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New Insights into Rosacea Part I: Pathogenesis

Rosacea is a common, chronic inflammatory disease affecting the face whose incidence is around 3 % of the world population, affecting more likely women aged between 30 and 50.

Classification of rosacea, based on clinical features of flushing, non-transient erythema, papules, pustules and telangiectasia, includes four subtypes: erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea with one variant, granulomatous rosacea.

Possible factors responsible for rosacea are various and include autoimmune dysregulation, neurovascular disorders, exogenous factors such as sun exposure, heat and cold or stress, degeneration of connective tissue elements, functional disorders of the pilosebaceous unit, nutritional factors such as intake of alcohol or spicy foods, and infectious factors.

This paper is discussing these potential causative factors of rosacea, explaining how they can separately interfere with the occurrence and development of the disease, and which is the possible relationship between each other in order to constitute the particular clinical pattern of rosacea.

In conclusion, the pathogenesis of rosacea, a multifactorial skin disorder, is more and more elucidated but there is still a lack of investigations, which could permit to close the loop.

Key words

Rosacea, pathogenesis, epidemiology, classification.

Rosacea is a common, chronic inflammatory skin disease affecting the face. Although epidemiological data are scarce and controversial, its incidence is reported to be up to 3 % of the world's population [1]. Rosacea has long been named «Curse of the Celts» as it is thought to affect more likely individuals with phototypes I or II. However, we personally think that we should review this sentence, as rosacea is also very frequent in patients with phototype III. Rosacea usually affects people between the ages of 30 and 50, but may also be observed in children, although it is much less frequent in the paediatric population [2]. It is roughly three times more common in women than in men [3]. In men, rosacea tends to be more severe than in women and men have an increased tendency to develop phyma subtype [1]. Rosacea is characterized by a heterogeneous clinical picture characterized by transient flushing, persistent facial redness, telangiectasia, and inflammatory papules and pustules. Ocular changes and hypertrophy of the sebaceous glands, with subsequent fibrosis, may also be present [4]. Factors that exacerbate the disease, such as emotional stress, spicy foods, extreme high or cold temperatures, alcohol intake and sun exposure, are well defined. The course of rosacea will partly depend on the exposure to such factors, but is always unpredictable. Essentially, a person with rosacea will relapse from time to time while going through weeks, months or even years without a single symptom. However, if rosacea is left untreated, it will eventually worsen. As rosacea affects visually apparent areas of the facial skin, it can lead to self-abasement, depression, anxiety and social phobia [5]. Usually, rosacea's impact on quality of life is often underestimated by dermatologists [6].

Classification of rosacea

In 2002, the National Rosacea Society assembled a committee to develop a standard classification system that can serve as a diagnostic instrument to investigate the manifestations and relationships of the several subtypes and potential variants of rosacea [7].

To date, most physicians are following this classification system which is recognized worldwide. This system is based on morphologic characteristics, describing the primary features of rosacea and

defines four subtypes and one variant. The presence of one or more of the following signs with a central face distribution is indicative of rosacea [7]:

- *Flushing (transient erythema)*. A history of frequent blushing or flushing is common.
- *Non-transient erythema*. Persistent redness of the facial skin is the most common sign of rosacea.
- *Papules and pustules*. Dome-shaped red papules with or without accompanying pustules, often in crops, are typical. Nodules may also occur. Although patients with concomitant acne may exhibit comedones, comedones should be considered part of an acne process unrelated to rosacea [7].
- *Telangiectasia*. Telangiectases are common but not necessary for a rosacea diagnosis.

Secondary features include burning or stinging, plaque, dry appearance, edema, ocular manifestations, peripheral location and phymatous changes [7].

Subtypes as defined by the National Rosacea Society are as follows [7]:

Subtype 1: *Erythematotelangiectatic rosacea*
Erythematotelangiectatic rosacea is mainly characterized by flushing and persistent central facial erythema. The appearance of telangiectases is common but not essential for a diagnosis of this subtype. Central facial edema, stinging and burning sensations, and roughness or scaling may also be reported. A history of flushing alone is common among patients presenting with erythematotelangiectatic rosacea.

Subtype 2: *Papulopustular rosacea*
Papulopustular rosacea is characterized by persistent central facial erythema with transient papules or pustules or both in a central facial distribution. The papulopustular subtype resembles acne vulgaris, except that comedones are absent. Rosacea and acne may occur concurrently, and such patients may have comedones as well as the papules and pustules of rosacea. Burning and stinging sensations may be reported by patients with papulopustular rosacea. This subtype is often seen after or in combination with subtype 1, including the presence of telangiectases. The telangiectases may be obscured by persistent erythema, papules, or pustules, and tend to become more visible after successful treatment of these masking components [7].

Subtype 3: *Phymatous rosace*a
Phymatous rosacea includes thickening skin, irregular surface nodularities, and enlargement. Rhinophyma is the most common presentation, but phymatous rosacea may occur in other locations, including the chin, forehead, cheeks, and ears. This subtype is frequently observed after or in combination with subtypes 1 or 2. It affects more likely men than women.

Subtype 4: *Ocular rosacea*
The diagnosis of ocular rosacea should be considered when a patient's eyes have one or more of the following signs and symptoms: watery or bloodshot appearance, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, telangiectases of the conjunctiva and lid margin, or lid and periocular erythema. Blepharitis, conjunctivitis, and irregularity of the eyelid margins also may occur. Ocular rosacea is most frequently diagnosed when cutaneous signs and symptoms of rosacea are also present [7]. Approximately half of the patients experience skin lesions first, and a minority have both manifestations simultaneously [8]. Presence or suspicion of ocular rosacea must lead to a consultation with an ophthalmologist.

The same committee has only recognized one variant of rosacea, namely granulomatous rosacea [7], characterized by hard, yellow, brown, or red cutaneous papules or nodules that may be severe and lead to scarring. These lesions tend to be less inflammatory than papules and pustules and sit upon relatively normal-appearing skin. They can vary in size among patients but are monomorphic in each individual patient, and typically appear on the cheeks and periorificial areas. Granulomatous rosacea may occur in locations other than those in which the phymas are observed [7].

Classification of rosacea must be of major concern for the dermatologist: it will not only permit a harmonization, but also guarantee the lack of subjectivity of the practitioner at the time of evaluating the results of prescribed treatment.

Pathogenesis of rosacea

Possible factors responsible for rosacea are various and include autoimmune dysregulation, neurovascular disorders, exogenous factors, degeneration of connective tissue elements, functional disorders of the pilosebaceous unit, nutritional and infectious factors [4].

Autoimmune dysregulation

A dysregulation of the innate immune system in patients with rosacea is often suggested.

In innate immunity, the pattern recognition system, which includes the TLR (toll-like receptor) and NLR (nucleotide-binding domain and leucine-rich repeat-containing) families, respond to environmental stimuli such as UV, microbes, physical and chemical trauma [9]. Triggering the innate immune system normally leads to a controlled

increase in cytokines and antimicrobial molecules in the skin [10]. Some of these antimicrobial molecules are peptides known as cathelicidins. They feature a family of peptides ranging in size from 12 to 80 amino acid residues and have a wide range of structures. Some forms of cathelicidins are known to have a unique capacity to be both vasoactive and pro-inflammatory [10], both of these events forming part of rosacea symptoms. It was shown that individuals with rosacea expressed abnormally high levels of cathelicidins and the cathelicidins peptide forms found in rosacea patients were not only more abundant but were different from those in normal individuals11. The presence of the vasoactive and inflammatory cathelicidin peptides in rosacea was subsequently explained by abnormal production of local protease kallikrein 5 (KLK5), which controls the production of cathelicidin peptides in epidermis [11]. Injecting these peptides or the enzymes that produce cathelicidin into the skin of mice rapidly resulted in skin inflammation resembling pathological changes in rosacea [11] confirming the role of an abnormal expression of cathelicidins in rosacea skin. The normal innate immune system of the skin detects microbes, tissue damage such as UV-induced apoptosis, or damage of the extracellular matrix, all shown to trigger rosacea [12]. It was also shown that TLR2 expression was altered in rosacea skin, which enhances skin susceptibility to innate immune stimuli and leads to increased cathelicidin and kallikrein production [11, 13]. These findings and accumulated knowledge on rosacea suggest the innate immune response in rosacea has gone awry. For a variety of reasons these patients are more susceptible to stimuli that do not cause inflammatory reactions in normal patients. Innate immunity is triggered by the events commonly associated with worsening of the disease [9].

Neurovascular disorders

Neurovascular dysfunction is another aspect of the neural interactions and cutaneous vascular alterations that are thought to have a key role in rosacea pathophysiology, and is activated by trigger factors [14]. Most patients with rosacea report flushing episodes, thus leading to a common hypothesis that vascular hyper reactivity and increased blood flow play a role in the susceptibility to this disease. An increase in blood flow in skin lesions of patients with rosacea was reported [15, 16]. Factors such as emotional stress, spicy food, hot beverages, high environmental temperatures and menopause, which enhance flushing, also worsen rosacea. The increased vasculature response and persistent facial erythema in rosacea is of particular interest because of the increasing evidence that blood vessels and possibly lymphatic vessels have significant roles in the control of acute and chronic inflammatory disorders [17]. In inflamed skin, vessels remodel and become hyper permeable, blood flow is increased, which facilitates influx of inflammatory cells from chronic inflammation sites, but also leakage of proteins which will lead to edema. Increased expression of Vascular Endothelial Growth Factor (VEGF) receptors, both by vascular endothelium and infiltrating mononuclear cells, is observed in rosacea [18].

This may contribute to the vascular changes and cellular infiltration that occurs in rosacea, as VEGF proliferates vascular endothelial cells as well as increases permeability of vessels. Activation of precapillary arterioles by VEGF results in vasodilation (flushing, erythema), whereas activation of post capillary venules by the same leads to protein leakage (edema).

VEGF is also an inducer of angiogenesis and lymph angiogenesis, because it is a highly specific mitogen for endothelial cells [19]. This could explain the frequent occurrence of telangiectasia in rosacea. On the other hand, various pathways involved in vasodilation have been found to be significantly upregulated such as neuropeptides, tryptophan metabolites, lipids, or radical oxygen species [20]. Together, both vasodilation of blood vessels and lymphatic vessels as well as activation of vasoregulatory mediators and receptors play a significant role in rosacea.

Exogenous factors

We all know that a myriad of exogenous factors are susceptible of triggering rosacea.

Among them, hot or cold temperatures and sudden changes between cold and hot, or inversely, emotional stress, and mainly sun exposure.

How do such different factors influence rosacea?

First of all, sun radiation. Let's remember that sunlight is constituted by UV rays (UVA and UVB), visible light and infrared radiation (IR). Since the end of the eighties, thanks to experiments on hairless mice epidermis, it was known that a single exposure to near ultraviolet (> 320 nm) was capable of producing oxidative stress in the skin, including impairment of cutaneous catalase and glutathione reductase and decrease in cutaneous tocopherol, ubiquinone and ascorbic acid levels [21]. Furthermore, a decrease of levels of superoxide dismutase was reported in analogous experimental conditions [22]. These results were later confirmed, along with a simultaneous increase of cutaneous lipid hydroperoxides [23, 24]. We shall see later how reactive oxygen species can affect the skin of rosacea patients. UVB, particularly at

307 nm, is the most effective waveband for eliciting erythema in the human skin, which is a major symptom in rosacea. UVA (10 or 20 J/cm^2) and UVB (200 or 800 mJ/cm^2) light affected several inflammatory markers: an up-regulation of Interleukin-1β (IL-1β) and Interleukin-6 (IL-6) and decrease in Interleukin-10 (IL-10) were observed mainly after 4 hours [25], which explains how sun exposure may worsen the inflammatory component of rosacea. Of lesser energy than UVA, visible light (400—700 nm) accounting for approximately 50 % of the total solar spectrum, penetrates deeply into biological tissues and about 20 % reaches the hypodermis [26]. Similar to what is seen with UVA and UVB, irradiation of skin with visible light was reported to generate ROS following photon-induced activation of endogenous photosensitizers. To quantify the relative contribution of UVB, UVA and visible light to ROS generation, ex vivo skin explants were exposed to natural midday sunlight in the presence of a set of filters. Results estimated the generation of ROS at 4 % for UVB, 46 % for UVA and 50 % for visible light [27]. Visible light was also found to increase the release of pro-inflammatory cytokines from epidermal equivalents. IL-1a release was increased, such as IL-1 receptor antagonist, IL-6, GMCSF, and IL-8 [28]. Matrix Metalloproteinases (MMP) release was also increased after exposure to visible light, especially MMP-1 and MMP-9 [28]. IR has the lowest energy. However, its contribution to the solar spectrum reaching human skin is around 45 %.

Similar to UV radiation, the acute exposure of human skin to IR induces the production of ROS. The formation of ROS in the human skin following infrared-A (IRA) and near-infrared (NIR) irradiations was confirmed using electron paramagnetic resonance spectroscopy [29, 30].

IR irradiation has also heating action on the skin and tissues. An enormous increase in the ROS generation during IR irradiation, when the skin temperature exceeds 39 °C, was shown in ex vivo experiments [27]. The relative contribution of IRA to free radicals generation, in Berlin summer midday sunlight, has been estimated to be as high as one fourth of that of UV [27]. Sun exposure is known to cause a flushing response and appears to worsen the clinical symptoms of rosacea [31]. Mechanistically, in mice, UVB induces cutaneous angiogenesis that is histologically similar to the telangiectasia seen in rosacea histopathology [32]. Acute UV exposure of human skin is also known to induce angiogenesis, that is, to form new blood vessels, in human skin. These new vessels are immature and leaky, resulting in cutaneous inflammation by extravasation of inflammatory cells and by the inflammatory mediators produced by these cells [33]. As is the case with UVB, exposure of human skin to near-IR induces dermal angiogenesis and alters the balance between epidermal angiogenic factor (that is, VEGF) and endogenous angiogenic inhibitor (that is, Thrombospondin-2) [34]. In skin, epidermal keratinocytes are a major source of angiogenic factor VEGF and FGF2 (fibroblast growth factor 2, also known as basic FGF) [35]. UV-B increases VEGF and FGF2 secretion from human keratinocytes and expression in mouse epidermis [36]. This upregulation of VEGF was also observed with IR [34].

Another widely recognized triggering factor of rosacea is heat. Enhanced sensitivity to noxious heat stimuli in rosacea-affected skin, which was more prominent in the papulopustular rosacea group, was demonstrated [16]. The endoplasmic reticulum (ER), an interconnected network of flattened, membrane-enclosed sacs and cisternae contiguous with the nuclear envelope, is the major site of protein folding and processing, and functions as a dynamic calcium store, which responds to growth factors, hormones and many stimuli that perturb cellular energy levels, nutrient availability or redox status. The ER is a key site where extracellular and intracellular signals are sensed, integrated and transmitted, allowing coordinated repair or initiation of defence responses [37]. To avoid an overload of misfolded proteins accumulating in the ER, a condition referred to as ER stress, the unfolded protein response (UPR) has evolved as a repair mechanism that modifies the cell's transcriptional and translational programmes to cope with stressful conditions such as UV irradiation or heat shock [37]. Three protein sensors located in the luminal ER membrane sense misfolded proteins and initiate the UPR: inositol-requiring 1a (IRE1a), double-stranded RNA-dependent protein kinase (PKR)-like ER kinase (PERK) and activating transcription factor 6 (ATF6) [37].

The previously described angiogenic switch in human skin induced by infrared is partially mediated by heat [34]. In non-stressed cells, the ER chaperone BiP binds to the luminal domains of the ER stress sensors IRE1a, PERK and ATF6 maintaining them in an inactive state. However, during ER stress, BiP preferentially binds to misfolded proteins and due to its translocation activates the three ER sensors [37]. Thus, ER stress results in enhanced expression of the transcription factor ATF4 (2). The UPR can directly promote NF-κB activation, which enhances proinflammatory cytokine expression [37]. Furthermore, the UPR is associated with enhanced generation of reactive oxygen species (ROS) required for protein refolding processes [38]. ROS are important mediators of

inflammation and play a role in rosacea pathogenesis. Heat stress can alter innate immune responses by the generation of heat-shock proteins. Heat shock upregulates the expression of HSP70 as well as TLR2 and TLR4 associated with the activation of p 38 kinase and NF-κB, a reaction pattern resembling the UPR [39].

Cold is another commonly mentioned triggering factor of rosacea. Exposure to cold induces a stress response in microorganisms. Although it looks like paradoxical, cold shock stimulates a stress response in human epidermis altering the spectrum of proteins expressed and inducing the synthesis of heat shock proteins by keratinocytes [40]. Hence, cold or heat, we are in the presence of a similar mechanism which will culminate in an inflammatory pattern.

Degeneration of connective tissue elements

The major components of normal skin's connective tissue include collagen, elastic fibres, proteoglycans and other glycoproteins. Of these matrix proteins, collagen is the most prevalent, comprising 75 % of dermis dry weight [41]. Whilst these elements are produced by dermal fibroblasts, their regulation is under the control of proteases. Protease actions are at least partly responsible for rosacea histology. Serine protease kallikrein 5 (KLK5, also known as stratum corneum tryptic enzyme SCTE) was identified as the processing enzyme of cathelicidin and high KLK5 expression was found in rosacea skin [11]. KLK5 expresses in upper epidermis (granular to cornfield cell layer) in normal skin, and rosacea skin expresses KLK5 in the entire epidermis [9]. KLK5 digests corneodesmosome proteins desmocollin 1 and desmoglein 1 in epidermis, and is supposed to affect desquamation of epidermal keratinocytes [42]. KLK5 also efficiently digests the extracellular matrix components, collagens type I, II, III, and IV, fibronectin, and laminin [43]. Considering the high KLK5 expression in basal cells of rosacea epidermis, KLK5 could play a role in skin inflammatory reactions in rosacea by affecting dermal matrix and vascular remodeling [9]. Matrix metalloproteinases (MMPs) digest dermal matrixes such as collagens, fibronectin, elastin etc... and balances of MMPs and their inhibitor TIMPs dictate dermal components and vascular remodeling [44]. Tear fluid levels of MMP-8 were found to be elevated in ocular rosacea [45]. In granulomatous rosacea, the expression of MMP-9 was significantly increased in the dermis of lesions compared with non-granulomatous rosacea lesions, as well as MMP-2 expression [46].

Functional disorders of the pilosebaceous unit

The colonization of pilosebaceous units by Demodex folliculorum is thought to be one of the causative factors of rosacea. It will be further discussed in this paper. By the way, depending or not on this colonization, it was reported an abnormal fatty acid profile in patients with papulopustular rosacea (PPR) [47]. Myristic acid (C14 : 0) was present in greater concentrations in PPR sebum, while the long chain saturated fatty acids arachidic acid (C20 : 0), behenic acid (C22 : 0), tricosanoic acid (C23 : 0) and lignoceric acid (C24 : 0) as well as the monounsaturated fatty acid cis-11-eicosanoic acid (C20 : 1) were present in the sebum of patients with PPR in lesser concentrations as compared with controls. There is increasing evidence that sebaceous fatty acids play a role in the maintenance of skin barrier integrity, and this finding could have therapeutic implications for the development of sebum-modifying non-antibiotic treatments for patients with PPR.

Nutritional factors

Intake of alcohol, tea and coffee, spicy foods are all known triggers of rosacea.

It's well established that alcohol does not cause rosacea and that this condition is not the result of excessive drinking, but the popular perception is that it is. As a result, many rosacea patients suffer embarrassment and stigmatization because other people think their red nose and red face is caused by heavy drinking, even if they don't drink at all. Alcohol is just a trigger of rosacea. Alcohol induces a wide range of physiological derangements in the human body. Alcohol impairs the vasomotor centre of the brain, inducing peripheral vasodilatation. Hence, it has been suggested that this resultant cutaneous vasodilatation may exacerbate rosacea, contributing to the hallmark redness and flushing. Furthermore, one factor that has been suggested as playing a central role in many pathways of alcohol-induced damage, and which has been the focus of much research, is the excessive generation of ROS which can result in oxidative stress [49]. Many processes and factors are involved in causing alcohol-induced oxidative stress, including changes in the NAD+/NADH ratio in the cell as a result of alcohol metabolism, production of acetaldehyde during alcohol metabolism, which through its interactions with proteins and lipids also can lead to ROS formation and cell damage, damage to the mitochondria resulting in decreased ATP production, alcohol-induced oxygen deficiency (hypoxia), increase in the expression of cytokines, and effects on antioxidant enzymes and chemicals, particularly glutathione (GSH) and xanthine dehydrogenase [49].

Tea and coffee are also involved in the worsening of rosacea symptoms. Their common main active ingredient is caffeine, which is generally con-

sidered as a vasoconstrictor, and hence cannot worsen rosacea through this property. Furthermore, it was demonstrated that caffeine was an effective inhibitor of lipid peroxidation, at millimolar concentrations, against three reactive species, namely hydroxyl radical, peroxyl radical and singlet oxygen. The antioxidant ability of caffeine was similar to that of the established biological antioxidant glutathione and significantly higher than ascorbic acid [50]. Hence, it could not be damageable in rosacea, all the contrary. The reason seems to be other than the caffeine content of these beverages, and more likely be the temperature of the same. In an interesting study [51], Wilkin gave volumes of 180 ml of coffee at 60 °C, water at 60 °C, coffee at 22 °C and caffeine 200 mg with 180 ml water at 22 °C to 24 volunteers with erythematotelangiectatic rosacea. Flushing, defined as the objective reddening of the face accompanied by an increase in both the malar skin temperature and the malar thermal circulation index was investigated. No significant change was observed in these values after intake of coffee at 22 °C and caffeine 200 mg with 180 ml water at 22 °C nonetheless a significant increase with coffee at 60 °C and water at 60 °C. Flushing provoked by hot water was similar to that caused by hot coffee. It was concluded that the heat, and not the active ingredients of coffee, is the provocative principle of flushing when ingesting hot coffee. In coffee or tea at 60 °C it is heat and not caffeine that leads to the flushing reaction, obviously by liberation of heat shock protein when the hot beverage enters in contact with the oral mucosa.

Spicy food owes its characteristic to the use in the recipe of black, white, pink or green peppers, or chili peppers. Whilst pepper contains piperine, chili pepper contains capsaicin.

The pungency of capsaicin and piperine is caused by activation of the heat- and acidity-sensing Transient receptor potential vanilloid 1 (TRPV1) ion channel on nociceptors [52].

TRPV1 is widely expressed on primary sensory neuron endings and non-neuronal cells such as keratinocytes [53]. They are deeply involved in the pathophysiology of rosacea due to their polymodal activation, including cold and hot temperature, pungent products from vegetable and spices, reactive oxygen species, and mechanical stimuli [53].

Chemical factors

Rosacea skin is easily irritated by various skin irritants such as sodium lauryl sulphate and the acute irritant threshold in facial rosacea skin correlates with barrier function [54]. Components of terminal differentiation and epidermal barrier repair are signalled by ER stress via the release of ER calcium stores in the stratum granulosum [55]. Skin barrier perturbation has been associated with keratinocyte calcium depletion activating the ER stress response via induction of the transcription factor XBP1 [55]. Thus, there is substantial evidence for an intimate crosstalk between barrier homeostasis and the ER stress response in rosacea skin.

This explains its frequent intolerance to various chemical factors.

Stress

Psychological stress promotes flushing and exacerbation of rosacea and people with severe rosacea are anxious about the social consequences of blushing and generally prefer to avoid situations that might involve scrutiny by others [56]. The cutaneous nervous system is multifunctional and regulates various physiological and pathophysiological mechanisms including cell growth and differentiation, immunity and inflammation as well as tissue repair [57]. Both classical neurotransmitters such as catecholamines and acetylcholine and neuropeptides including substance P, calcitonin gene related peptide (CRGP), vasointestinal peptide (VIP) or proopiomelanocortin (POMC) derived peptides such as α melanocyte stimulating hormone (αMSH) may be released from sensory or autonomic nerve fibres and several epidermal as well as dermal cells [57]. Common symptoms of rosacea are vasodilation, flushing, increased skin sensitivity and lower pain threshold are caused by neuromediators, and for this reason the involvement of skin's nervous system can be anticipated [16]. Neuroinflammatory mediators involved in rosacea include transient receptor potential (TRP) ion channels of vanilloid type (TRPV), which can be activated by many trigger factors of the disease [58]. Dermal immunolabelling of TRPV2 and TRPV3 and gene expression of TRPV1 appeared to be significantly increased in erythematotelangiectatic rosacea [58]. Papulopustular rosacea displayed an enhanced immunoreactivity for TRPV2, TRPV4, and also of TRPV2 gene expression. In phymatous rosacea-affected skin, dermal immunostaining of TRPV3 and TRPV4 and gene expression of TRPV1 and TRPV3 is enhanced, whereas epidermal TRPV2 staining is decreased [58]. Thus, dysregulation of TRPV channels also expressed by non-neuronal cells may be critically involved in the initiation and/or development of rosacea [58]. The neuronal TLRs expressed on peripheral nerves are new players in the processing of pain and itch by increasing the excitability of primary sensory neurons [59], thus linking neuronal TLR signalling to the ER stress response.

ROS and rosacea

It was shown that in the mild involvement phase of rosacea patients, superoxide dismutase activity was stimulated to protect the skin against reactive oxygen species so that the malondialdehyde (MDA) levels were maintained. In contrast, in more severe disease, due to a decrease in the capacity of the antioxidant defence system, the MDA levels were increased, supporting the «antioxidant system defect hypothesis» in rosacea patients [60]. This hypothesis was confirmed by findings that the plasma MDA levels were higher and antioxidant potential (AOP) levels were lower in patients with rosacea than in controls, regardless of the severity of the disease [61, 62]. Inhibition of ROS generation in neutrophils by tetracyclins [63], azelaic acid [64], metronidazole [65], and retinoids [66], which are used for rosacea treatment, also support the hypothesis of ROS involvement in rosacea pathology. Although the precise localization of ROS activities is not determined in rosacea skin, the source of ROS would probably be infiltrated leukocytes and epidermal keratinocytes [9]. It was demonstrated that H_2O_2 increases macrophage VEGF through an oxidant induction of VEGF promoter. This oxidant stimulation can be mediated by activated neutrophils [67]. More globally, ROS derived from NAD(P)H oxidase, especially superoxide anion, were shown to be critically important for VEGF signalling in vitro and angiogenesis in vivo [68]. It was also reported that oxidative stress mediates chemical hypoxia-induced injury and inflammatory response through activation of NF-κB-COX-2 pathway in HaCaT cells, with an oversecretion of proinflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) [69]. On the other hand, evidence was provided that H_2O_2 is an important intermediate in the downstream signalling pathway finally leading to the induction of increased steady state MMP-1 mRNA levels, which contributes to connective tissue damage [70]. ROS also result in a dose-related increase in the level of MMP-2 mRNA and a decrease in the level of TIMP-2 mRNA in human dermal fibroblasts [71]. Thus, increased ROS activity in skin would enhance inflammatory reactions and degenerate collagens and matrix in dermis.

Infectious factors

Here is the heart of an already ancient debate which is still not completely elucidated.

From 1994 onward, the potential role of *Helicobacter pylori* in rosacea was under scrutiny.

H. pylori, a helical gram-negative bacteria that reside in the stomach, is one of the most common human pathogens, likely infecting more than 50 % of the general population [72]. Although a majority of individuals are asymptomatic, *H. pylori* is recognized as a causative factor of chronic gastritis, peptic ulcers, and gastric cancers [73]. *H. pylori* seropositivity has been linked with rosacea [74]. Since this first publication of a possible association between *H. pylori* and rosacea in 1994, a wealth of controversial literature has equally confirmed and refuted this hypothesis (see Holmes [75] for more details). Similarly, studies evaluating the efficacy of *H. pylori* eradication therapy in rosacea have met with conflicting results [75]. Because antibiotic therapy is a common treatment for both PPR and *H. pylori* infection, some results may be easily confounded. Mechanisms of *H. pylori*-induced rosacea have been proposed, which include triggering of inflammation by *H. pylori* cytotoxins and gastrin-induced flushing [76]. In summary, to date there is no substantial evidence that rosacea symptoms occur or may be aggravated in response to *H. pylori*.

Demodex folliculorum is another, longer and more sophisticated story

Demodex belongs to the class of arachnids (Arachnida), the scab mites subdivision (Acarida) and the hair follicle mites family (Demodiacidae) The name Demodex comes from the combination of two Greek words: demos (skin) and dex (worm) [77]. They occur in mammal hair follicles, sebaceous glands and eyelid glands. They may evoke demodecosis in both humans and animals, the course of which is chronic [78]. The two kinds of Demodex mites that have been identified in humans (*Demodex folliculorum* and *Demodex brevis*) commonly appear in seborrheic areas of the facial skin (the forehead, chin, and around the eyes and mouth). They are also observed on the pileous skin of the head, on hairy chests or in the genital area [79]. Demodex mites are white or yellow in colour, and have an elongated oval shape that narrows towards the rear [77]. The mites' developmental cycle lasts 3—4 weeks.

Demodex folliculorum is 300—400 μm long and feeds on sebum, lymph, plasma and epithelial cells [77]. Demodex occurs all over the world in almost all human races, and about 80—90 % of the human population is infected with Demodex; however, *D. folliculorum* is more often found in females than in males [77]. This story started in 1932, when Brodie evoked for first time a potential role of Demodex in rosacea [80]. Demodex mites were originally perceived to be commensals, having a symbiotic relationship with the human host. This is supported by the fact that the extent of Demodex colonization in the human population is high (80—90 %), reaching 100 % in elderly people [81].

Mite density starts to rise in the sixth decade of life and stays at the same level until the eighth decade of life [81]. Contrarily, mite density is very low in young adults, even though their levels of sebum production, a potential source of food for mites, are very high [82]. Patients with papulopustular rosacea produce sebum with an altered fatty acid profile, suggesting that the nature of the sebum, rather than its quantity, may favour the development of Demodex mites [47]. Due to the fact that Demodex mites are commonly found in healthy individuals and the density of mites is generally low, the presence of mites on the skin in rosacea is not enough to suspect its pathogenicity.

The mean density of Demodex mites on the skin of rosacea patients is 10.8 mites per cm^2 in comparison to 0.7 mites per cm^2 in healthy people. However, when all types of rosacea are taken into account, statistically larger mite densities per cm^2 are found in cases of papulopustular rosacea [83]. In a study conducted in patients with papulopustular rosacea, the presence of *D. folliculorum* in follicle secretions was found in 90.2 % of patients and only 11.9 % of control samples. Additionally, histopathological examination of skin obtained from these patients revealed that the presence of Demodex mites was connected with severe perifollicular lymphocytary infiltration [84]. It seems that the presence of Demodex mites within the skin is more important than their presence on the skin and dermal symptoms occur when mites residing in hair follicles penetrate into the surrounding tissues [85]. Meanwhile, there is absolutely no objective reason for considering Demodex as a primary pathogenic factor in rosacea, it is most probable that its pathogenicity starts with the increase of its density in the skin [86]. This increased mite density may play a role in the pathophysiology of rosacea by triggering inflammatory or specific immune reactions, mechanically blocking the follicles [87], leading to distension and causing intrafollicular hyperkeratosis [88]. It was also suggested that the waste products of Demodex mites and/or associated bacteria may activate the elements of innate immune system or stimulate the immune system through the mechanism of delayed hypersensitivity reaction [89]. Based on the fact that clinical improvement is noted in patients with rosacea who are administered tetracycline antibiotics, and that the latter have no activity on Demodex, it was hypothesized that Demodex could be a vector for some microorganisms that cause and aggravate skin lesions [90]. The bacteria *Bacillus oleronius* was once isolated from a Demodex mite, obtained from a patient with papulopustular rosacea [91]. The species features an endosporic Gram-negative bacterium (*genus Bacillus*, family *Bacillaceae*) and was shown to produce proteins capable of stimulating peripheral blood mononuclear cell proliferation in 16 out of 22 (73 %) patients with papulopustular rosacea compared to only 5 out of 17 (29 %) in control patients [91]. The sera of patients with papulopustular rosacea was found to react to two antigens isolated from the bacterium which bear similarity to the heat-shock proteins [91].

In another study, there was a significant correlation between serum immunoreactivity to these two proteins derived from *B. oleronius* and facial rosacea, lid margin inflammation and ocular Demodex infestation [92]. In a subsequent work, neutrophils exposed to proteins from *B. oleronius* demonstrated increased levels of migration and elevated release of matrix MMP-9, an enzyme known to degrade collagen, and cathelicidin, an antimicrobial peptide. In addition, neutrophils exposed to the bacterial proteins demonstrated elevated rates of interleukin 8 and tumour necrosis factor-α production [93], suggesting that this bacteria may play a role in the inflammatory erythema associated with rosacea. If this occurs in vivo it would lead to inflammation and tissue degradation in the vicinity of the pilosebaceous unit, which is often the case.

Recently, neutrophils activated by *B. oleronius* proteins were shown to display increased levels of IP1 production, F-actin formation, chemotaxis, and production of the pro-inflammatory cytokines IL-1β and IL-6 following stimulation by *B. oleronius* protein preparations. In addition, the same neutrophils demonstrated increased release of internally stored calcium (Ca^{2+}), a hallmark of the IP3 pathway of neutrophil activation. Thus, neutrophils play a significant role in the inflammation associated with rosacea [94]. In patients with erythematotelangiectatic rosacea, serum reactivity to the 62 and 83 kDa *B. oleronius* proteins was found in 82.6 % but only in 26.9 % of controls, and in those rosacea patients whose sera reacted to *B. oleronius* proteins, the level of sebum was statistically lower than in controls. The density of *D. folliculorum* on the face of *Bacillus* positive rosacea patients was statistically higher than controls, suggesting a potential role for this bacterium in the aetiology of rosacea [95].

Staphylococcus epidermidis is another potential bacteria which has been isolated from the pustules of patients with papulopustular rosacea, whereas this bacterium was not detected on unaffected areas of the skin [96]. *Staphylococcus epidermidis* is a Gram-positive bacterium, and one of over 40 species belonging to the genus *Staphylococcus*. It is part of the normal human flora, typically the skin microbiota. In rosacea, facial erythema and increa-

sed blood flow in the skin causes the temperature of the skin to become elevated and interestingly, it was found that S*taphylococcus epidermidis* isolated from patients with rosacea was consistently beta-haemolytic, whereas that from control subjects were non-haemolytic and isolates from patients with rosacea secreted more proteins, and generally more of each protein at 37 °C compared with 30° C [97].

A possible role for *Propionibacterium acnes* was also discussed, probably because of some symptomatic similarities between acne and rosacea. Facial skin biopsies from rosacea patients and controls were stained with a *P. acnes*-specific monoclonal antibody and only 8.5 % of patients tested positive for *P. acnes* suggesting that *P. acnes* does not play a major role in the pathogenesis of rosacea [98].

Conclusion

Twenty years ago, we used to tell that the exact pathogenesis of rosacea was unknown, even if we had several hypothesis for explaining it, but none was definitely demonstrated. To date, our knowledge has evolved, and even if the loop has not yet been completed, we are closer and closer to a definitive explanation. Obviously, rosacea is a multifactorial disease where autoimmune dysregulation is implicated, and where the increased presence of the vasoactive and inflammatory cathelicidin peptides in rosacea skin was subsequently explained by abnormal production of local protease kallikrein 5 (KLK5), which controls the production of cathelicidin peptides in epidermis [11]. This could partly explain the vascular hyper reactivity and increased blood flow observed in rosacea where abnormally increased expression of VEGF also plays a key role. Sun exposure, known to be a major triggering factor in rosacea is also in favour of this increased expression of VEGF and worsening of symptoms.

The increased production of ROS and proinflammatory cytokines after sun exposure explains the worsening of inflammatory component of rosacea in this case. Heat and cold, also well-known triggering factors in rosacea, are responsible of the expression of heat shock protein, which provokes a reaction pattern resembling the UPR39, enhancing proinflammatory cytokine expression [37]. A similar mechanism can explain the triggering role of hot drinks such as coffee or tea. The negative role of alcohol can be easily explained by the increase of vasodilation, but also augmented expression of ROS. The dysregulation of TRPV channels is at least partly responsible for the worsening effect of intake of spicy food and stress in rosacea. Whilst the role of *H. pylori* is more and more disregarded in the pathogenesis of rosacea, more is known about the potential mechanism of action of *D. folliculorum*. Besides an activation of the elements of innate immune system and/or stimulation the immune system through the mechanism of delayed hypersensitivity reaction [89] caused by this mite, it seems that *D. folliculorum* is a vector for some microorganisms that cause and aggravate skin lesions [90]. *B. oleronius* and *S. epidermidis*, but not *P. acnes* are interesting targets. *B. oleronius* was shown to increase the levels of migration of neutrophils and the release of matrix MMP-9, an enzyme known to degrade collagen, cathelicidin, and proinflammatory cytokines [93]. All these are interesting issues for further investigations to warrant these hypothesis and complete the circle.

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Нові погляди на розацеа
Частина 1. Патогенез

Розацеа — хронічне запальне захворювання, що уражує шкіру обличчя близько 3 % популяції земної кулі. Найчастіше хворіють жінки віком 30—50 років.

Класифікація розацеа ґрунтується на клінічних особливостях гіперемії, еритеми, папул, пустул, телеангіектазії і містить чотири підтипи: еритематозно-телеангіектазійний, папуло-пустульозний, фімарний та очний (окулярний) з варіантом гранулематозного розацеа.

До можливих факторів, що провокують розацеа, належать: автоімунна дисрегуляція, нервово-васкулярні розлади, екзогенні чинники, наприклад, вплив сонця, тепло, холод або стрес, порушення елементів сполучної тканини, функціональні розлади пілосебаційного комплексу, такі чинники харчування, як алкоголь або гостра їжа, інфекційні чинники.

У статті обговорюються причини розвитку розацеа, пояснюється їх окремий вплив на появу й розвиток захворювання, визначаються можливі зв'язки між ними, які призводять до специфічної клінічної моделі розацеа.

Стосовно патогенезу розацеа розглядається як мультифакторне шкірне захворювання, однак на сьогодні це питання до кінця не вивчено.

Ключові слова: розацеа, патогенез, епідеміологія, класифікація.

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Новые взгляды на розацеа
Часть 1. Патогенез

Розацеа — хроническое воспалительное заболевание, поражающее кожу лица около 3 % популяции земного шара. Чаще всего болеют женщины в возрасте 30—50 лет.

Классификация розацеа основана на клинических особенностях гиперемии, эритемы, папул, пустул, телеангиэктазии и включает четыре подтипа: эритематозно-телеангиэктазийный, папуло-пустулезный, фимарный и глазной (окулярный) с вариантом гранулематозного розацеа.

Возможные факторы, провоцирующие розацеа, включают аутоиммунную дисрегуляцию, нейроваскулярные расстройства, экзогенные факторы, например, контакт с солнцем, тепло, холод или стресс, нарушения элементов соединительной ткани, функциональные расстройства пилосебацейного комплекса, такие факторы питания, как алкоголь или острая пища, инфекционные факторы.

В статье обсуждаются причины развития розацеа, объясняется их отдельное воздействие на появление и развитие заболевания, определяются возможные связи между ними, которые приводят к специфической клинической модели розацеа.

В плане патогенеза розацеа рассматривается как мультифакторное заболевание кожи, однако на сегодняшний день этот вопрос до конца не изучен.

Ключевые слова: розацеа, патогенез, эпидемиология, классификация.

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