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Rosacea: the Cytokine and Chemokine Network

Peter Arne Gerber[1], Bettina Alexandra Buhren[1], Martin Steinhoff[2] and Bernhard Homey[1]

Rosacea is one of the most common dermatoses of adults. Recent studies have improved our understanding of the pathophysiology of rosacea. Current concepts suggest that known clinical trigger factors of rosacea such as UV radiation, heat, cold, stress, spicy food, and microbes modulate Toll-like receptor signaling, induce reactive oxygen species, as well as enhance antimicrobial peptide and neuropeptide production. Downstream of these events cytokines and chemokines orchestrate an inflammatory response that leads to the recruitment and activation of distinct leukocyte subsets and induces the characteristic histopathological features of rosacea. Here we summarize the current knowledge of the cytokine and chemokine network in rosacea and propose pathways that may be of therapeutic interest.

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INTRODUCTION

Rosacea is a common, often underdiagnosed, chronic inflammatory syndrome of the adult that usually develops between the ages of 30 and 50 years (Wilkin *et al.*, 2002; Powell, 2005). Up to one-third of individuals of northern European origin report a family history of rosacea (Rebora, 1993). Rosacea mainly affects the areas of the skin that bear a high density of seborrhoic glands, such as cheeks, nose, chin, and forehead (Korting and Schollmann, 2009a). The disease is characterized by a variety of primary and secondary features. Primary features are flushing (transient erythema), persistent erythema, teleangiectasia, as well as papules and pustules. Secondary features are burning or stinging, plaques, dry appearance, edema, or phyma (Wilkin *et al.*, 2002). An ocular involvement can be found in more than 50% of rosacea patients, and may present as dryness, irritation, blepharitis, conjunctivitis, or keratitis. It must be warranted that ocular rosacea can compromise eyesight (Powell, 2005; Elewski *et al.*, 2011).

Patterns or groupings of primary and secondary features are used to specify rosacea into four subtypes (Wilkin *et al.*, 2002). Subtype 1, the erythematoteleangiectatic rosacea, is defined by the presence of flushing and central facial erythema. Additional possible features are edema, stinging, and burning sensations, as well as roughness or scaling. Subtype 2, papulopustular rosacea, is defined by persistent erythema and transient papules or pustules. Subtype 3, phymatous rosacea, presents with thickening skin, irregular surface nodularities, and enlargement. Areas affected by phymatous rosacea are chin, forehead, cheeks, ears, and nose, with nose or rhinophyma being the most common phenotype by far. Ocular rosacea, finally, is defined as subtype 4. Granulomatous rosacea does not present with the morphological patterns or combinations seen in the subtypes 1–4, and is therefore regarded as a rosacea variant. It is characterized by hard, yellowish–brownish or red papules and nodules that may lead to scarring.

Rosacea-like conditions include rosacea fulminans (pyoderma faciale), steroid-induced acneiform eruptions, and the perioral dermatitis (Wilkin *et al.*, 2002). Finally, in recent years, the development of targeted cancer drugs directed against the EGFR has led to the recognition of novel, rosacea-like cutaneous adverse effects (Lacouture, 2006).

Rosacea histopathology is characterized by solar elastosis, edema, perivascular lymphocytic infiltrates, abundant mast cells, and dilated, partly irregular vascular channels (Aroni *et al.*, 2008; Fimmel *et al.*, 2008). Vascular dilatations are found at the upper and mid-dermal blood vessels (Gomaa *et al.*, 2007). The pustular stage of rosacea shows a dense follicular infiltrate composed of neutrophils, as well as abundant macrophages and dermal dendritic cells in the perifollicular region. Interestingly, rosacea lesions with an association of the saprophyte *Demodex folliculorum* display dermal infiltrates with a predominance of CD4+ T-helper (T_H) cells over CD8+ T cells, supporting the hypothesis that cell-mediated immune responses have an important role in the pathogenesis of the disease (Rufli and Buchner, 1984). Moreover, an increased number of dermal mast cells correlated with the duration of the disease (Aroni *et al.*, 2008). Immunofluorescence analyses of rosacea reveal anticollagen antibodies along with eluted antinuclear antibodies directed against scattered dermal, endothelial, and eccrine duct cells (Nunzi *et al.*, 1980).

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Abbreviations: D. folliculorum, Demodex folliculorum; EGFRI, EGFR inhibitor; MMP, matrix metalloproteinase; ROS, reactive oxygen species; TCN, tetracycline; T_H, T helper; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

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Finally, histopathological analyses in granulomatous rosacea show mixed lymphohistiocytic infiltrates in association with scattered epithelioid granulomas or epithelioid granulomas (Helm *et al.*, 1991).

Despite its prevalence, the underlying molecular and cellular mechanisms of rosacea have remained largely elusive. Nevertheless, clinical and histopathological findings suggest that the features of all subtypes or variants are the result of inflammatory processes. Accordingly, recent studies propose that rosacea is caused by a consistently aberrant innate immune response that finally results in the characteristic inflammatory and vascular phenotype (Yamasaki and Gallo, 2009). Herein, environmental stressors, such as UV radiation, heat, cold, stress, glucocorticosteroids, hormones, spicy food, or microbes, generate, modulate, and/or induce reactive oxygen species (ROS), matrix metalloproteinases (MMPs), Toll-like receptor (TLR) signaling, as well as antimicrobial or neuropeptides. Eventually, these events modulate the expression of crucial mediators of the immune system such as cytokines and chemokines.

CYTOKINES

Cytokines comprise a family of structurally diverse proteins that are best known for their important role in the immune system. They often have pleiotropic functions and show cell type-specific activities. Ligand-dependent cytokine receptor signaling regulates cell activation, proliferation, differentiation, survival, and migration of leukocytes and many other cell types including keratinocytes, fibroblasts, endothelial cells, and neuronal cells. Leukocytes are a rich source of cytokine expression. However, structural cells may also produce and/or store significant amounts of cytokines. An example is the production of IL-1 family members by human keratinocytes (Marionnet *et al.*, 1997). Within the broad spectrum of cytokines, subfamilies can be identified based on receptor binding or structural aspects.

The IL-1 subfamily (IL-1α, IL-1β, IL-1 receptor antagonist (RA), IL-18, IL-1F7, IL-1F10, IL-33, IL-36α, IL-36β, IL-36γ, and IL-36RA) is characterized by a conserved amino-acid sequence, as well as a similar gene and three-dimensional structure. IL-1 family members have a critical role in innate immune responses and host defense. Notably, IL-1 receptors share a common Toll/interleukin1 receptor-like domian motif with TLRs and are expressed on a large variety of cell types (Dinarello, 2009).

On the basis of receptor usage, the common β-chain receptor-binding cytokines (GM-CSF, IL-3, and IL-5) are separated from the common γ-chain receptor subfamily (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). Members of both families represent major growth and differentiation factors for hematopoietic cells (Bagley *et al.*, 1997).

On the other hand, the IL-6 subfamily (IL-6, IL-11, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, ciliary neurotrophic factor, cardiotrophin-like cytokine, and IL-31) is characterized by a helical cytokine structure and a shared receptor subunit. Members stimulate hematopoiesis, leukocyte differentiation, and link the immune system to the nervous system (Hibi *et al.*, 1996; Dillon *et al.*, 2004).

The IL-10 cytokine subfamily includes, based on sequence homology, IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26, and is separated from the IFN subfamily (Pestka *et al.*, 2004). The IFN subfamily is further divided into type I IFNs, including IFN-α, -β, -ω, -κ, and Limitin, as well as the type II IFN, IFN-γ. IFNs are best known for their crucial role in host defense and orchestrate antiviral or antitumor immune responses, are angiostatic, and initiate autoimmune responses (Haller and Weber, 2009; Kalliolias and Ivashkiv, 2010).

The IL-17 subfamily represents secreted proteins that share a conserved cysteine-knot structure and comprise IL-17, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. T cells are a major source of IL-17 and use this cytokine to interact with a broad range of cell types (Weaver *et al.*, 2007). In particular, IL-17 was shown to be secreted by activated CD4 + T cells (Harrington *et al.*, 2005). This discovery has led to the distinction of IL-17-producing T_H17 cells from T_H1 or T_H2 cells. Interestingly, T_H17 cells have been shown to have a crucial role in autoimmunity and neutrophilic inflammation (Alcorn *et al.*, 2010; Marzano *et al.*, 2010).

Within the tumor necrosis factor (TNF) family of cytokines (TNF-α, TNF-β, TRAIL, RANKL, TWEAK, APRIL, OX40L, CD27L, CD30L, CD40L, LIGHT, lymphotoxin-α, and lymphotoxin-β), most members are type II transmembrane proteins. Their extracellular domains can be cleaved by specific metalloproteinases to generate soluble cytokines and exert pleiotropic functions in the immune system, organ development, and cancer (Watts, 2005). Notably, their most prominent member TNF-α is stored in high amounts in dermal mast cells and is rapidly secreted upon cell activation. Members of the TGF-β family (TGF-β_1, TGF-β_2, and TGF-β_3) represent structurally related proteins that form homo- or heterodimers and signal through heteromeric receptor serine/threonine kinases to activate Smad signaling cascades. Next to its role in development and morphogenesis, TGF-β signaling has been associated with fibrosis in systemic sclerosis, idiopathic pulmonary fibrosis, keloids, and notably phymatous tissues (Pu *et al.*, 2000; Payne *et al.*, 2002, 2006; Margadant and Sonnenberg, 2010). Finally, there is a large amount of cytokines that have not yet been clustered in larger groups, including IL-12, IL-13, IL-16, IL-23, IL-27, IL-32, and IL-34.

CHEMOKINES

Chemokines represent a superfamily of cytokine-like proteins that critically regulate leukocyte trafficking (Zlotnik and Yoshie, 2000; Zlotnik *et al.*, 2006; Kabashima *et al.*, 2011). Chemokine ligands interact with 19 different seven transmembrane-spanning G protein-coupled receptors (CCR1-10, CXCR1-7, XCR1, CX_3CR1; Zlotnik and Yoshie, 2000). In humans, 46 different chemokine ligands are classified into four subfamilies based on the alignment of the first two cysteine residues of their amino-acid sequence. Chemokines with two consecutive cysteines are referred to as members of the CC subfamily (CCL1-28), whereas chemokines with two cysteines separated by one amino acid are referred to as members of the CXC subfamily (CXCL1-17). The other two subfamilies consist of chemokines with only one residue

(XCL1) or chemokines with three residues in between their cysteines (CX_3CL1; Zlotnik and Yoshie, 2000). Members of these chemokine subfamilies critically regulate the organ-specific recruitment of distinct leukocyte subsets. With regard to effector memory T-cell recruitment, it has been shown that T_H1 cells preferentially express CCR5 and CXCR3, T_H2 cells predominantly show CCR3, CCR4, and CCR8 on their cell surface, whereas T_H17 cells abundantly express the chemokine receptor CCR6. During skin inflammation, their corresponding ligands orchestrate lymphocyte recruitment to distinct anatomical sites of the skin (Table 1: chemokine receptor repertoire of distinct leukocyte subsets). Cutaneous dendritic cells and macrophages serve as sentinels of the immune system and represent a heterogeneous family of cells. Their precursors migrate from postcapillary venules into the skin and express many chemokine receptors, including CCR1, CCR2, CCR5, CCR6, CXCR4, and CX_3CR1, on their cell surface. Most pronounced responses were observed for CCR2 and its ligand CCL2 *in vitro* and *in vivo*. The formation of pustules clinically indicates the infiltration of neutrophils into perifollicular spaces. With regard to neutrophil recruitment to the skin, ligands of CXCR2 such as CXCL1 and CXCL8 have a dominant role and are frequently observed in neutrophilic inflammation.

Besides their involvement in inflammation, chemokines are involved in embryogenesis and promote tumor progression and metastasis (Muller *et al.*, 2001; Homey *et al.*, 2002; Charo and Ransohoff, 2006; Pivarcsi *et al.*, 2007; Raz and Mahabaleshwar, 2009). During recent years, several studies identified chemokine receptor expression on endothelial cells and demonstrated that ligands for CCR2 (CCL2), CCR3 (CCL11), CXCR2 (CXCL1, CXCL8), CXCR4 (CXCL12), and CX_3CR1 (CX_3CL1) promote angiogenesis. Conversely, IFN-inducible and CXCR3-binding chemokines such as CXCL9, CXCL10, and CXCL11 have been shown to inhibit angiogenesis and are classified as angiostatic chemokines (Gerber *et al.*, 2009).

Here we summarize the current knowledge of the cytokine and chemokine network in rosacea and propose a model for their involvement based on current pathophysiological concepts.

Table 1. Chemokine receptor repertoire of human leukocyte subsets

Cell type	Chemokine receptor	Chemokine ligand
T_H1 cells	CCR5	CCL3, 4, 5, 8, 14, 16
	CXCR3	CXCL4, 9, 10, 11
T_H2 cells	CCR3	CCL5, 7, 8, 11, 13, 15, 16, 24, 26, 28
	CCR4	CCL17, 22
	CCR8	CCL1
T_H17 cells	CCR6	CCL20
Monocytes, macrophages, dendritic cells	CCR1	CCL3, 5, 7, 13, 14, 15, 16, 23
	CCR2	CCL2, 7, 8, 13, 16
	CCR5	CCL3, 4, 5, 8, 14, 16
	CCR6	CCL20
	CCR7	CCL19, 21
	CXCR4	CXCL12
	CX_3CR1	CX_3CL1
Neutrophils	CXCR2	CXCR1, 2, 3, 5, 6, 7, 8
Mast cells	CCR1	CCL3, 5, 7, 8, 13, 14, 15, 16, 23
	CCR3	CCL5, 7, 8, 11, 13, 15, 16, 24, 26, 28
	CCR4	CCL17, 22
	CCR5	CCL3, 4, 5, 8, 14, 16
	CXCR1	CXCL6, 7, 8
	CXCR2	CXCL1, 2, 3, 4, 5, 6, 7, 8
	CXCR3	CXCL4, 9, 10, 11
	CXCR4	CXCL12
	CX_3CR1	CX_3CL1

Abbreviation: T_H, T helper.

THE CYTOKINE AND CHEMOKINE NETWORK IN ROSACEA

Despite limited data on a direct involvement of cytokines and chemokines in rosacea, these essential effectors of skin inflammation are key mediators of the majority of symptoms, which, according to recent studies, are proposed to be crucial or characteristic to the pathophysiology of rosacea. Therefore, we will discuss the role of cytokines and chemokines in the context of these events.

INNATE IMMUNITY AND MICROBES

Current concepts propose that rosacea is caused by a consistently aberrant innate immune response (Yamasaki and Gallo, 2009). Herein, TLR signaling has a crucial role by mediating the effects of well-known rosacea trigger factors. TLRs recognize conserved products derived from microbes (e.g., *D. folliculorum*) and respond to stress induced by chemical or physical trauma (e.g., UV radiation). Subsequent TLR activation leads to the induction of conserved anti-pathogen signaling cascades including the secretion of antimicrobial peptides and the production of proinflammatory cytokines and chemokines (Meylan and Tschopp, 2006). Recent studies propose a central role of TLR2 in the pathophysiology of rosacea (Yamasaki and Gallo, 2009). In fact, the authors demonstrate that lesional skin of rosacea patients is characterized by an altered TLR2 expression, which enhances the susceptibility toward innate immune stimuli (Schauber *et al.*, 2007; Yamasaki *et al.*, 2011). In rosacea, activation of TLR2 leads to the expression of abnormally high levels of the antimicrobial peptide cathelicidin, which has been shown to promote leukocyte

trafficking through the induction of CXCL8 and induce angiogenesis (De *et al.*, 2000; Koczulla *et al.*, 2003; Yamasaki *et al.*, 2007). In particular, the induction of CXCL8 by the cationic cathelicidin peptide LL-37 in keratinocytes is regarded as a crucial event for the recruitment of neutrophils and hence the formation of pustules (Zhang *et al.*, 2011). Moreover, a recent study on the role of *Propionibacterium acnes* (*P. acnes*) in acne vulgaris demonstrates the TLR2-dependent induction of NF-κB, IL-6, CXCL8, and IL-12 (Kim, 2005). These data correlate with analyses in steroid-induced acneiform eruptions or rosacea-like dermatitis (Shibata *et al.*, 2009). In fact, Kis *et al.* (2006) demonstrated for the first time that the synthetic glucocorticosteroid budenoside enhances TLR2 in human primary keratinocytes; subsequently, Shibata *et al.* (2009) confirmed these findings by showing that dexamethasone and cortisol in combination with IL-1α and TNF-α synergistically increase the expression of TLR2 in keratinocytes. Subsequently, microbial products derived from *P. acnes* activate TLR2 signaling, leading to the induction of proinflammatory effectors, such as cytokines and chemokines, and hence, mediating skin inflammation as previously described. Taking into account the high prevalence of *D. folliculorum* in rosacea, similar mechanisms may be proposed for this saprophyte and its associated so-called mite-related bacteria, e.g., *Bacillus olenorium*, in rosacea (Lacey *et al.*, 2007; Hsu *et al.*, 2009; Lazaridou *et al.*, 2011). Correspondingly, a recent study on the concentration of inflammatory cytokines and chemokines in the tear fluids of patients with *Demodex* blepharitis demonstrated an increase of IL-7, IL-12, and IL-17 as compared with *Demodex*-free blepharitis (Kim *et al.*, 2011). Interestingly, IL-1 and the TLR2-induced IL-6 (as well as IL-23) promote the T_H17 differentiation of human T cells, with T_H17 cells representing an abundant source of IL-17, IL-21, and IL-22 (Chen and O'Shea, 2008). Moreover, a recent study reports an increase of T_H17 cells and elevated levels of the T_H17 cytokine IL-22 in peripheral blood of patients with acute generalized exanthematous pustulosis. Acute generalized exanthematous pustulosis is an inflammatory dermatosis that is characterized by a massive subcorneal infiltration of neutrophils. In these cases, the IL-17/IL-22-mediated induction of CXCL8 in keratinocytes is the proposed mechanism for the recruitment of neutrophil granulocytes to the skin, and hence for the formation of pustules (Kabashima *et al.*, 2011). In summary, these findings may point toward a potential role for IL-17 and IL-10 family members in the initiation of pustular lesions seen in rosacea patients.

With regard to IL-1α, it has been proposed to have a crucial role in the pathophysiology of ocular rosacea by inducing a set of MMPs that subsequently degrade extracellular matrix components of the eyelid and the ocular surface (Matsubara *et al.*, 1991a; Barton *et al.*, 1997; Afonso *et al.*, 1999; Rao *et al.*, 2008). Specifically, the expression of MMP9 strongly correlated with the level of IL-1α in the tear fluid of rosacea patients (Afonso *et al.*, 1999). MMP9 is produced by the corneal epithelium and has been shown to be overexpressed in nonhealing corneal ulcers and to critically participate in the degradation of the corneal epithelial basement membrane (Matsubara *et al.*, 1991b; Ye and Azar, 1998). Nevertheless, a study by Robinson *et al.* (2003) reports different results for the expression of IL-1α in the skin of rosacea patients. The authors detected decreased levels of IL-1α in lesional and non-lesional skin of rosacea patients ($n=11$) as compared with the skin of normal subjects ($n=22$). However, they observed significantly increased levels of the IL-1α-inhibiting IL-1RA and elevated IL-1RA/IL-1α ratios. Notably, the authors themselves discuss these somewhat surprising results and argue that increased levels of IL-1α may qualify as an indicator of acute inflammation, whereas chronic inflammation may result in decreased IL-1α levels and reactive induction of IL-1RA (Robinson *et al.*, 2003). Further research is required to solve the involvement of IL-1 family members in different stages of rosacea.

UV RADIATION AND ROS

Rosacea is considered to be a UV-aggravated disease (Murphy, 2004; Buechner, 2005; Fimmel *et al.*, 2008; Yamasaki and Gallo, 2009). This concept is supported by the histopathological observation that all subtypes and variants of rosacea start as actinic lymphatic vasculopathy (Fimmel *et al.*, 2008). This condition is accompanied by a distinct perivascular lymphocytic infiltrate (Fimmel *et al.*, 2008). Notably, UV irradiation induces IL-1β, IL-6, IL-10, TNF-α, and CXCL8 in a time- and dose-dependent manner (Brink *et al.*, 2000; Caricchio *et al.*, 2003; Pauloin *et al.*, 2009). In particular, the primary proinflammatory cytokines IL-1β and TNF-α are known to induce the expression of a subset of proinflammatory chemokines (CXCL1, CXCL8, CCL20, CCL27) in keratinocytes. Recently, Meller *et al.* (2005) demonstrated that UVB irradiation significantly enhances the expression of the inflammatory chemokines CCL5, CCL20, and most notably CXCL8, suggesting a potential pathway for T_H1 (CCL5) and T_H17 (CCL20) cells, as well as neutrophil (CXCL8) recruitment. Moreover, UV radiation is the most important source of ROS in the skin. Elevated levels of ROS have been observed in the skin of rosacea patients as compared with healthy individuals (Jones, 2004; Bakar *et al.*, 2007). ROS exert significant proinflammatory effects in the skin. In fact, TLR2-ROS signaling has been shown to mediate the expression of CCL2 and CXCL8 in primary human monocytes (Lee *et al.*, 2009a). Finally, current concepts on rosacea pathophysiology suggest a prominent role for the 'Myleoid Differentiation Factor 88' (MyD88) as an effector of UV-induced aggravation (Yamasaki and Gallo, 2009). MyD88 is an essential adaptor molecule for TLR signaling and is overexpressed in both UV-irradiated human primary keratinocytes and chronically UV-exposed and photoaged human skin (Lee *et al.*, 2009b). Herein, MyD88 regulates the basal and UV-induced expression of MMP-1 and IL-6 (Lee *et al.*, 2009b). These molecular observations may provide a clue for the susceptibility of UV-sensitive 'celtic' individuals to develop rosacea. Surprisingly, a recent study by Salamon *et al.*, (2008) reported significantly decreased levels of IL-6 and IL-18 in the serum levels of 60 rosacea patients as compared with 25 healthy

controls, whereas alterations in the concentrations of TNF-α and c-reactive protein (CRP) were not detected. Nevertheless, it is debatable whether serum levels of cytokines reflect inflammatory processes in lesional skin of rosacea patients.

VASCULAR AND PHYMATOUS CHANGES

Rosacea is defined as an actinic vasculopathy (Fimmel *et al.*, 2008). The concept of an altered vascular function or a vascular hyperreactivity is supported by the characteristic clinical features including flushing, persistent erythema, and teleangiectasia. Functional analyses have demonstrated that papulopustular rosacea exposed an increased blood flow as compared with unaffected skin. Moreover, the increased blood flow showed a high correlation with the skin temperature (Guzman-Sanchez *et al.*, 2007). Nevertheless, vascular changes in rosacea are not limited to functional changes. Recent studies point toward a vascular endothelial growth factor (VEGF)-mediated angiogenesis and lymphangiogenesis in rosacea (Gomaa *et al.*, 2007). Interestingly, IL-17 mediates the induction of VEGF in fibroblasts *in vitro*, pointing toward a potential role of this cytokine in rosacea-associated angiogenesis (Numasaki *et al.*, 2003; Tartour *et al.*, 2011). Conversely, the therapeutic effect of retinoids in rosacea may in part be mediated by an impairment of the secretion of VEGF by keratinocytes (Lachgar *et al.*, 1999). Interestingly, increased vascular densities were correlated with the subtype of papulopustular rosacea and ocular rosacea (Aroni *et al.*, 2008).

Notably, chemokines have been shown to exert bimodal functions on the vasculature. Whereas IFN-inducible and CXCR3-binding chemokines such as CXCL9, CXCL10, and CXCL11 have been classified as angiostatic chemokines, CCL2, CCL11, CXCL1, CXCL8, CXCL12, and CX_3CL1 have been demonstrated to promote angiogenesis (Gerber *et al.*, 2009). Nevertheless, their role in rosacea-associated vasculopathy and angiogenesis or lymphangiogenesis remains to be elucidated.

A somewhat separate aspect in the context of cytokines and rosacea is the proposed role of TGF-β signaling in phymatous rosacea (Payne *et al.*, 2002, 2006). A persistent overexpression or dysregulated activation of this cytokine is suggested to promote fibrosis in phymatous tissue. In fact, the fibrogenic TGF-β isoforms TGF-β_1 and TGF-β_2, along with the TGF-β type II receptor, have been shown to be overexpressed in rhinophyma (Pu *et al.*, 2000; Payne *et al.*, 2002, 2006).

NEUROGENIC INFLAMMATION

The concept of cutaneous neurobiology includes a complex system of closely related mono- and/or bidirectional pathways that link the skin with the endocrine, the immune, and the nervous system. These regulate a variety of physiological and pathophysiological functions including cellular development, growth, differentiation, vasoregulation, pruritus, wound healing, and most importantly immunological processes and leukocyte recruitment or neurogenic inflammation. Mediators involved in these processes are defined as neuropeptides, neurotransmitters, neurotrophins, and neurohormones, which target various skin cells including keratinocytes, mast cells, Langerhans cells, microvascular endothelial cells, fibroblasts, and infiltrating immune cells (Steinhoff *et al.*, 2003). The release of these mediators is induced by a broad range of stressors and stimuli, including rosacea trigger factors such as UV radiation, heat, cold, microbial agents, or chemicals (including spicy food). The neuropeptide that has been shown to be dysregulated in rosacea is substance P (Powell *et al.*, 1993; Fimmel *et al.*, 2008; Kulka *et al.*, 2008). Substance P induces the production of TNF-α, IL-3, CCL2, CXCL9, CXCL10, CCL5, and CXCL8 in human mast cells (Kulka *et al.*, 2008). Hence, neuropeptide-induced mast cell activation in rosacea might support dendritic cell/macrophage precursor recruitment via CCL2, enhance T_H1 lymphocyte infiltration through CCL5, CXCL9, or CXCL10, and finally facilitate perifollicular neutrophil infiltration and pustule formation through the release of CXCL8.

INHIBITION OF EGFR-SIGNALING

In recent years, pharmacological EGFR inhibitors (EGFRI) have been successfully established in the targeted therapy of various cancer entities (Ciardiello and Tortora, 2008). Rosacea-like papulopustular eruptions (rash) are the most frequent adverse effects of EGFRI and occur in >90% of the treated patients (Lacouture, 2006; Gerber *et al.*, 2010b). Besides inflammatory papules and pustules, the rash is also characterized by additional features and characteristics of rosacea such as teleangiectasia, stinging, and burning, the presence of large numbers of dermal mast cells, a high density of *D. folliculorum*, or an aggravation by UV exposure, as well as therapeutic responses to systemic tetracyclines (TCN) or topical calcineurin inhibitors (Gerber *et al.*, 2010a, b, 2011a, b). Therefore, the EGFRI-associated rash is a probable pharmacological model of rosacea. In accordance with rosacea, cytokines and chemokines have a crucial role in the pathophysiology of EGFRI rashes. EGFRI induce the expression of cytokines such as IL-6 and IL-7, along with a set of chemokines, including CCL2, CCL3, CCL5, CCL18, XCL1, CXCL9, CXCL10, and CX_3CL1 (Mascia *et al.*, 2003; Pastore *et al.*, 2005; Lacouture, 2006).

REGULATION BY ANTI-ROSACEA DRUGS

TCN derivates such as doxycycline are well established in the treatment of papulopustular dermatoses such as acne vulgaris or rosacea for decades (Sneddon, 1966; Korting and Schollmann, 2009b). Herein, not the antibiotic but rather the immunomodulatory properties of TCN are regarded responsible for the therapeutic effects (Del Rosso, 2007). Notably, doxycycline in subantimicrobial doses (40 mg once daily) has been approved in the United States for the long-term treatment of rosacea for up to 12 months (Baldwin, 2007). The immunomodulatory effects of TCN are caused by the regulation of cytokines and chemokines to a large extent. A study by Shapira *et al.* (1996) demonstrates that TCN derivatives significantly impair the secretion of IL-1β and TNF-α in human monocytes. Recently, Bender *et al.* (2008)

could demonstrate that TCN derivatives dose dependently inhibit the release of CXCL8 and CXCL1, and to a smaller extent CCL2, in primary human dermal microvascular endothelial cells *in vitro*. Down this line, Eklund and Sorsa (1999) showed that TCN derivatives inhibited the production of CXCL8 in mast cells. Finally, TCN derivatives have been shown to affect the expression of IL-10 (Chung *et al.*, 2008). Besides their direct effects on chemokines and cytokines, antibiotics modulate the effects of a variety of rosacea trigger factors, thereby indirectly affecting the expression of cytokines and chemokines. In this line, TCN and metronidazole have been shown to impair the generation of ROS in neutrophilic granulocytes (Miyachi *et al.*, 1986; Akamatsu *et al.*, 1990; Sapadin and Fleischmajer, 2006; Golub *et al.*, 2008). Additional antibiotics that are applied in the management of rosacea and those that expose antioxidative properties include erythromycin and azithromycin (Jain *et al.*, 2002; Bakar *et al.*, 2007). Finally, metronidazole, which is regarded as a standard therapy for rosacea, has been shown to effectively reduce the density of *D. folliculorum*, thereby likely impairing a potential induction of NF-κB, IL-6, IL-7, CXCL8, IL-12, and IL-17 via TLR2 activation by conserved products derived from *D. folliculorum* (Kocak *et al.*, 2002; Schaller *et al.*, 2003).

CONCLUSION

Clearly, our current understanding of the involvement of cytokines and chemokines is insufficient and further systematic research is required. Nevertheless, a model for the cytokine and chemokine network of rosacea may be postulated by extrapolating from known clinical trigger factors and current pathophysiological concepts: external and internal trigger factors induce primary proinflammatory cytokines such as TNF-α and IL-1 family members through TLR2 signaling or other mechanisms (Figure 1). Subsequently, a first wave of chemokines is produced that leads to the recruitment of T cells into the perifollicular space. Given the histopathology of rosacea lesions that show an early recruitment of lymphocytes followed by neutrophil infiltration, it is conceivable that T_H1 or T_H17 cells are initially recruited. In turn, T cell-derived cytokines such as IL-17 or IL-22 may, together with UV radiation, activate keratinocytes to produce CXCL1 and CXCL8 and facilitate neutrophil recruitment. Interestingly, T_H17 cells preferentially express the chemokine receptor CCR6, and its specific ligand CCL20 is upregulated by UVB irradiation or TNF-α/IL-1 stimulation in keratinocytes. Simultaneously, IL-17 promotes angiogenesis via the induction of VEGF. Besides VEGF, the formation of the vascular phenotype observed on rosacea is likely to be supported by the chronic effect of other angiogenic mediators such as CCL2, CXCL1, or CXCL8. An interesting aspect for further research is the involvement of cytokines and chemokines in changes of the lymphatic vessel system seen in rosacea.

Taking into account the crucial role of cytokines and chemokines in a broad variety of physiological and pathological processes, the systematic analysis of the cytokine and chemokine network in rosacea is a promising step toward a better understanding of this disease, as well as the development of novel, mechanism-based therapies.

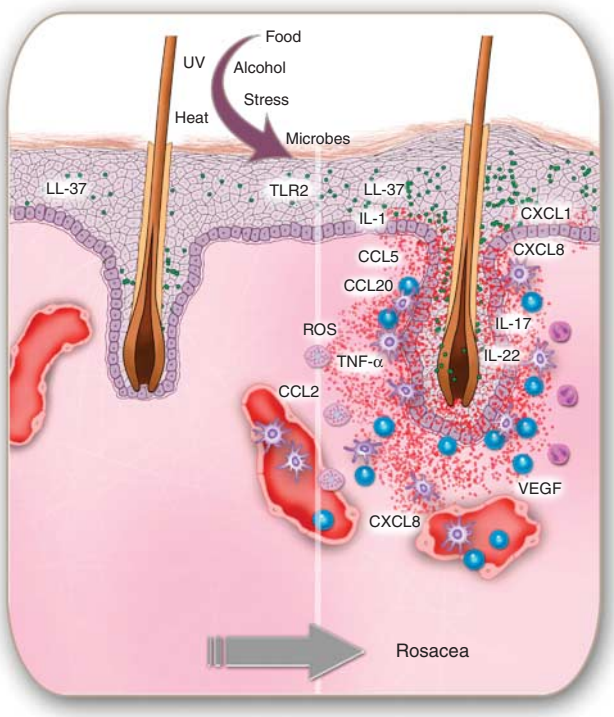

Figure 1. **Cytokines and chemokines are key effectors of rosacea trigger factors.** Rosacea trigger factors such as UV radiation, heat, spicy food, alcohol, stress, or microbes induce primary proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and IL-1 family members, as well as LL-37 through Toll-like receptor 2 (TLR2) signaling or other mechanisms. Subsequently, a first wave of chemokines is produced that leads to the recruitment of T cells into the perifollicular space. Subsequently, T cell-derived cytokines such as IL-17 and IL-22, together with UV radiation, activate keratinocytes to produce CCL20, CXCL1, and CXCL8. CCL20 attracts additional T-helper 17 (T_H17) cells, whereas CXCL1 and CXCL8 recruit abundant neutrophils, leading to the formation of pustules. Simultaneously, IL-17 promotes angiogenesis via the induction of vascular endothelial growth factor (VEGF). Additional angiogenic mediators include CCL2, CXCL1, CXCL8 and reactive oxygen species (ROS).

Conflict of Interest
The authors state no conflict of interest.
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