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Clinical, Cellular, and Molecular Aspects in the Pathophysiology of Rosacea

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Abstract

Rosacea is a chronic inflammatory skin disease of unknown etiology. Although described centuries ago, the pathophysiology of this disease is still poorly understood. Epidemiological studies indicate a genetic component, but a rosacea gene has not been identified yet. Four subtypes and several variants of rosacea have been described. It is still unclear whether these subtypes represent a “developmental march” of different stages or are merely part of a syndrome that develops independently but overlaps clinically. Clinical and histopathological characteristics of rosacea make it a fascinating “human disease model” for learning about the connection between the cutaneous vascular, nervous, and immune systems. Innate immune mechanisms and dysregulation of the neurovascular system are involved in rosacea initiation and perpetuation, although the complex network of primary induction and secondary reaction of neuroimmune communication is still unclear. Later, rosacea may result in fibrotic facial changes, suggesting a strong connection between chronic inflammatory processes and skin fibrosis development. This review highlights recent molecular (gene array) and cellular findings and aims to integrate the different body defense mechanisms into a modern concept of rosacea pathophysiology.

CLASSIFICATION AND EPIDEMIOLOGY OF ROSACEA

Rosacea is a common, almost exclusively facial inflammatory skin disease characterized by erythema and telangiectasia (erythematotelangiectatic rosacea, ETR, subtype I, RI), papulopustular rosacea (PPR, subtype II, RII), and phymatous rosacea (PhR, subtype III, RIII; Figure 1a). Ocular structures may also be involved (ocular rosacea, subtype IV). Several additional variants have been described (Wilkin *et al*., 2002, 2004), although their subdivision into the entity rosacea is not yet clear. Rosacea prevalence is highest (between 2.7 and 10%) in patients of northern European or Celtic heritage (Webster, 2009; Abram *et al*., 2010b; McAleer *et al*., 2010). Humans with fair skin (Fitzpatrick skin phenotypes I–II) are more likely to be affected, whereas Asians and African Americans are less affected, indicating a genetic component (Abram *et al*., 2010a). This is also supported by the finding

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CONFLICT OF INTEREST

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that often African Americans are affected when one parent is of northern European origin (Steinhoff M, unpublished observation). Rosacea is more common among female patients, and incidence peaks between the ages of 30 and 50 years.

Analyzing the molecular and protein profiles of the different rosacea subtypes has increased our understanding of rosacea pathophysiology and will continue to do so. Gene array (Figure 1b and 2b) and subsequent real-time PCR analysis (not shown) indicate that the clinically defined subtypes of rosacea also differ in their gene profile. All rosacea subtypes show a different gene profile compared with healthy skin. Each subtype can be differentiated by a selective gene profile (Figure 1b). Thus, the pathomechanisms of the different subtypes may vary with respect to the molecular pathways and molecules involved. Our gene array analysis indicates that certain genes overlap, which means that a developmental “march” among the different rosacea subtypes can be assumed in most cases (Figure 1). Despite that, it is still unclear whether patients in whom rosacea becomes clinically apparent not earlier than in the PhR subtype undergo a subclinical form of ETR and PPR.

Rosacea’s clinical features and trigger factors indicate a complex dysregulation of inflammatory, vascular, and neuronal systems at an early stage

The impact of a dysregulatory vascular system in rosacea patients has long been hypothesized (Flint and Wilkin, 1994; Huggenberger and Detmar, 2011). Substantial evidence indicates that sun exposure is important in the pathophysiology of rosacea (reviewed by Powell, 2005; Marks, 2007; McAleer *et al.*, 2010; Webster, 2010). The impact of UV radiation versus heat during sun exposure is still controversial, although clinical experience suggests that both have an impact because flushing can develop from heat without sun exposure (e.g., hot steam from a coffee pot (Wilkin, 1981) and *vice versa* (sun exposure in a cold environment)). Moreover, temperature changes modulate vascular function (Wilkin, 1981, 1983; Crawford *et al.*, 2004) and affect bacterial protein production (Dahl *et al.*, 2004). Both UV light and temperature changes can activate sensory nerves (Spiro *et al.*, 1987; McArthur *et al.*, 1998; Roosterman *et al.*, 2006; Aubdool and Brain, 2011). Thus, an activated nervous system in the skin correlates well with the early phase of rosacea, although it is still unclear whether neuronal activation precedes or follows the inflammatory infiltrate. The extent to which the autonomic and/or sensory nervous system is involved in the neuronal dysregulation during rosacea has received considerable attention, as modulation of α-adrenergic receptors or β-adrenergic blockers is helpful in some patients (Craige and Cohen, 2005; Shanler and Ondo, 2007; Gallo *et al.*, 2010). It is noteworthy that by gene array analysis and reverse transcriptase PCR we found that substantial upregulation of proinflammatory genes involved in vasoregulation (e.g., adrenergic receptors, tryptophan metabolites, proteases) and neurogenic inflammation (e.g., transient receptor potential (TRP) vanilloid receptor 1 (TRPV1), pituitary adenylate cyclase-activating polypeptide), along with a marked inflammatory infiltrate (Th1 cells, macrophages, mast cells), can already be observed at a very early stage of rosacea, even before it is clinically visible in terms of papules, nodules, or pustules (Figures 1–3). Thus, despite its origin, early rosacea has to be regarded as an inflammatory disease characterized by neuroimmune dysfunction and neurovascular dysregulation.

Molecular and immunohistochemical (IHC) characterization reveals a role of innate and adaptive immunity in rosacea

The PPR subtype of rosacea consists of an inflammatory infiltrate leading to papules, pustules, and, sometimes even, cysts. Occasionally, neutrophils or B cells are found in rosacea biopsies. Various microbial agents, including *Demodex folliculorum*, *Helicobacter pylori*, *Staphylococcus epidermidis*, or *Chlamydiae*, have been implicated in the

pathophysiology of rosacea (reviewed by Powell, 2005; Lazaridou *et al.*, 2011). The studies on *H. pylori* are contradictory (Mc Aleer *et al.*, 2009; Gallo *et al.*, 2010; Tuzun *et al.*, 2010; Lazaridou *et al.*, 2011). As for *D. folliculorum*, recent studies support its role as a key factor in at least certain subtypes of rosacea, predominantly subtype II, which is characterized by papules and pustules. Increased numbers of *Demodex* mites have been found in these patients as compared with healthy skin (Lazaridou *et al.*, 2010). In addition, these mites may harbor bacteria that may exacerbate rosacea (Lacey *et al.*, 2007; McAleer *et al.*, 2010). Thus, it is reasonable to hypothesize that *Demodex* may activate immune mechanisms in predisposed rosacea patients, in whom *Demodex* serves as a trigger factor leading to exacerbation of the papular and/or pustular phenotype. However, PPR is also found in patients whose lesions have a normal number of *Demodex*; other yet unknown cofactors can be hypothesized.

Our findings of upregulated genes involved in innate immunity and enhanced immune cells (Figures 1–3) indicate the involvement of the adaptive and innate immune system in all subtypes of rosacea, but to different extents. Although genes of the innate immune response are activated in all three subtypes of rosacea, the adaptive immune response seems to be more distinct in PPR and PhR and less in ETR (Figures 1 and 2). This is supported by our IHC characterization of the inflammatory infiltrate within the various subtypes of rosacea, suggesting that inflammatory cells of the innate and adaptive immune system are involved (Figure 3). Our gene array and morphometric data further reveal three important issues: First, neutrophils and B cells are only rarely found in certain patients, indicating that multiple trigger factors lead to the same symptom (papule, pustule). IL-8 mRNA is significantly upregulated in PPR, but the trigger that leads to upregulation of IL-8 and thus to neutrophil formation is currently unknown. Second, gene array and quantitative real-time RT-PCR data demonstrate upregulation of genes involved in innate and adaptive immunity, including cathelicidin, which has been implicated in rosacea pathophysiology by interacting with kallikrein-5 (Yamasaki *et al.*, 2007; Morizane *et al.*, 2010). Third, the inflammatory infiltrate in ETR is predominantly perivascular, not periglandular. Accordingly, our gene array studies and histological data do not support an important role for known microbial agents in the early phases of rosacea. However, further investigations about the impact of the innate immune system on neurovascular and neuroimmune function are warranted to fully understand the neuroimmune and immune defense connection in the pathophysiology of rosacea.

Molecular and morphological characterization reveals differences in the inflammatory infiltrate within different rosacea subtypes

Although various studies indicate that a lymphomonocytic infiltrate dominates in rosacea, few examined the whole spectrum of involved inflammatory cells in all subtypes of rosacea by immunohistochemistry, including morphometry. Involvement of T cells (Rufli and Buchner, 1984), macrophages (Marks and Harcourt-Webster, 1969), mast cells (Bamford, 2001; Aroni *et al.*, 2008), and neutrophils (Ramelet and Perroulaz, 1988; Akamatsu *et al.*, 1990; Millikan, 2003) has been described. Plasma cells have been described in PhR (Aloi *et al.*, 2000).

Our IHC and morphometric analyses of rosacea subtypes I–III suggest that the dominating activated cells in rosacea are $CD4^+$ Th1 cells, macrophages, and mast cells (Figure 3; Steinhoff *et al.*, 2010; Schwab V *et al.*, 2011). It is noteworthy that the early stage of rosacea already presents as a Th1-cell-mediated inflammatory skin disease accompanied by macrophages and mast cells, without enhancement of Langerhans cells, eosinophils, or natural killer cells (Figure 3). Additional trigger factors not yet known seem to activate neutrophils and B cells in rosacea patients under certain conditions, resulting in pustules

(neutrophils) and probably development into a hyperglandular–phymatous stage (increased density of B cells).

In contrast with other inflammatory skin diseases such as psoriasis, lupus erythematosus, or atopic dermatitis, the crucial cytokines and chemokines that orchestrate the initiation and perpetuation of rosacea are not fully known. Our molecular characterization of the different subtypes of rosacea as compared with healthy human skin by gene array analysis and real-time PCR indicates that a variety of cytokines, chemokines, metalloproteinases, proteases, and reactive oxygen species molecules, as well as lipid mediators, contribute to dysregulation of the inflammatory responses in rosacea (Figure 2a; Gerber *et al.* 2011). Still lacking, however, is a systematic profile of the inflammatory mediators involved in rosacea pathophysiology, both at the gene and protein level.

Molecular and morphological characterization indicates predominantly vasodilatation, but not angiogenesis in early rosacea

The importance of the vascular cutaneous system in rosacea is supported by the clinical and histopathological characteristics of flushing, erythema, and telangiectasia. Furthermore, edema results from plasma extravasation; i.e., the vascular leakage of blood vessels and rosacea is characterized by edema derived from blood and lymphatic vessels. Edema intensity varies in rosacea, and the maximal clinical stage is represented by morbus morbihan, in which lymphedema is the predominant clinical appearance.

Blood and lymphatic vessels have an extraordinary role in skin development, body homeostasis, and wound repair (reviewed by Roosterman *et al.*, 2006; Huggenberger and Detmar, 2011; Meyer-Hoffert and Schröder, 2011). Both are apparently involved in chronic inflammatory diseases such as psoriasis. Recent data indicate that blood and lymphatic vessels are also involved in rosacea (Gomaa *et al.*, 2007; Smith *et al.*, 2007; Aroni *et al.*, 2008; Bender *et al.*, 2008). The crucial growth factors, vasoregulatory molecules, and receptors contributing to the development of vasodilatation, edema formation, or lymphedema are poorly understood in the context of rosacea (Nakamura and Rockson, 2008; Ogunbiyi *et al.*, 2011). Although immunoreactivity for vascular endothelial growth factor, CD31 (blood vessel marker), and D2-40 (lymphatic vessel marker) has been described as enhanced in rosacea (Gomaa *et al.*, 2007), the impact of angiogenetic or vasoregulatory mechanisms appears to be irrelevant in the pathophysiology of ETR and PPR. Our combined IHC and morphometric analyses (Figure 3), together with gene array and RT-PCR studies (Figures 1 and 2), indicate that blood vessels and lymphatic vessels are dilated in ETR and PPR and that angiogenesis and lymphangiogenesis are part of the rosacea pathophysiology only in the PhR subtype (Schwab *et al.*, 2011).

Flushing can be activated by the autonomic or the sensory nervous system, although both systems are no longer completely divided but communicate with each other (Gibbons *et al.*, 2010; Mousa *et al.*, 2011). The kinetics of flushing, however, resemble the pattern of sensory C-fiber activation more. Moreover, non-neuronal mediators such as lipid metabolites and tryptophan derivates are ultimately involved in vasoregulation (Wang *et al.*, 2010). Thus, vasodilatation may be induced by neuronal stimulation, but could also result from inflammatory mediators released during the early phase of rosacea, in which inflammatory cells are already abundantly present (Figure 3; Roosterman *et al.*, 2006; Graepel *et al.*, 2011).

In rosacea, which is characterized by marked infiltration of T cells, macrophages, and occasionally neutrophils or B cells, an important role of blood vascular endothelial cells lies in their capacity to express selectins and cell adhesion molecules, which are important for the recruitment of leukocytes to the site of inflammation (Hua and Cabot, 2010; Muller,

2011). The chemokines involved in the recruitment of these cells in rosacea are still unknown. Recently, inhibition of blood vessel activation was found to exert potent anti-inflammatory properties (reviewed by Huggenberger *et al.*, 2010; Huggenberger and Detmar, 2011) and may be a target for anti-inflammatory therapies, even topically. Activation of lymphatic vessel function via topically applied vascular endothelial growth factor-C may be a promising pathway to block inflammation in rosacea and other diseases (Huggenberger *et al.*, 2010).

NEUROVASCULAR CHANGES IN ROSACEA: THE TRPV1 HYPOTHESIS

The clinical features of rosacea indicate that several body defense mechanisms are involved in its complex pathophysiology, reflecting the inflammatory, vascular, neuronal, and fibrotic components of the different disease subtypes (Figure 4). The role of the skin nervous system in the control of inflammation, immunity, and vascular regulation is now well established (Roosterman *et al.* 2006). A direct involvement of neurovascular dysregulation in rosacea skin is also supported by the characteristics of certain cell surface receptors that are intriguingly activated by trigger factors of rosacea—namely, spicy food, heat, noxious cold, exercising, and ethanol—and are simultaneously involved in inflammation, vasoregulation, and neuronal function, notably the TRPV1 (Figure 5; see Aubdool and Brain, 2011 for details). It is noteworthy that rosacea patients present with an enhanced susceptibility to trigger factors such as “hot” spicy food, noxious heat and cold, UV radiation, physical exercise, stress, alcohol (ethanol), and medications (sympathomimetics, niacin). Many of these trigger factors activate ion channels such as TRPV1 (Figure 5; see also Aubdool and Brain, 2011; Schwab *et al.*, 2011). TRPV1 is expressed by sensory nerves (Figure 5) and is ultimately involved in vasoregulation (Caterina *et al.*, 1997; Earley, 2010) and nociception. Thus, neurovascular dysregulation through TRPV1 might contribute to the early symptoms of rosacea characterized by transient flushing (“pre-rosacea”). This is also supported by our finding that the density of TRPV1+ nerve fibers is increased in ETR as compared with healthy skin (Steinhoff M and Voegel JJ, unpublished observation). Transient flushing later often results in persistent erythema with dysesthesia (burning, prickling, pain, rarely itch). Dysesthesia is controlled by sensory A-delta and/or C-fibers (Steinhoff *et al.*, 2003; Ma, 2010). On this basis, one may hypothesize that rosacea patients are subjected to a dysregulation of TRPV1, which is activated by spicy food, heat, and pH changes (Figure 5). In healthy humans, TRPV1 activation by these trigger factors leads to a short experience of flushing and burning pain. In rosacea patients, however, TRPV1 is eventually hyperactive, resulting in sustained flushing, a feeling of warmth, and “neurogenic” inflammation with edema and inflammatory cell infiltration (Figure 5), which can be extensive (Scharschmidt *et al.*, 2011). In accordance with this hypothesis, our own data confirm that rosacea patients demonstrate a high density of epidermal and dermal TRPV1+ nerve fibers (Figure 5), as well as enhanced expression levels of TRPV1 mRNA in skin biopsies of rosacea patients (Steinhoff M and Voegel JJ, unpublished observation). Thus, TRPV1 may be a therapeutic target for rosacea treatment. Other TRPV ion channels are likely to have a role in rosacea, but further exploration is needed (see Aubdool and Brain, 2011, for details).

THE RELATIONSHIP OF CHRONIC INFLAMMATION AND FIBROSIS IN ROSACEA

The PhR rosacea subtype is more common in male patients and develops mostly from PPR. However, in a certain subgroup of rosacea patients, PhR is present without obvious clinical signs of ETR or PPR, probably derived from a subclinical form of rosacea (Figure 1). The genes and molecules that may regulate the interaction between the inflammatory system and the extracellular matrix during the fibrotic process are poorly understood. Candidates include reactive oxygen species (Bakar *et al.*, 2007), metalloproteinases (Maatta *et al.*,

2006), serine proteases (Yamasaki *et al.*, 2011), and growth factors and cytokines/chemokines (reviewed by Gallo *et al.*, 2010; Meyer-Hoffert and Schröder, 2011; Gerber *et al.*, 2011). On the basis of our knowledge from other skin diseases or animal models, it appears that certain receptors for cytokines, chemokines, growth factors, or proteases are involved in the switch from an inflammatory to a fibrotic stage (see also Gerber *et al.*, 2011; Meyer-Hoffert and Schröder, 2011). The cellular mechanisms underlying this switch from inflammation to fibrosis are in general poorly understood, and for rosacea, completely unknown. Good candidates for such a "link" between the chronic inflammatory and fibrotic stages appear to be fibroblast growth factors (Shaw *et al.*, 2010; Craik *et al.*, 2011; Meyer-Hoffert and Schröder, 2011), cytokines (Gerber *et al.* 2011), and proteases (Steinhoff *et al.*, 2000, 2005). Future molecular and cellular characterization of fibroblast growth factors, extracellular matrix proteins, and proteases in the context with inflammatory changes in rosacea development will shed new light on disease pathophysiology and potential new treatment options against rosacea.

Our immunohistological and gene array studies indicate that fibroblasts are already activated in the earliest stages of rosacea (Schwab *et al.*, 2011). It remains unclear which cells and mediators upregulate the function and number of fibroblasts and myofibroblasts in ETR and PPR before the phymatous phenotype becomes clinically evident. It is noteworthy that the observed increased number of fibroblasts correlates well with enhanced numbers of mast cells (Schwab *et al.*, 2011), which are known to modulate fibroblast function and fibrosis (Hermes *et al.*, 2001; Chujo *et al.*, 2009). Thus, mast cells (Aroni *et al.*, 2008; Schwab *et al.*, 2011) along with T cells (Rufli and Buchner, 1984; Figure 3) and macrophages (Marks, 1973, Figure 3) may be ultimately involved in the development of PhR. Moreover, further studies indicate that keratinocytes are no longer passive bystanders in the pathobiology of rosacea but actively contribute to inflammation and fibrosis by releasing cytokines, chemokines, growth factors, metalloproteinases, and proteases, and regulate expression of intergrins, occludins, and claudins (Eslami *et al.*, 2009; Liu *et al.*, 2009; Huggenberger and Detmar, 2011; Meyer-Hoffert and Schröder, 2011). However, the exact role of keratinocytes, innate immunity, and epidermal barrier dysregulation in the context of rosacea still needs to be explored.

Innate immunity and neural receptors as sensors for "outside danger": potential role in rosacea

Recent evidence indicates that the innate immune system and epidermal barrier are impaired in rosacea, leading to increased susceptibility of the skin ("hypersensitive skin") toward toxins, temperature changes, microbe invasion, tissue injury, UV radiation, and endogenous mediators (e.g., pH changes, medication, and so on). This activation of cells involved in skin innate immune regulation and barrier function may subsequently stimulate the release of mediators that aggravate inflammatory cascades such as cytokines, chemokines (Gerber *et al.* 2011), antimicrobial peptides (Yamasaki and Gallo, 2011), radical oxygen species (Meyer-Hoffert and Schröder, 2011), neuromediators (Aubdool and Brain, 2011; Schwab *et al.*, 2011), or proteases (Meyer-Hoffert and Schröder, 2011). Moreover, Toll-like receptor-2 expression is enhanced in rosacea but not in atopic dermatitis or psoriasis (Yamasaki *et al.*, 2011), indicating a role of Toll-like receptors in rosacea. Among antimicrobial peptides, cathelicidin (LL37) appears to have an important role in innate immunity by regulating inflammation, reactive oxygen species production, angiogenesis, and protease function (Yamasaki *et al.*, 2006, 2007). In support of this finding, our gene array data confirm that mRNA expression levels of LL37 were found to be significantly increased in all subtypes of rosacea (Schwab *et al.*, 2011). How the various trigger factors compromise the innate immune system and skin nervous system needs to be explored. Understanding the role of the innate immune system and its key factors in rosacea may lead to new strategies for treatment

of rosacea at an early stage (Meylan *et al.*, 2006; Yamasaki and Gallo, 2009). Recent findings strongly indicate an important role of antimicrobial peptides and proteases as "alarmins" (mediators activated in the skin at an early stage of tissue injury) and are thereby part of the innate immune system. Upon activation by trigger factors, they can respond to "danger" molecules that may impair epidermal homeostasis (reviewed by Meyer-Hoffert and Schröder, 2011; Yamasaki and Gallo, 2011). As peripheral nerves are also part of the defense system in the epidermal skin barrier, the relationship among nerves, antimicrobial peptides, and proteases needs to be further deciphered (Figure 5 and 6; Schwab *et al.*, 2011).

CONCLUSIONS AND FUTURE DIRECTIONS

The pathophysiology of rosacea is still poorly understood. Recent cellular, IHC, molecular, and pharmacological approaches helped to further decipher new molecules and pathways in the pathobiology of rosacea. Our current hypothesis (Figure 6) is that a genetic predisposition, together with trigger factors, leads to the clinical occurrence of transient flushing, which may be because of overstimulation of the sensory and/or autonomic nervous system in the skin and induction of innate immune responses. The concrete relationship between the skin nervous system and the innate immune system is still unclear. Neurovascular mechanisms are very likely involved in vascular dysregulation characterized by flushing, persistent erythema, and telangiectasia. Sustained chronic inflammation characterized by a mainly Th1 macrophage and mast cell-driven infiltrate further leads to the release of incompletely understood mediators involved in vasoregulation, immunity, and fibrosis.

Many details of the new cellular and molecular observations are still unexplained and raise new critical questions: (1) What are the roles of the innate and adaptive immune systems, especially Th1 cells, mast cells, and macrophages, in the various subtypes? (2) What is the impact of mast cell infiltration and activation in all subtypes of rosacea? (3) What are the roles of the sensory and autonomic nervous system and which receptors and mediators are involved in inflammation, vasoregulation, and the hypersensitive skin of rosacea patients? (4) How are the immune and neurovascular systems linked to each other in terms of disease initiation and aggravation? (5) Which are the crucial factors initiating the transient flushing and vasodysregulation? (6) What are the crucial factors modulating vasodilatation of blood and lymphatic vessels—are these the same factors and can they be targeted therapeutically? (7) What is the impact of keratinocyte and fibroblast activation in rosacea, and could they be targets for therapy to control inflammation and thus prevent fibrosis? The many questions reflect our poor understanding of rosacea and emphasize the need for advanced scientific approaches, adequate *in vivo* and *ex vivo* models, and preclinical proof-of-principle studies in rosacea research.

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Abbreviations

ETR	erythematotelangiectatic rosacea
PhR	phymatous rosacea
PPR	papulopustular rosacea

TRPV1 transient receptor potential (TRP) vanilloid receptor 1

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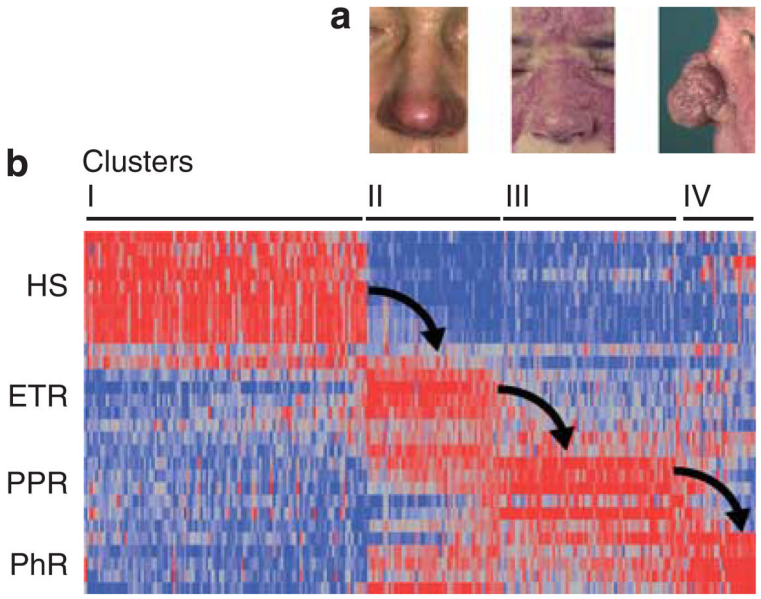
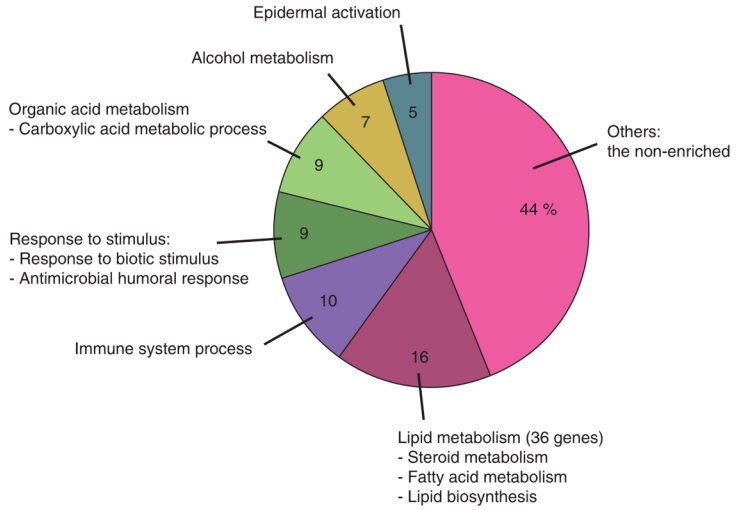


Figure 1. Relationship between clinical characteristics and gene array profile of rosacea

Three clinical subtypes have been studied by gene array analysis from facial skin biopsies and compared with healthy facial or uninvolved skin (healthy skin, HS). ETR, erythematotelangiectatic rosacea (subtype I, RI); PPR, papulopustular rosacea (subtype II, RII); PhR, phymatous rosacea (subtype III, RIII). (**a**) ETR is characterized by a prolonged flushing erythema and teleangiectasia. PPR is characterized by papules and, more rarely, pustules, in addition to erythema and telangiectasia. PhR is characterized by fibrotic changes and glandular hyperplasia, less clinically obvious inflammation, and erythema. Although flushing and discomfort are the predominant clinical features, and no papules are visible in ETR, a marked inflammatory infiltrate of $CD4^+$ T lymphocytes, macrophages, and mast cells is visible already in ETR by immunohistochemistry (see also Figure 3). (**b**) Gene array analysis of biopsies from patients with rosacea (subtypes I–III; n=6–8 patients per subtype) reveals differential regulation of various selective genes among the various subtypes (RI=ETR=cluster II; RII=PPR=cluster III; RIII=PhR=cluster IV) as compared with healthy or uninvolved skin (cluster I). Because certain genes overlap, a developmental “march” from rosacea I to III can be assumed, although it is not always clinically visible (arrows).

a



b

Chemokines, hits		ETR	PPR	PhR
WFDC12	WAP four-disulfide core domain 12	3.09	3.33	4.45
CRIP1	Cysteine-rich protein 1 (intestinal)	–4.47	–4.1	–4.26
IL7R	Interleukin 7 receptor	3.33	9.66	6.31
KLRB1	Killer cell lectin-like receptor subfamily B, member 1	3.61	7.68	4.04
LTF	Lactotransferrin	8.84	53.36	25.43
OAS1	2',5'-oligoadenylate synthetase 1, 40/46 kDa	3.08	4.73	5.57
IL26	Interleukin 26	4.14	22.5	6.94
CCL5	Chemokine (C-C motif) ligand 5	3.56	7.22	4.77
CCL18	Chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	5.7	17.86	9.92
CCL19	Chemokine (C-C motif) ligand 19	4.63	10.39	8.25
CCL20	Chemokine (C-C motif) ligand 20	3.96	5.6	5.54

Figure 2. Analysis of inflammatory and immune changes in rosacea on the basis of gene array analysis

(**a**) Biological interpretation of genes upregulated in cluster II (erythematotelangiectatic rosacea, ETR). Of the 221 known genes that clustered in various dominant biological processes, about 20% can be implicated in inflammation and immune defense. A surprising and thus far unacknowledged increase of genes involved in alcohol and lipid metabolism was observed. About 5% of the genes are involved in epidermal activation or development, indicating the involvement of keratinocytes at an early stage of rosacea. (**b**) Gene array analysis of cytokines and chemokines involved in the pathophysiology of rosacea indicates a role of interleukin (IL)-7, IL26, and various chemokines already in early subtypes of rosacea (see Gerber *et al.*, 2011, for details). RI, ETR; RII, papulopustular rosacea (PPR); RIII, phymatous rosacea (PhR). WAP, whey acidic protein.

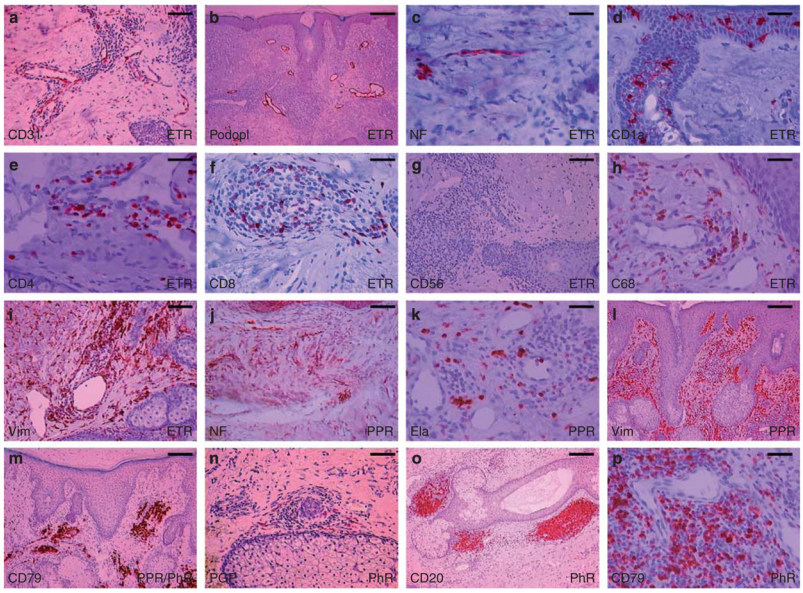


Figure 3. Histopathological characteristics of rosacea subtypes (erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PhR))

All three subtypes were stained for inflammatory and immune markers to determine the inflammatory infiltrate and skin structures involved in inflammation and fibrosis (T cells: CD4, CD8; B cells: CD20, CD79a; Langerhans cells: CD1a; macrophages: CD68; natural killer cells: CD56; neutrophils: CD15, elastase; mesenchymal cells: vimentin (VIM); nerves: PGP9.5, NF200; blood vessels: CD31; lymphatic vessels: podoplanin (Podpl)) in the various subtypes. An increased mast cell infiltrate can also be observed in all subtypes of rosacea (Schwab *et al.*, 2011). (**b**) Bar=200 μm; (**a**, **g**, **i**, **j**, **l**–**o**), bar=100 μm; (**c**, **d**, **f**, **h**, **k**, **p**), bar=50 μm.

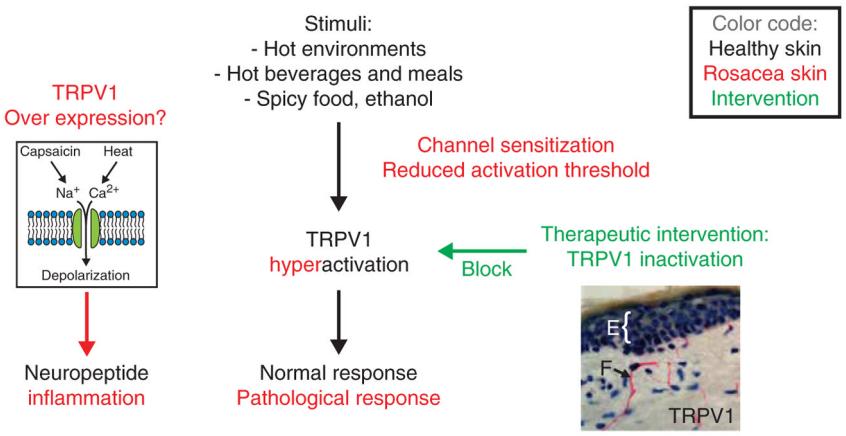


Figure 4. Potential role of neurogenic inflammation in the early phase of rosacea

Genetic predisposition, along with exogenous or endogenous trigger factors, stimulates peripheral nerve endings of the skin. Central transmission of neuronal activation leads to facial discomfort (stinging, burning pain), perceived by the central nervous system. The sensory axon reflex of primary afferents in the dermis and epidermis releases vasoactive neuropeptides such as pituitary adenylate cyclase-activating polypeptide or vasoactive intestinal peptide (VIP) into the microenvironment. Binding of neuromediators to high-affinity neuropeptide receptors on arterioles or venules leads to vasodilatation (flushing, erythema) or plasma extravasation (edema). Activation of T cells, macrophages, and mast cells by neuropeptides results in activation or aggravation of inflammatory responses. It is unknown to what extent neuromediators may also exert anti-inflammatory capacities in human skin diseases. Bi-directional communication between the innate immune and nervous systems may aggravate early rosacea leading to chronic disease. Ca^{2+}, calcium; E, epidermis; F, nerve fibre; Na^{2+}, sodium; TRPV1, transient receptor potential (TRP) vanilloid receptor 1.

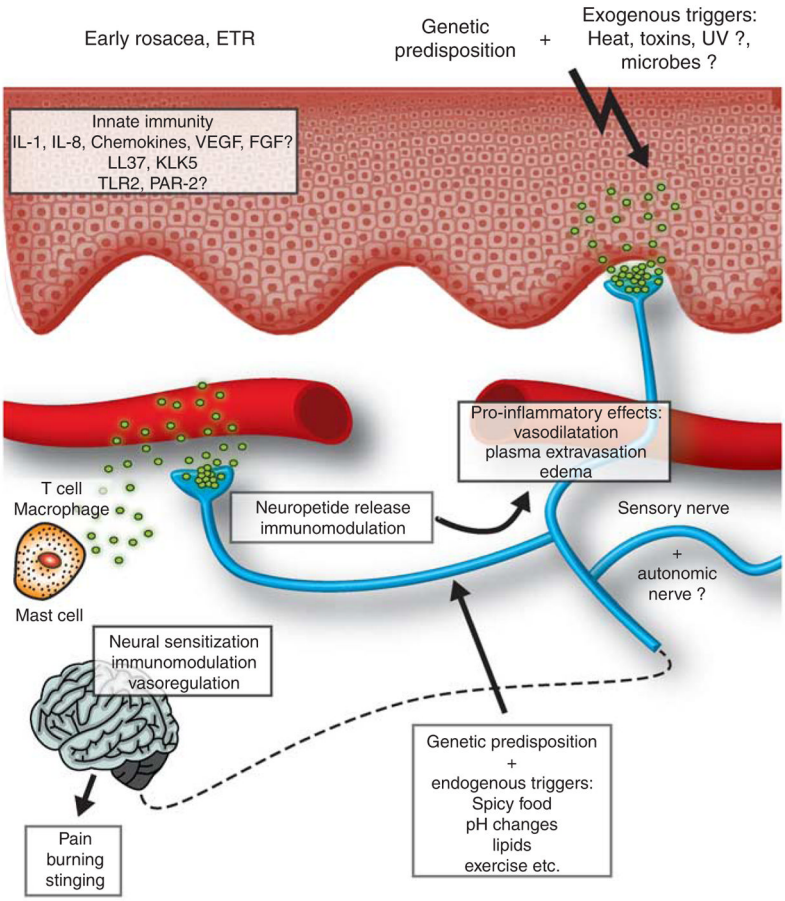


Figure 5. Neurovascular transient receptor potential (TRP) vanilloid receptor 1 (TRPV1) hypothesis in rosacea

TRPV1 localized in abundance on epidermal and dermal perivascular sensory nerve endings (lower right picture) can be stimulated by various trigger factors of rosacea such as spicy food, “hot” temperature changes, ethanol or inflammatory acidosis, or prostanoids. In healthy humans (black), stimulation of TRPV1 on nerve endings leads to a transient dilatation, followed by rapid recovery. In rosacea patients (red), overexpression or overstimulation of TRPV1 by a possibly genetic predisposition leads to neuropeptide release and thereby neurogenic inflammation (see Figure 4 for details), characterized by flushing, erythema, edema, and inflammation. It is unknown whether TRPV1 dysregulation is based on increased ion channel sensitization or a reduced activation threshold. Thus, therapeutic intervention of TRPV1 overstimulation may be a new therapeutic strategy in rosacea (green). ETR, erythematotelangiectatic rosacea; FGF, fibroblast growth factor; KLK5, kallikrein-related peptidase-5; PAR-2, proteinase-activated receptor-2; TLR-2, Toll-like receptor 2; VEGF, vascular endothelial growth factor.

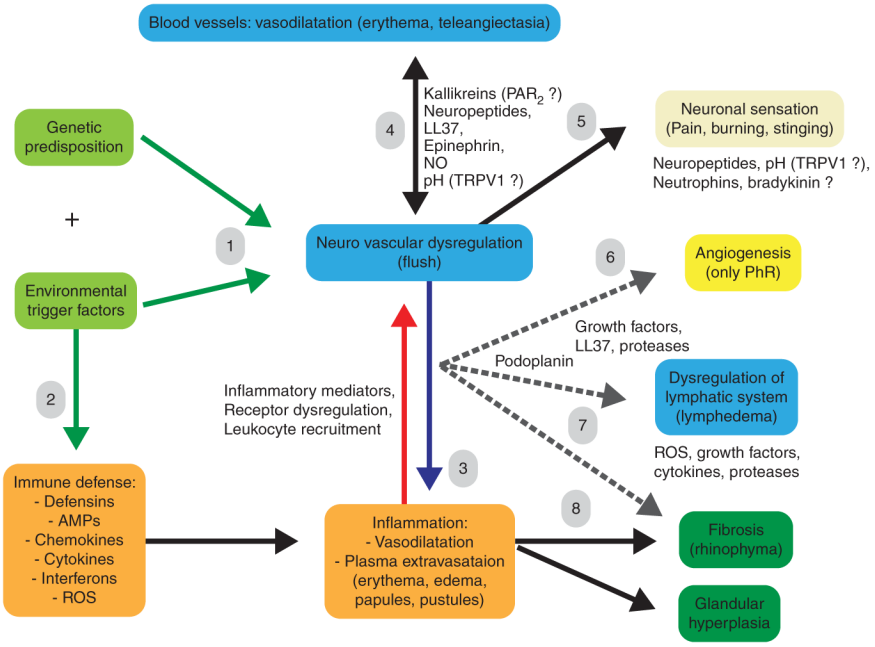


Figure 6. Potential pathophysiology of rosacea integrating clinical, immunological, neurovascular, and molecular characteristics

(1) Genetic predisposition plus trigger factors activate hypersensitive sensory nerve endings in the skin. Alternatively (2), trigger factors may stimulate innate immune mechanisms in the skin, thereby "alarming" the neuronal defense system in the skin, which is hypersensitive (3) Neural activation results in vasodilatation, edema (4), and discomfort (pain, burning) (5). (6) Chronic neurogenic inflammation may lead to persistent erythema, and, at later stages, to angiogenesis, which is probably limited to the phymatous rosacea (PhR) subtype. (7) It is unknown whether dilation of lymphatic vessels is dependent or independent on neuronal stimulation. (8) Chronic inflammation characterized by Th1 cells, macrophages, and mast cells because of sustained innate immune and neurogenic stimulation results in induction of profibrotic growth factors, probably via mast cells, and thereby activation of myofibroblasts, rearrangement of the extracellular matrix, and finally fibrosis. AMP, antimicrobial peptide; NO, nitric oxide; PAR-2, proteinase-activated receptor-2; ROS, reactive oxygen species; TRPV1, transient receptor potential (TRP) vanilloid receptor 1.