clinical finding (Figure 1). This latter observation is of major significance, as it underscores the fact that alterations in vascular response and physical changes in cutaneous vasculature are major fundamental components of both ETR and PPR and correlate with the frequent development of persistent facial erythema that is usually diffuse and accentuated in the central facial region in the vast majority of patients (Table 1).

Rosacea as an inflammatory disorder. Another important observation is that data from gene array profiles and histological evaluations do not support a microbial source as a major primary or initiating pathophysiological factor in the early phases of rosacea.[10] This observation provides additional support that rosacea, even in its early stages, is considered to be an inflammatory disorder characterized by accentuation of innate immune response associated with multiple triggers and dysregulation of several interactive cutaneous systems and/or pathways. These include enhanced innate immunity related to increases in the expression of TLR2, cathelicidin, cathelicidin-derived peptides, and SP (KLK-5) in keratinocytes; increases in some matrix metalloproteinases (MMPs) and their associated effects; SC permeability barrier dysfunction resulting in increased central facial transepidermal water loss (TEWL) and skin sensitivity; and dysregulation of neuroimmune and neurovascular activities including alterations in mediators, receptors, and some changes in density of mast cells and sensory nerves.[2,4,6–13,18–36] As already discussed, neurogenic inflammation is believed to be another predominant pathogenic factor, including early in the course of rosacea.[10] However, it is not known whether the effects of neuroimmune and neurovascular dysregulation noted in rosacea precede or follow the early inflammatory infiltrate that is characteristic of an innate immune response and present in rosacea-affected skin characterized by diffuse central facial erythema even in the absence of inflammatory lesions.[10,13]

Potential roles of photodamage. Although it remains somewhat controversial whether chronic photodamage is a primary pathogenenic factor associated with rosacea, changes associated with chronic photodamage, such as dermal matrix degradation, loss of perivascular structural integrity, telangiectasia formation, and persistent erythema, can stack upon similar structural alterations and visible features observed in both ETR and PPR.[2,37] Ultraviolet (UV) light exposure may also serve as a major external trigger that induces the activation of innate immune response and/or neurogenic effects.[2,8–10] Ultraviolet B (UVB) exposure has been shown to induce secretion of several immunomodulatory cytokines (i.e., IL-1, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha), and UVA exposure can inhibit collagen synthesis and modulate the activity of some MMPs involved in degradation and remodeling of the dermal extracellular matrix.[38,39] Quantitative real-time PCR analysis has demonstrated the greatest magnitude of gene upregulation for MMP-1 and MMP-12, followed by MMP-10, MMP-3, and MMP-9 predominantly in PPR and phymatous rosacea, with downregulation of all MMP inhibitors noted at the RNA level.[10]

Interestingly, generation of reactive oxygen species (ROS)—the earliest measurable response of human skin to UV exposure—upregulates the epidermal and dermal expression of MMP-1, MMP-3, and MMP-9, all of which contribute to dermal matrix degradation. This finding is also consistently observed histologically in several evaluations of rosacea-affected skin.[2,40,41] It has been suggested that dermal matrix degradation is a primary mechanism contributing to the pathogenesis of rosacea, although definitive confirmation is lacking.[2]

Another potential pathophysiological mechanism in rosacea related to MMP upregulation is that certain MMPs contribute to the activation of epidermal serine proteases

from their inactive precursor forms, thus promoting the formation of cathelicidin-derived proinflammatory peptides (i.e., LL-37) that are increased in rosacea-affected skin (as reviewed earlier).[7,8,18,42,43] Utilizing this same innate immunity pathway in keratinocytes, an increase in MMPs promoted by UV light exposure may contribute to serine protease activation in rosacea-prone skin. In addition, MMP-9, shown to be upregulated in both rosacea-affected skin (especially in PPR and phymatous rosacea) and in human skin by ROS induced by UV exposure, has been linked to angiogenesis, as has MMP-2.[44]

The role of ROS in the pathophysiology of rosacea has also been evaluated in two studies utilizing different measures to determine the presence and degree of rosacea-associated oxidative stress.[45,46] The first showed both a statistically significant direct correlation between the magnitude of reduction in cutaneous antioxidant capacity and increased severity of rosacea ($P<0.05$) and augmented utilization of antioxidant activity in subjects with mild rosacea as compared with the control group ($P<0.05$).[45] Antioxidant activity was assessed by measuring the activity of superoxide dismutase, the major enzyme involved in protecting skin from oxidative stress, and levels of malondialdehyde, a biomarker that reflects increased antioxidant activity in response to oxidative stress. In a second study of patients with rosacea compared with healthy controls, the study arm with rosacea exhibited increased serum levels of peroxide, decreased total serum antioxidative potential, and increased cutaneous ferritin positivity (especially in severe rosacea).[46] These data further support depletion of cutaneous antioxidant capacity in rosacea, with suggestion in this study of involvement of systemic oxidative stress in rosacea. To summarize, it appears that rosacea-affected skin predisposes to easier depletion of cutaneous antioxidant reserve as compared with normal skin. Therefore, when rosacea-affected skin is exposed to environmental factors that cause oxidative stress, such as UV light exposure, the inherent antioxidative mechanisms that normally counteract the effects of ROS are more likely to be compromised by the depletion of antioxidant reserve associated with rosacea. Depending on the magnitude of ROS production, this can result in a greater likelihood in rosacea-affected skin that ROS-induced pathophysiological effects can be set into motion and perpetuated.

Certain byproducts of host injury, such as tissue-related changes induced by chronic UV light (radiation) exposure, can trigger an innate inflammatory response mediated via specific TLRs.[33] In one model, UV exposure induced keratinocytes to secrete ligands that activate TLR2 and TLR4.[38] As noted earlier, increased TLR2 expression has been documented in rosacea, thus suggesting that an increase in TLR2-activating ligands could possibly link UV-induced photodamage to augmentation of innate immune response in rosacea.

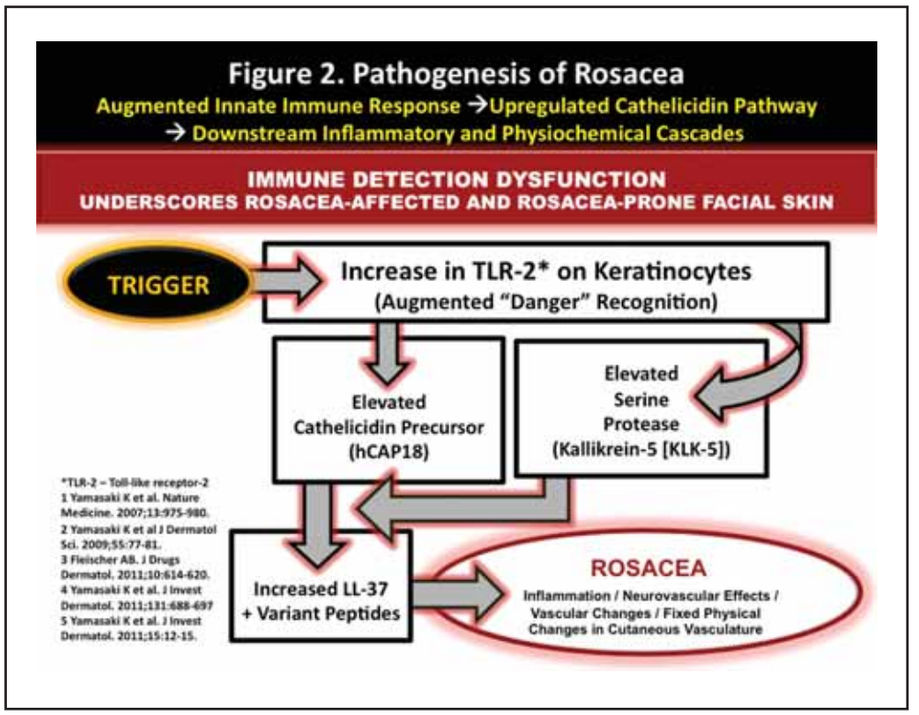
It may also be possible that acute UV light-induced altered proteins in keratinocytes activate a specific TLR pathway that will then promote an innate immunological response and subsequent inflammation. However, the mechanistic relationship between acute exposure to UV light and precipitation of rosacea has not been well-defined other than an association with increased heat exposure, a common trigger associated with exacerbation of ETR and PPR.

Ultimately, UV-related photodamage is capable of triggering innate immune response that can contribute to jump-starting and perpetuating underlying patho-physiological mechanisms in facial skin of rosacea-prone individuals and cause persistent erythema and telangiectasia formation via promotion of inflammation, vasodilation, and angiogenesis.[2,8,18,33,38,47] Some factors that may contribute to UV-induced angiogenesis include ROS-induced increase in expression of MMP-9, and possibly increased production of VEGF by keratinocytes exposed to UVB.[40,44,47,48]

Demodex mites and rosacea. It should be recognized that proliferation of *Demodex* mites (*D folliculorum, D brevis*), especially *D folliculorum*, can in some cases trigger an inflammatory response that produces a rosacea-like eruption that some have termed rosacea-like demodicidosis or *Demodex* dermatitis.[2,32,47,49–53] However, others consider the possibility that *Demodex* proliferation may be a primary causative factor in some cases of PPR, a suggestion that has been sustained in dermatology literature for approximately eight decades.[2,47] In one study of patients with rosacea, a linear correlation between the presence of *D folliculorum* and the magnitude of fibroblast-related MMP-9 expression was observed.[54] Thus, in patients who exhibit concomitant PPR, *Demodex* proliferation may serve as a proinflammatory cofactor. Overall, *Demodex* mite proliferation is not considered to be a mandatory pathogenic factor in rosacea, is not believed to be a causative factor in most cases of PPR, and has not been correlated with the development of ETR.[2,32]

It is important to recognize that rosacea-like demodicidosis can in some cases simulate rosacea, especially PPR. However, many cases of PPR present as nonspecific facial eruptions (i.e., patchy erythema, small diffuse scaly facial papules and/or pustules, acneiform eruptions) that are only partially or poorly responsive to conventional rosacea therapies[47,53] Other cases may be diagnosed initially as nonclassical presentations of seborrheic dermatitis or rosacea.[53] However, a common observation suggestive of rosacea-like demodicidosis (*Demodex* dermatitis) is the lack of central facial predominance of inflammatory lesions, with a tendency for more diffuse and even distribution involving both the central and peripheral face. These cases often respond to topical antiparasitic agents (i.e., permethrin, crotamiton) and oral ivermectin.[50,53]

Rosacea symptomatology. A newer consideration regarding rosacea-associated symptoms is their possible relationship, at least partially, to augmented expression of specific cell surface receptors that elicit proinflammatory neurogenic effects.[10,22] This includes characteristic dys-esthesias, such as burning and stinging, in response to



commonly reported "rosacea triggers" (i.e., exogenous heat exposure, physical exercise, spicy foods, UV radiation). Specifically, transient receptor potential vanilloid receptor 1 (TRPV1), a cutaneous vasoregulatory receptor, is increased in density in ETR as compared with healthy skin, with a high density of epidermal and dermal TRPV1+ nerve fibers and an overexpression of TRPV1 mRNA also found in skin biopsies from patients with rosacea.[10]

Symptoms innate to rosacea-prone and rosacea-affected skin are well recognized by clinicians who encounter patients with rosacea.[2,16,35,55–58] Quantification of the innate symptomatology associated with untreated facial skin has been captured at baseline in studies of patients with PPR of predominantly moderate severity prior to initiation of treatment.[55,56] The range of reported findings among three randomized, vehicle-controlled, double-blind studies inclusive of 915 patients was scaling in 51 to 58 percent, burning in 33 to 36 percent, stinging in 29 to 34 percent, and dryness in 65 to 69 percent.[55,56]

Stratum corneum permeability barrier impairment. SC permeability barrier impairment affecting central facial skin is another important factor in many patients with ETR and PPR that appears to contribute to the common finding of sensitive skin with or without visible signs of "low-grade" facial dermatitis (fine scaling, flaking, pink erythema), referred to as rosacea dermatitis.[34,35] Increased TEWL and decreased SC hydration associated with impairment of the SC permeability barrier at least partially explains the inherent signs and symptoms reported by patients with PPR at baseline when not undergoing active treatment, as described previously.[55,56] In addition, SC permeability impairment also predisposes rosacea-prone facial skin to intolerability after use of several common skin care products and topical medications, with gentle cleansing and pre-emptive moisturization shown to improve skin tolerability in many cases.[36,57,58] It is also important to recognize that the SC permeability barrier and the antimicrobial barrier, including the cathelicidin system and SPs, are structurally and functionally interrelated, and coregulated. Expression and secretion of AMPs increases in response to permeability barrier disruption, with the cathelicidin-derived peptide, LL-37, required for maintenance of permeability barrier homeostasis.[59]

Early pathophysiological pathways and signals. An augmented innate immune response mediated via increased expression and possibly hyper-reactivity of TLR2 appears to be operative consistently in PPR and likely ETR, although the magnitude of activity may be variable at different times in a given patient and from patient to patient.[7,8,10] From a clinical perspective, this augmentation of innate immune response, present early on in the development of the disorder, translates to a state of immune detection dysfunction, thus providing a framework for the promotion of other pathways that correlate with many of the common clinical features associated with PPR and ETR (Figure 2). The augmented innate immune response of rosacea is thought to be set in motion by a variety of potential "triggers" (e.g., UV light exposure), with other mechanisms operative either downstream or concurrently with innate immune response.[2,6–10] SC permeability barrier dysfunction and neural dysregulation are also potential contributors to the early development of clinical features and symptoms of PPR and ETR.[10,13]

Missing puzzle pieces. It is very important to recognize that although our understanding of potential pathophysiological mechanisms has vastly increased based on strong evidence from several basic science studies, additional research is needed to further substantiate what has been observed to date and to establish clinical relevance. Ultimately, several pieces of the pathophysiology puzzle remain unanswered at the present time, with the hope that additional research will provide further understanding of the underlying causes and pathways that create the spectrum of clinical presentations encompassed under the designation of rosacea. Some voids in our knowledge regarding the pathophysiology of rosacea are the need for a better understanding of genetic influence, biological determinants of individual clinical presentations and their severity, factors that influence durations of remission, and whether patho-

physiological processes continue to simmer subclinically during periods of clinical remission.

Relative contributions of different pathophysiological pathways. Many pathophysiological mechanisms have been associated with individual clinical presentations or subtypes of rosacea. Due to the considerable variations in clinical manifestations of rosacea, including both ETR and PPR, it is believed that one single mechanism is not consistently dominant in all cases, certain mechanisms may be consistently present in most or all presentations of rosacea but can vary in magnitude, some mechanisms are likely to be more active in some presentations than in others, and specific pathways or cascades may be fully dormant or never operative in individual cases or subtypes. In addition, the clinical features of rosacea in a given patient may differ in their character and/or severity at different points in time, reflecting the relative participation of specific underlying mechanisms that correlate with certain clinical features.[10]

Table 2. Common Presentations of Cutaneous Rosacea
Intermittent vs Persistent Clinical Features

Major clinical features of common presentations of rosacea*

- ***INTERMITTENT FEATURES***
  - Inflammatory lesions
  - Perilesional erythema
  - Early background erythema (vascular, neurogenic, others)
- ***PERSISTENT FEATURES***
  - Background erythema (vascular, neurogenic, other)
  - Telangiectasias
  - Phymatous changes

*Common presentations refers to the classic subtype designations of erythematotelangiectatic rosacea (subtype 1) and papulopustular rosacea (subtype 2)

CONNECTING THE DOTS BETWEEN UNDERLYING PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Although a fully comprehensive review of mechanisms involved in the pathogenesis of rosacea is beyond the scope of this article, attempts have been made to "connect the dots" between pertinent research observations and clinical applications in both diagnosis and treatment. After considering the wide variety of intertwined and sequenced pathophysiological mechanisms in rosacea and the most common and consistent clinical features, it becomes apparent that vasodilation and the associated increased blood flow at sites of rosacea-affected facial skin correlate with greater intensity of erythema during initial flares of both ETR and PPR. Early in the course of the disease, this is recognized clinically as intermittent facial erythema.[2,16] Based on current evidence, the signals that induce vasodilation of facial vasculature in rosacea that account for this diffuse erythema are inflammation secondary to an augmented innate immune response and neuroimmune/neurovascular dysregulation.[2,6–13,18,24,33,47] Ultimately, the multiple changes in cutaneous vascular response and physical alteration of the vasculature of the skin that occur in rosacea over time are fundamental components that correlate with visible clinical manifestations and some aspects of rosacea symptomatology (Table 1). Inflammation and skin sensitivity are further accentuated by SC permeability barrier impairment.[34,35] Some patients do not develop as-sociated inflammatory lesions (i.e., papules, pustules) and encompass the group classically designated as ETR. Those who develop inflammatory lesions are designated as PPR. Nevertheless, diffuse and persistent facial erythema is common to both groups, demonstrating that inflammatory lesions are not central to or mandatory for the development of facial erythema in rosacea (Figure 1).

Importantly, perilesional erythema associated with papules and pustules certainly contributes to the overall appearance of facial redness as the focal zones of erythema surrounding individual inflammatory lesions intermingle with the background of diffuse erythema. However, perilesional erythema is distinct from diffuse persistent facial erythema, its presence is dependent solely upon association with inflammatory lesions, its formation is due primarily to the focal collection of inflammatory cell infiltration and localized hyperemia, and its disappearance occurs in concert with inflammatory lesion clearance. On the contrary, persistent facial erythema is fixed and usually diffuse, tends to persist at least to some degree despite resolution of inflammatory lesions, and is related to more diffuse inflammatory cell infiltration and vasodilation.

Over time, after repeated bouts of vasodilation and secondary inflammatory responses, several mediators, such as cathelicidin-derived LL-37 and other variant peptides, VEGF, and some MMPs, produce fixed structural alterations within the skin, such as persistent dilation of blood and lymphatic vessels, neoangiogenesis, formation of telangiectasias, and dermal matrix degradation.[2,8–10,18,20,23–28,40,44,47] At this point in the disease course, diffuse facial erythema becomes persistent (fixed), as the cutaneous vasculature has been structurally altered (Table 1). During disease flares, there

is increased vasodilation, cutaneous blood flow, and fluid extravasation secondary to the inflammatory effects associated with the flare (as discussed earlier).[25] As the disease flare wanes, there is some persistence of diffuse facial erythema as the "baseline setting" of cutaneous vessels has been reset over time to a more fixed vasodilated state, and angiogenesis has led to further vascularity as evidenced by telangiectasia formation. These findings are consistent with what has been demonstrated using videocapillaroscopy, discussed earlier.[14] Despite the presence of these fixed changes in facial vasculature, the blood vessels retain their ability to respond to vasoactive stimuli, making them a therapeutic target for vasoactive agents.[2] Table 2 delineates the intermittent clinical features and the fixed clinical features characteristic of the common presentations of rosacea.

In Part 2 of this article, emphasis will be placed on the common denominator present in most cases of cutaneous rosacea—diffuse facial erythema—which is typically diffuse, persistent, central facial in predominance, and is distinct from perilesional erythema. This will be followed by an overview of cutaneous vasculature and adrenoreceptors and a discussion of available medical therapies and treatment selection, including emerging topical options for diffuse facial erythema.

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