Pathogenesis of Rosacea

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Rosacea is a chronic, common skin disorder whose pathogenesis is incompletely understood. An interplay of multiple factors, including genetic predisposition and environmental, neurogenic, and microbial factors, may be involved in the disease process. Rosacea subtypes, identified in the recently published standard classification system by the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea, may in fact represent different disease processes, and identifying subtypes may allow investigators to pursue more precisely focused studies. New developments in molecular biology and genetics hold promise for elucidating the interplay of the multiple factors involved in the pathogenesis of rosacea, as well as providing the bases for potential new therapies.

Rosacea is a common, chronic skin disorder primarily affecting the central and convex areas of the face. The nose, cheeks, chin, forehead, and glabella are the most frequently affected sites. Less commonly affected sites include the infraorbital, submental, and retroauricular areas, the V-shaped area of the chest, and the neck, the back, and the scalp.

The disease has a variety of clinical manifestations, including flushing, persistent erythema, telangiectasias, papules, pustules, and tissue and sebaceous gland hyperplasia. Diagnosis of rosacea is based on clinically recognizable morphologic characteristics. However, establishing precise, comprehensive diagnostic criteria is difficult given the variety of clinical manifestations and the lack of laboratory testing.

The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea defines and classifies rosacea into the following clinical subtypes based primarily on morphologic characteristics: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea, and ocular rosacea.

The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea identifies primary and secondary features needed for the clinical diagnosis of rosacea. Primary features include flushing (transient erythema), persistent erythema, papules and pustules, and telangiectasias. Secondary features include burning and stinging, skin dryness, plaque formation, dry appearance, edema, ocular symptoms, extrafacial manifestations, and phymatous changes. One or more of the primary features is needed for diagnosis.[1]

Several authors have theorized that rosacea progresses from one stage to another.[2-4] However, recent data, including data on therapeutic modalities of various subtypes, do not support this notion.[5] A possible exception is PPR, which may progress to the phymatous form. The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea does not qualify the rosacea subtypes as a spectrum from ETR to phymatous. Rosacea subtype designation is of pivotal importance because the therapeutic implications are different for various subtypes, and individual subtypes may in fact represent pathologically distinct disease processes.

To confirm diagnosis of rosacea, several diseases with similar cutaneous manifestations must be excluded. These include polycythemia vera, connective tissue diseases (lupus erythematosus, dermatomyositis, and mixed connective tissue disease), carcinoid syndrome, mastocytosis, photosensitivity, and allergic or irritant contact dermatitis.[6]

The pathogenesis of rosacea is complex and a subject of literature controversy. One hindering factor is that much of the data on rosacea were acquired before the National Rosacea Society Expert Committee on the Classification

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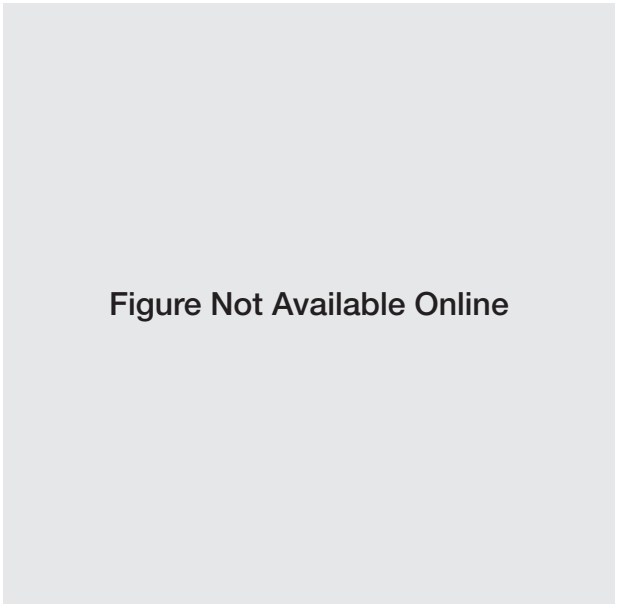

Figure 1. Patient with erythematotelangiectatic rosacea displaying persistent erythema and telangiectasias. Photograph courtesy of the National Rosacea Society.

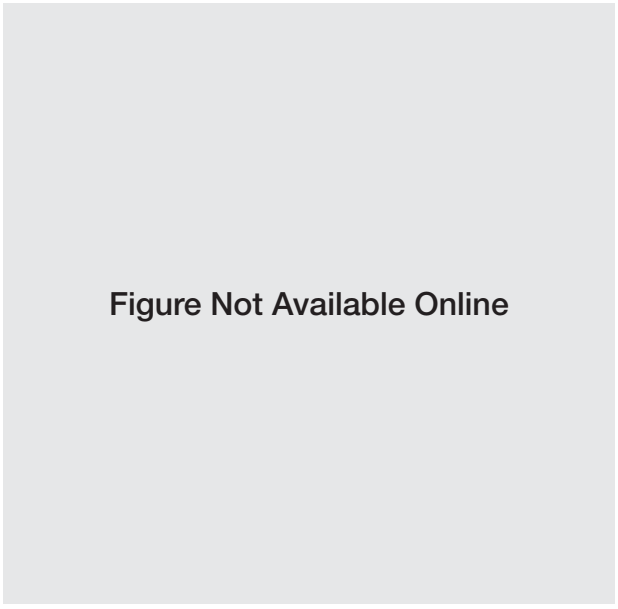

Figure 2. Patient with papulopustular rosacea displaying persistent central erythema with inflammatory papules and pustules in a centrofacial distribution. Photograph courtesy of the National Rosacea Society.

and Staging of Rosacea established strict diagnostic criteria. Moreover, various clinical subtypes of rosacea that may or may not represent the same clinicopathologic process were studied simultaneously, possibly masking true insights into rosacea.

ROSACEA SUBTYPES

Erythematotelangiectatic Rosacea

The predominant sign of ETR is centrofacial flushing lasting more than 10 minutes, accompanied by a burning or stinging sensation with or without persistent erythema (Figure 1). The erythema usually spares the periocular and submental skin but may involve the ears, neck, or upper part of the chest. Typically, patients with ETR will possess skin with a fine texture without oiliness or the prominence of sebaceous glands. The erythematous areas of the face may appear rough with scales likely from chronic, low-grade inflammation. Telangiectasias are common but not essential for diagnosis.[6]

Papulopustular Rosacea

PPR is characterized by persistent central erythema with inflammatory papules or pustules in a centrofacial distribution (Figure 2). This subtype may involve perioral and perinasal areas. Prolonged periods of facial erythema or flushing may lead to soft tissue edema lasting up to several days. Reports of patients developing solid, hard, nonpitting edema of the forehead, glabella, upper eyelids, nose, and cheeks (Morbihan disease) have been described in the literature. A history of flushing may also be reported. Telangiectasias may be present but difficult to distinguish from the erythematous background. Irritation from external stimuli is not a constant feature; thus, scaling and roughness are often absent.

Phymatous Rosacea

Phymatous rosacea is characterized by marked skin thickening and edema with irregular surface nodularities of the nose, chin, forehead, ears, or eyelids (Figure 3). The skin surface is often pitted with prominent sebaceous glands and enlarged follicular openings. The clinical changes result from extensive chronic inflammatory infiltration, connective tissue hypertrophy with fibrosis, and marked sebaceous gland hyperplasia.[7]

Four distinct histologic variants may occur with rhinophyma (nasal phymatous rosacea): glandular, fibrous, fibroangiomatous, and actinic. In addition to the nose, other commonly affected areas include the chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyelids (blepharophyma).

Ocular Rosacea

The prevalence of ocular rosacea is the subject of debate, with incidence rates of 3% to 58% reported in the literature.[8] Ocular manifestations may precede the cutaneous signs of rosacea in approximately 20% of patients or they may develop concurrently with skin manifestations.[9]

Ocular manifestations include blepharitis, conjunctivitis, inflammation of the eyelids and meibomian glands,

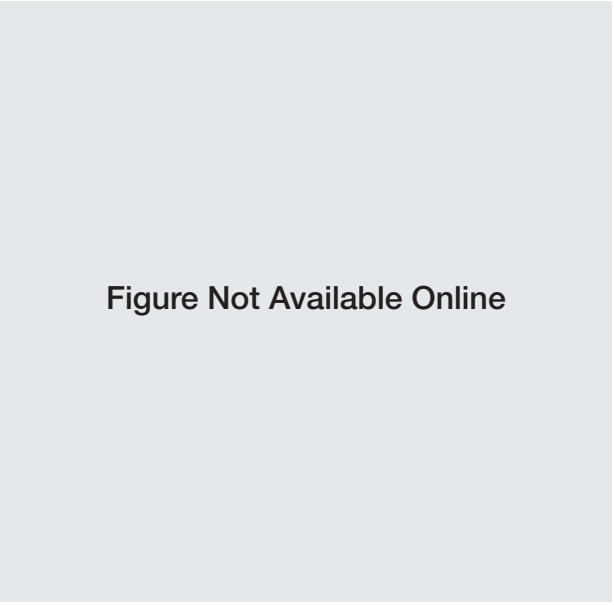

Figure 3. Patient with phymatous rosacea displaying marked skin thickening and edema with irregular surface nodularities of the nose (rhinophyma). Photograph courtesy of the National Rosacea Society.

Figure 4. Patient with ocular rosacea displaying eyelid and conjunctival involvement. Photograph courtesy of the National Rosacea Society.

interpalpebral conjunctival hyperemia, corneal infiltrates, ulcers, and vascularization (Figure 4).[9,10] In one series, conjunctival telangiectasias and irregularity of eyelid margins were noted in 81% of patients with ocular rosacea.[11] Meibomian gland dysfunction occurs in 78% of patients with ocular rosacea, leading first to decreased lipid secretion and then to inflammation and foreign body sensation.[11] Patients with rosacea frequently describe eye stinging or burning, dryness, irritation from light, or foreign body sensation. A potentially vision-threatening complication of ocular rosacea is *Staphylococcus aureus* keratitis that may lead to corneal opacity, scarring, and vision loss.[12]

Ocular rosacea frequently occurs in association with other rosacea subtypes, although there is no direct correlation between the severity of ocular and facial rosacea.[13]

EPIDEMIOLOGY OF ROSACEA

Rosacea is a common skin condition affecting approximately 14 million Americans. Rosacea is most common in fair-skinned individuals, especially those of northern and eastern European ancestry, and within certain ethnic groups, such as Celts.[14]

Most patients affected by rosacea are 30 to 60 years of age.[8] Nonetheless, the disorder is occasionally seen in younger adults, although rarely in the pediatric population.

Women are more often affected than men, but generally experience a less severe disease course. Men progress to the advanced stages with tissue and sebaceous gland hyperplasia and rhinophyma more often than women.[12,15]

Recent data from a large epidemiologic study of the Irish population, conducted with strict diagnostic criteria and using precise clinical definitions, showed no significant difference in the prevalence of PPR between males and females and no significant association between rosacea and UVR exposure and cutaneous solar damage.[16] The study also revealed no correlation between family history of PPR and later development of PPR.

PATHOGENESIS OF ROSACEA

Despite decades of study, the etiology of rosacea remains unknown. The pathogenesis of rosacea is likely to be multifactorial, resulting from the interplay of genetic and environmental factors.

GENETIC CONTRIBUTION TO ROSACEA

There is a strong genetic predisposition to flushing, the earliest cutaneous manifestation of facial rosacea. Facial rosacea typically occurs in fair-skinned individuals. Facial rosacea is less common in dark-skinned individuals, who are also less susceptible to flushing or actinic damage.

Yazici et al[17] demonstrated a significant association between the glutathione S-transferases (GSTs) *GSTT1* and *GSTM1* null genotypes and rosacea. GSTs act as a cellular defense mechanism against free reactive oxygen species (ROS). Increased ROS activity or decreased antioxidant potential, possibly induced by GST gene polymorphism, may play a pathogenic role in rosacea.

PATHOPHYSIOLOGY OF ROSACEA

Several factors, including vasculature, weather and climate, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities, and microbes, likely play a role in rosacea development. Furthermore, the distinct subtype of rosacea may be determined by a patient's unique sensitivity to various triggers.

ENVIRONMENTAL FACTORS

Various environmental factors have been shown to trigger flushing in susceptible individuals (Table). Extreme temperatures or exposure to UV radiation (UVR) or high winds may initiate a flushing episode. Consuming spicy foods, hot foods or drinks, or alcoholic beverages, as well as experiencing emotional stress, may also trigger flushing. Although not pathogenic, chronic exposure to any of these triggers may lead to the permanent vasodilation typical of ETR rosacea or the inflammatory lesions of PPR.

UVR AND ROSACEA

A clinical correlation between UVR exposure and rosacea has been widely endorsed in dermatologic literature. The pivotal role of UVR is supported by the distribution of erythema and telangiectasias on the convexities of the facial skin. Supraorbital, infraorbital, submental, and other sun-protected areas are typically spared. Rosacea may also be triggered by acute UVR exposure or sunburn. Furthermore, UVR exposure may precipitate acute episodes of flushing in patients with ETR.[3,18,19]

Nonetheless, studies on acute UVR-related rosacea have not shown increased skin sensitivity or worsening of rosacea. Moreover, Marks[18] and Nunzi et al[20] independently showed that only 17% and 31% of patients with rosacea report aggravation of their symptoms after direct UVR exposure. The aforementioned large epidemiologic study of the Irish population showed no significant association between PPR and UVR exposure or cutaneous solar damage.[16]

The detrimental effects of UVR exposure involve both cutaneous blood vessels and dermal connective tissue.[1,21,22]

Marks and Harcourt-Webster[22] studied the extent of actinic damage and solar elastosis in 39 patients with rosacea and 39 control subjects. The authors noted a marked increase in the incidence of solar elastosis and more severe elastosis in patients with rosacea compared with the control group. The authors hypothesized that the loss of upper dermal connective tissue leads to vascular and lymphatic dilatation with clinically visible telangiectasias and tissue edema.

Neumann and Frithz[23] postulated that UVR exposure directly leads to the development of erythema and telangiectasias by stimulating de novo angiogenesis via a transforming growth factor (TGF) β–mediated pathway.

It is likely that the combination of mechanical factors and angiogenic chemokines results in clinically visible telangiectasias.

Both UVA and UVB radiation disrupt the extracellular matrix. Dermal changes in the deep reticular dermis suggest that UVA radiation plays a key role, since only a small percentage of UVB penetrates into the superficial papillary dermis.[24,25]

The mechanism of UVR-mediated dermal damage includes decreased procollagen I and III synthesis and increased collagen degradation by activator protein A.

Potential Rosacea Triggers

Climate and weather
Extreme temperatures: hot or cold
UV radiation
Humidity
High winds
Emotional influences
Stress
Anxiety
Anger
Temperature-related activities
Hot baths
Physical exertion
Beverages
Alcohol
Hot beverages
Foods
Hot foods
Spicy foods
Dairy products
Chocolate
Soy sauce, vinegar
Fruits (eg, avocados, bananas, raisins, figs, citrus, red plums)
Medications
Topical fluorinated corticosteroids
Vasodilators (eg, nicotinic acid)
Angiotensin-converting enzyme inhibitors, calcium channel blockers
Statins
Topical agents (eg, cosmetics, astringents) containing alcohol, witch hazel extract, acetone, or fragrance

Activator protein A induces matrix metalloproteinases, infiltration of inflammatory cells (predominately neutrophils) into the dermis, and release of ROS from neutrophils.

VASCULAR DYSFUNCTION AND ROSACEA

Numerous studies have implicated inherent abnormalities of the cutaneous vascular homeostasis in the pathogenesis of rosacea.

Transient erythema, or flushing of rosacea, is mediated by both neuronal and humoral factors.[3] Studies have shown that the cutaneous vessels of patients with rosacea exhibit adequate response to both local and systemic vasoactive mediators.[4,26,27] Wilkin[28] demonstrated a proportional increase in cutaneous blood flow in both the forearm and the face after neural (oral thermal challenge) and humoral (nicotinic acid) activation. Differential clinical response to local and systemic vasoactive mediators of the face may be explained by increased facial blood flow at baseline, increased red blood cell capacitance of facial vasculature (eg, larger, more tortuous vessels), and location of the facial vessels closer to the skin surface.

Several lines of evidence support the role of pathogenic vasodilation in the development of rosacea. First, vasodilators used for treating cardiac disease and hypertension have been linked to rosacea outbreaks. Second, Berg and Liden[8] showed increased prevalence of migraine headaches in the rosacea group compared with an age- and sex-matched cohort of 27% versus 13%, respectively. Third, patients with conditions associated with paroxysmal cutaneous flushing, such as carcinoid syndrome or mastocytosis, may develop rapidly progressive rosacea. Fourth, hormonal imbalance may lead to vasomotor instability and subsequent intense flushing episodes comparable with those seen in patients with early rosacea. Perimenstrual aggravations of rosacea are frequently noted in young women.[29,30]

Studies suggest that dysregulation of thermal mechanisms may play a role in the vasodilation seen in rosacea.[31,32] When challenged with thermal stimuli, patients with rosacea flush more easily and in a more pronounced fashion than control subjects.[26,27,32] Normally, countercurrent heat exchange occurs between the internal jugular vein and the carotid artery. The increased carotid artery temperature and subsequent increased cranial blood flow are sensed by the hypothalamus, which then causes vasodilation (flushing reaction) to dissipate unnecessary heat. In patients with rosacea, venous blood flow from the face to the brain is decreased, suggesting an abnormal carotid hypothalamic cooling response.[32]

Many small neuropeptides and neurotransmitters, such as substance P, vasoactive intestinal peptide, gastrin, serotonin, histamine, and prostaglandins, have been implicated in the vasodilation seen in rosacea. However, comprehensive studies of these mediators are still pending.[6,33] Our group demonstrated that the adenosine triphosphate (ATP) analog, ATP-γS, enhanced the production of inflammatory mediators such as interleukin 6, interleukin 8, monocyte chemoattractant protein 1, and growth-related oncogene-α in a human dermal endothelial cell line. The ATP-γS–mediated mechanism occurs via purinergic receptor signaling. The study supports the notion that purinergic nucleotides may mediate acute physiologic and possibly pathophysiologic inflammation in the skin.[34] As ATP is a sympathetic cotransmitter, release of ATP by sympathetic nerves when activated by stress may play a role in stress-induced flares of rosacea.

MICROBIAL FACTORS

Cathelicidin Antimicrobial Peptides

Cathelicidins are widely expressed innate immunity-response proteins that have been shown to protect against bacteria and some viruses.[35-37]

In addition to directly mediating antimicrobial activity, cathelicidins may trigger immune host tissue response. They may promote leukocyte chemotaxis, angiogenesis, and expression of components of the extracellular matrix.[38]

Patients with rosacea express higher levels of cathelicidin peptides in the affected facial skin compared with similar anatomic regions of unaffected control subjects. Moreover, a posttranscriptionally modified, proteolytically processed cathelicidin proprotein, an 18-kDa cationic antimicrobial protein, in rosacea is different from that of control subjects. The 37–amino acid peptide LL-37 is a main cathelicidin peptide identified in rosacea patients. It is significantly less abundant in skin not affected by rosacea.

Abnormal cathelicidin processing is associated with increased epidermal stratum granulosum and stratum corneum tryptic enzyme (SCTE), a serine protease of the kallikrein family.

In mouse models, injection of cathelicidins equivalent to those found in the facial skin of patients with rosacea (eg, LL-37 and others), the addition of SCTE, and the increased protease activity by targeted deletion of the serine protease inhibitor gene *Spink5* have been shown to independently increase skin inflammation.[39]

The role of cathelicidins as SCTE-inflammation mediators was further verified in mice with targeted deletion of *Camp*, the gene encoding cathelicidins. After application of irritant contactant, *Camp*–/– mice showed considerably less inflammation than wild-type control subjects.[39]

In a recent small pilot study of 10 patients with rosacea treated with either intense pulsed light (IPL) or a pulsed dye laser (PDL), 5 of the patients (3 following IPL treatment and 2 following PDL treatment) had lower levels of cathelicidin.[40] Although the results did not reach statistical significance, the study raised an interesting mechanism of clinical improvement of rosacea symptoms after IPL or PDL treatment.[40]

Helicobacter pylori Infection

The role of *Helicobacter pylori* infection in the pathogenesis of rosacea is controversial. The worldwide prevalence of *H pylori* infection is up to 50%.[41,42] The infection is usually acquired in childhood and early adulthood. Patients with rosacea are reported to have increased levels of anti–*H pylori* antibodies.[41,43] Several studies reported an association between the eradication of *H pylori* infection and the clinical improvement of rosacea symptoms,[44,45] although other studies failed to support *H pylori* as a causative factor.

A recent study using gastroscopic biopsy found the prevalence of *H pylori* infection to be the same in 50 patients with rosacea and 39 control subjects.[46] A double-blind, placebo-controlled study showed that treating and eradicating *H pylori* in patients with both *H pylori* infection and rosacea did not result in clinical improvement of facial rosacea.

Demodex Mites

The role of the hair follicle mites *Demodex folliculorum* and *Demodex brevis* in rosacea has remained a controversial topic in worldwide dermatology literature for over 60 years.[6,47-49] Infestation of humans with *Demodex* mites increases with age and reaches 100% in healthy, older adults.[48] Several studies using various sampling methods (adhesive bands, skin scrapings, comedone extractions, skin impressions, and skin biopsies) showed increased prevalence and number of organisms in patients with rosacea. Using standardized skin surface biopsy, a markedly higher density of *D folliculorum* mites has been found in patients with rosacea than in age-matched control subjects.[50]

Bonnar et al[51] showed significantly higher *Demodex* mite counts in patients with rosacea compared with a control group. However, the study showed no association between clinical improvements of rosacea after one month of tetracycline therapy and decreased *Demodex* mite counts.

In a study of 92 patients with pustular rosacea, Georgala et al[52] found *D folliculorum* mites in 90.2% of the patients with rosacea and only 11.9% of the age-matched control subjects. In addition, a significant correlation between the presence of *D folliculorum* mites and perifollicular inflammation was found in 75% of the patients with rosacea.

Several studies demonstrated *Demodex* mite–directed immune responses in patients with rosacea.[20,53] Grosshans et al[54] reported *Demodex*-species–specific antibodies in the serum of 7 of 31 patients with rosacea. Rufli and Büchner[47] detected predominately helper $CD4^+$ T cell infiltrate in the dermal granulomatous infiltrates surrounding *Demodex* mite parts. Forton[55] demonstrated a statistically significant relationship between the presence of *Demodex* mites and perifollicular, lymphohistiocytic inflammation in 69 biopsy specimens from patients with rosacea.

It should be noted, however, that other studies have failed to establish a relationship between *Demodex* mite infestation and rosacea.[20,54] Ramelet and Perroulaz[56] studied 53 patients with granulomatous rosacea and found *Demodex* mites to be present in only 9 biopsy specimens.

Whether *Demodex* mites play a direct role in the pathogenesis of rosacea is yet to be verified. It is possible that an increased density of the mites may be a consequence rather than a cause of rosacea. It is also possible that the density of the mites or their extrafollicular location rather than simple presence may be of greater importance in assessing pathogenesis.[50,51,57] *Demodex* mites may trigger a delayed hypersensitivity reaction, contributing to the formation of papules and pustules. Mite infestation into the deeper dermis may lead to granulomatous host response.[58]

A complicating factor in assessing the role of *Demodex* mites is that their role in pathogenesis may vary in different rosacea subtypes.

Using sensitive cyanoacrylate surface biopsies, Forton and Seys[50] and Erbağci and Ozgöztasi[59] independently showed that the density of *Demodex* mites was significantly higher in patients with PPR compared with the age-matched control subjects. However, both studies failed to demonstrate statistically significantly increased mite counts in patients with ETR.

Rosacea treatment with oral tetracycline[51] and topical 3% sulfur ointment[60] led to marked clinical improvement of rosacea without affecting *Demodex* mite prevalence. Some authors have postulated that benefits seen with metronidazole treatment may be related to its anti-*Demodex* activity.[61,62] *Demodex* mites, however, have been shown to survive in vitro in high metronidazole concentrations.[63]

Clinical overlap between rosacea and rosacealike demodicidosis seen in patients with AIDS again supports the role of *Demodex* mites.[57,64,65] Recent studies point to the development of rosacealike demodicidosis after treatment of facial dermatitis with topical calcineurin inhibitors.[66,67]

One can hypothesize that calcineurin inhibitor–mediated downregulation of T cells may lead to the proliferation of *Demodex* mites from the inhibition of local immune and inflammatory processes. This hypothesis, however, still needs to be tested.

Reactive Oxygen Species

Compared with other organs, skin is especially susceptible to ROS-induced damage because of constant exposure to environmental oxygen and UVR.

ROS have been implicated in dermatosis, physiologic aging, UV-induced immunosuppression, and photoaging. Patients with rosacea possess skin with increased levels of ROS as compared with healthy control subjects.

Oztas et al[68] found lower amounts of superoxide dismutase, an enzyme involved in the oxygen radical–quenching enzyme, and higher levels of lipid peroxidation products in patients with PPR compared with healthy control subjects.

In addition to environmental sources, free ROS are generated as part of the neutrophil-mediated inflammatory process seen in rosacea.

Although the exact role of free ROS in the pathogenesis of rosacea remains unclear, several hypotheses exist. First, the ROS generated by intrafollicular neutrophils may directly damage facial follicles in patients with rosacea. Second, UVR-induced ROS may activate matrix metalloproteinases, leading to dermal collagen breakdown by inhibiting matrix metalloproteinases and inducing activator protein A. Third, free ROS–induced actinic damage may contribute to rosacea symptoms via degradation of vascular and perivascular collagen and elastic tissue and weakening the mechanical integrity of blood vessels.[3]

NEUROGENIC MECHANISMS OF ROSACEA

In a recent study, Guzman-Sanchez et al[69] studied the heat pain threshold and skin blood flow of patients with rosacea using quantitative thermal sensory testing and laser Doppler imaging.

The authors noted that patients with either ETR or PPR had lower heat pain thresholds in rosacea-affected skin areas compared with unaffected areas. The mean heat pain threshold of ETR and PPR was lower than in healthy control subjects, although it did not reach statistical significance in the ETR group. Clinical severity of the disease and heat pain threshold showed a positive correlation in the ETR group but not in the PPR group.

In both groups, mean blood flow from the rosacea-affected areas was higher than in nonaffected areas. The value did not reach statistical significance in the ETR group.

No difference in skin temperature between the groups was noted. Overall, 15 of 16 patients reported a burning sensation, with the sensation markedly increased in the ETR group.

The authors concluded that abnormal quantitative thermal testing in rosacea-affected skin suggested the involvement of small nerve fibers and possible neurogenic inflammation.

In support of this hypothesis, Lonne-Rahm et al[70] showed that laser treatment decreased facial skin sensitivity in patients with rosacea. The possible mechanism of action was laser-induced reduction of protein gene product 9.5–positive fibers in the epidermis and papillary dermis, as well as reduction of protein P in the papillary dermis.

Minson et al[71] postulated that 2 independent mechanisms may contribute to the rise in cutaneous blood flow during local heating in patients with rosacea: a fast-responding vasodilator system mediated by an axon reflux and a slow-responding vasodilator system via local production of nitric oxide.

Also, ATP release from sympathetic nerve terminals may play a role in stress-related exacerbation of rosacea symptoms.[34]

ROSACEA AS AN INFLAMMATORY DISORDER

Inflammatory lesions (papules and pustules) are the characteristic finding of the inflammatory phase of PPR. Clinically, these lesions are almost always follicular in origin, affecting both sebaceous and hair follicles. Inflammatory lesions of rosacea are sterile and not associated with the bacterial disease of pilosebaceous units.

Marks and Harcourt-Webster[22] found pilosebaceous unit abnormalities on histologic analysis in approximately 20% of patients with early stages of rosacea. However, later stages of rosacea, such as rhinophyma, have clinically evident pilosebaceous apparatus dysfunction with markedly dilated pores and sebaceous hyperplasia. Perifollicular inflammation and decreased pilosebaceous units are seen histologically in severe rhinophyma.

SUMMARY

The precise mechanism of the pathogenesis of rosacea remains to be elucidated. It is likely that interplay of multiple factors, including genetic predisposition and environmental, neurogenic, and microbial factors, is central to the disease process. It is possible that distinct rosacea subtypes may in fact represent various disease processes with different etiologies. The recent development of strict diagnostic and classification guidelines by the National Rosacea Society Expert Committee on the Classification

and Staging of Rosacea allows more precise, focused investigations and clinical trials.

New and exciting developments from the fields of molecular biology and genetics not only elucidate the complexity of rosacea pathogenesis, but also open the way to new therapeutic interventions.

REFERENCES

1. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
2. Plewig G, Jansen T, Kligman AM. Pyoderma faciale: a review and report of 20 additional cases: is it rosacea? *Arch Dermatol*. 1992;128:1611-1617.
3. Wilkin JK. Rosacea: pathophysiology and treatment. *Arch Dermatol*. 1994;130:359-362.
4. Rebora A. Rosacea. *J Invest Dermatol*. 1987;88(suppl 3):56S-60S.
5. Dahl MV. Pathogenesis of rosacea. *Adv Dermatol*. 2001;17: 29-45.
6. Crawford GH, Pelle MT, James WD. Rosacea: I. etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol*. 2004;51: 327-341.
7. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med*. 1997;90:144-150.
8. Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol*. 1989;69:419-423.
9. Borrie P. Rosacea with special reference to its ocular manifestations. *Br J Dermatol*. 1953;65:458-463.
10. Quarterman MJ, Johnson DW, Abele DC, et al. Ocular rosacea: signs, symptoms, and tear studies before and after treatment with doxycycline. *Arch Dermatol*. 1997;133:49-54.
11. Akpek EK, Merchant A, Pinar V, et al. Ocular rosacea: patient characteristics and follow-up. *Ophthalmology.* 1997;104:1863-1867.
12. Valanconny C, Michel JL, Gain P, et al. Ocular rosacea [in French]. *Ann Dermatol Venereol*. 1999;126:450-454.
13. Starr PA. Oculocutaneous aspects of rosacea. *Proc R Soc Med*. 1969;62:9-11.
14. Bamford JT. Rosacea: current thoughts on origin. *Semin Cutan Med Surg*. 2001;20:199-206.
15. Zug KA, Palay DA, Rock B. Dermatologic diagnosis and treatment of itchy red eyelids. *Surv Ophthalmol*. 1996;40:293-306.
16. Jancin B. UV exposure and gender unrelated to rosacea risk: new findings go against common beliefs. *Skin & Allergy News*. 2007;38(10):1,8.
17. Yazici AC, Tamer L, Ikizoglu G, et al. GSTM1 and GSTT1 null genotypes as possible heritable factors of rosacea. *Photodermatol Photoimmunol Photomed*. 2006;22:208-210.
18. Marks R. Concepts in the pathogenesis of rosacea. *Br J Dermatol*. 1968;80:170-177.
19. Rebora A. The red face: rosacea. *Clin Dermatol*. 1993;11:225-234.
20. Nunzi E, Rebora A, Hamerlinck F, et al. Immunopathological studies on rosacea. *Br J Dermatol*. 1980;103:543-551.
21. Sibenge S, Gawkrodger DJ. Rosacea: a study of clinical patterns, blood flow, and the role of *Demodex folliculorum*. *J Am Acad Dermatol*. 1992;26:590-593.
22. Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol*. 1969;100:683-691.
23. Neumann E, Frithz A. Capillaropathy and capillaroneogenesis in the pathogenesis of rosacea. *Int J Dermatol*. 1998;37:263-266.
24. Lim HH, Buttery JE. Determination of ethanol in serum by an enzymatic PMS-INT colorimetric method. *Clin Chim Acta*. 1977;75:9-12.
25. Talwar HS, Griffiths CE, Fisher GJ, et al. Reduced type I and type III procollagens in photodamaged adult human skin. *J Invest Dermatol*. 1995;105:285-290.
26. Borrie P. The state of the blood vessels of the face in rosacea. II. *Br J Dermatol*. 1955;67:73-75.
27. Borrie P. The state of the blood vessels of the face in rosacea. I. *Br J Dermatol*. 1955;67:5-8.
28. Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution? *J Am Acad Dermatol*. 1988;19(2 pt 1):309-313.
29. Lewis VJ, Holme SA, Wright A, et al. Rosacea fulminans in pregnancy. *Br J Dermatol*. 2004;151:917-919.
30. Wilkin JK. Effect of subdepressor clonidine on flushing reactions in rosacea: change in malar thermal circulation index during provoked flushing reactions. *Arch Dermatol*. 1983;119:211-214.
31. Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol*. 1981;76:15-18.
32. Brinnel H, Friedel J, Caputa M, et al. Rosacea: disturbed defense against brain overheating. *Arch Dermatol Res*. 1989;281:66-72.
33. Powell FC, Corbally N, Powell D. Substance P and rosacea. *J Am Acad Dermatol*. 1993;28:132-133.
34. Seiffert K, Ding W, Wagner JA, et al. ATPgammaS enhances the production of inflammatory mediators by a human dermal endothelial cell line via purinergic receptor signaling. *J Invest Dermatol*. 2006;126:1017-1027.
35. Chen X, Niyonsaba F, Ushio H, et al. Synergistic effect of antibacterial agents human beta-defensins, cathelicidin LL-37 and lysozyme against *Staphylococcus aureus* and *Escherichia coli*. *J Dermatol Sci*. 2005;40:123-132.
36. Niyonsaba F, Nagaoka I, Ogawa H. Human defensins and cathelicidins in the skin: beyond direct antimicrobial properties. *Crit Rev Immunol*. 2006;26:545-576.
37. Niyonsaba F, Ogawa H. Protective roles of the skin against infection: implication of naturally occurring human antimicrobial agents beta-defensins, cathelicidin LL-37 and lysozyme. *J Dermatol Sci*. 2005;40:157-168.
38. Barak O, Treat JR, James WD. Antimicrobial peptides: effectors of innate immunity in the skin. *Adv Dermatol*. 2005;21:357-374.
39. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med*. 2007;13:975-980.
40. Jay H. Rosacea: molecular insights. *Skin and Aging*. 2007;15(9): 14-15.
41. Gürer MA, Erel A, Erbaş D, et al. The seroprevalence of *Helicobacter pylori* and nitric oxide in acne rosacea. *Int J Dermatol*. 2002;41: 768-770.
42. Gürakan F, Kocak N, Yüce A. *Helicobacter pylori* serology in childhood. *Turk J Pediatr*. 1996;38:329-334.
43. Sharma VK, Lynn A, Kaminski M, et al. A study of the prevalence of *Helicobacter pylori* infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am J Gastroenterol*. 1998;93:220-222.
44. Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol*. 1994;89:1603-1604.
45. Utaş S, Ozbakir O, Turasan A, et al. *Helicobacter pylori* eradication treatment reduces the severity of rosacea. *J Am Acad Dermatol*. 1999;40:433-435.
46. Bamford JT, Tilden RL, Blankush JL, et al. Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol*. 1999;135: 659-663.
47. Rufli T, Büchner SA. T-cell subsets in acne rosacea lesions and the possible role of *Demodex folliculorum*. *Dermatologica*. 1984;169: 1-5.
48. Rufli T, Mumcuoglu Y. The hair follicle mites *Demodex folliculorum* and *Demodex brevis*: biology and medical importance: a review. *Dermatologica*. 1981;162:1-11.

49. Rufli T, Mumcuoglu Y, Cajacob A, et al. *Demodex folliculorum*: aetiopathogenesis and therapy of rosacea and perioral dermatitis [in German]. *Dermatologica*. 1981;162:12-26.
50. Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using standardized skin-surface biopsy. *Br J Dermatol*. 1993;128:650-659.
51. Bonnar E, Eustace P, Powell FC. The *Demodex* mite population in rosacea. *J Am Acad Dermatol*. 1993;28:443-448.
52. Georgala S, Katoulis AC, Kylafis GD, et al. Increased density of *Demodex folliculorum* and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. *J Eur Acad Dermatol Venereol*. 2001;15:441-444.
53. Marks R. Histogenesis of the inflammatory component of rosacea. *Proc R Soc Med*. 1973;66:742-745.
54. Grosshans E, Dungler T, Kien TT, et al. *Demodex folliculorum* and rosacea: experimental and immunological studies [in German]. *Z Hautkr*. 1980;55:1211-1218.
55. Forton F. *Demodex* and perifollicular inflammation in man: review and report of 69 biopsies [in French]. *Ann Dermatol Venereol*. 1986;113:1047-1058.
56. Ramelet AA, Perroulaz G. Rosacea: histopathologic study of 75 cases [in French]. *Ann Dermatol Venereol*. 1988;115:801-806.
57. Ayres S Jr, Ayres S III. Demodectic eruptions (demodicidosis) in the human: 30 years' experience with 2 commonly unrecognized entities: pityriasis folliculorum (*Demodex*) and acne rosacea (*Demodex* type). *Arch Dermatol*. 1961;83:816-827.
58. Amichai B, Grunwald MH, Avinoach I, et al. Granulomatous rosacea associated with *Demodex folliculorum*. *Int J Dermatol*. 1992;31:718-719.
59. Erbağci Z, Ozgöztasi O. The significance of *Demodex folliculorum* density in rosacea. *Int J Dermatol*. 1998;37:421-425.
60. Robinson TW. *Demodex folliculorum* and rosacea: a clinical and histological study. *Arch Dermatol*. 1965;92:542-544.
61. Aronson IK, Rumsfield JA, West DP, et al. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm*. 1987;21:346-351.
62. Lowe NJ, Henderson T, Millikan LE, et al. Topical metronidazole for severe and recalcitrant rosacea: a prospective open trial. *Cutis*. 1989;43:283-286.
63. Persi A, Rebora A. Metronidazole and *Demodex folliculorum*. *Acta Derm Venereol*. 1981;61:182-183.
64. Buechner SA. Rosacea: an update. *Dermatology*. 2005;210:100-108.
65. Baima B, Sticherling M. Demodicidosis revisited. *Acta Derm Venereol*. 2002;82:3-6.
66. Lübbe J, Stucky L, Saurat JH. Rosaceiform dermatitis with follicular *Demodex* after treatment of facial atopic dermatitis with 1% pimecrolimus cream. *Dermatology*. 2003;207:204-205.
67. Bernard LA, Cunningham BB, Al-Suwaidan S, et al. A rosacea-like granulomatous eruption in a patient using tacrolimus ointment for atopic dermatitis. *Arch Dermatol*. 2003;139:229-231.
68. Oztas MO, Balk M, Ogüs E, et al. The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin Exp Dermatol*. 2003;28:188-192.
69. Guzman-Sanchez DA, Ishiuji Y, Patel T, et al. Enhanced skin blood flow and sensitivity to noxious heat stimuli in papulopustular rosacea. *J Am Acad Dermatol*. 2007;57:800-805.
70. Lonne-Rahm S, Nordlind K, Edström DW, et al. Laser treatment of rosacea: a pathoetiological study. *Arch Dermatol*. 2004;140:1345-1349.
71. Minson CT, Berry LT, Joyner MJ. Nitric oxide and neurally mediated regulation of skin blood flow during local heating. *J Appl Physiol*. 2001;91:1619-1626.