The potential role of microorganisms in the development of rosacea

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Summary
Rosacea is a chronic cutaneous disorder characterized by centrofacial persisting erythema, telangiectases, papules, pustules, edema, phymas and ocular involvement. Despite being one of the most common skin disorders, its pathogenesis remains unclear and controversial. Although the disease triggering factors are well recognized, the underlying causes of rosacea have not yet been identified. Several different postulates about its pathogenesis can be found in the medical literature. Abnormalities of the pilosebaceous unit, as well as genetic, vascular, inflammatory, environmental and microbial factors have been described. The microorganisms that have been associated include *Helicobacter pylori, Demodex folliculorum, Staphylococcus epidermidis,* and *Chlamydia pneumonia*; all the studies have been inconclusive. We review currently available scientific data on the potential pathogenetic role of microorganisms in the development of rosacea.

Introduction and Epidemiology

Rosacea is one of the most common dermatoses, accounting for almost 1 % of all the skin disorders diagnosed by dermatologists [1]. It affects primarily adults of 30–60 years of age, with women being more often affected, especially in the earlier disease stages [2]. Rosacea is diagnosed on clinical manifestations and specific morphologic characteristics; there is no laboratory test to confirm the diagnosis.

Clinical features and classification

Either a single or a clustering of signs such as flushing, persistent erythema, telangiectasia, papules, pustules and phymas with a centrofacial distribution is present. Additionally, eye involvement with blepharitis, iritis and conjunctivitis occurs in a considerable percentage [3]. Four subtypes of the disease have been recognized: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous and ocular [1, 3, 4]. Erythema has been proposed as the main morphological feature [5] with all the other manifestations having a supportive role towards the diagnosis and designation of disease subtype [5]. Disease classification is of great importance due to the fact that the pathogenetic mechanisms described in the literature relate to specific forms of the disease and the therapeutic interventions are different amongst the described subtypes.

Etiology and Pathogenesis

There are several different factors implicated in the pathophysiology of rosacea. Inherent abnormalities in the cutaneous vascular and lymphatic system and inappropriate responses to hyperthermia are mechanisms described as responsible for flushing [4, 5]. Solar radiation is also implicated through the destruction of cutaneous blood vessels and dermal connective tissue [4–7]. The presence of elastotic granulomas is a common histological finding in rosacea patients and rosacea appears mostly in sun exposed areas. These facts indicate that there is a link between chronic sun exposure, solar degenerative elastosis and disease development [7]. There is also the dermal matrix degeneration theory suggesting that the disease manifestations are due to the poor connective tissue support for the facial vessels [5]. Dietary agents and drugs have also been implicated as triggering factors inducing disease flares, however the pathophysiological association is not clear [5]. Abnormalities of the

pilosebaceous units have also been described in a considerable percentage of patients [8].

The role of microorganisms in the development of rosacea has been addressed in a variety of studies, but clear evidence for their pathogenic role in rosacea has not been demonstrated.

Helicobacter pylori

Helicobacter pylori has been presented as one of the potential causative factors, but the studies performed to date remain controversial. The pathogenetic mechanism through which *H. pylori* could be involved in rosacea has not been identified. It is proposed that the bacterium, through the production of specific cytotoxins and the release of vascular mediators such as histamine, prostaglandins, leukotrienes and cytokines might be the triggering factor for the development of rosacea, but robust evidence is lacking [5, 9]. There are no specific histological features identified in the patients in whom *H. pylori* is found [7].

The prevalence of *H. pylori* in rosacea patients is presented as being higher than in the healthy population in many studies [10–14], while other studies suggest that there is no substantial difference [15–17]. Powell et al. in 1992 found higher anti-Hp antibody levels in rosacea patients [10]. Szlachcic et al. examined the prevalence of gastric *H. pylori* infection in rosacea patients [11]. In this study, 67 % of the rosacea patients had strains of *H. pylori* which were positive for a known virulence factor cytotoxin-associated gene A (CagA), while only 32 % of patients with non-ulcer dyspepsia (NUD) had CagA positive strains [11]. Such correlation has been demonstrated also in the study of Argenziano et al. where the anti CagA antibodies were present in 75 % of patients with both rosacea and gastric symptomatology [12]. In this study serum IgG and anti IgA anti-Hp antibodies were evaluated and it was shown that IgG antibodies were detected in 81 % of the patients with rosacea and dyspepsia [12]. Both studies concluded that rosacea is associated with various gastrointestinal symptoms and is related to gastritis with *H. pylori* expressing CagA and elevated plasma levels of TNFα and IL-8. They suggest that rosacea could be an extragastric manifestation of *H. pylori* infection mediated by bacterial cytotoxins and cytokines [11, 12]. In 2002 Szlachcic demonstrated that there was a statistically significant greater prevalence of *H. pylori* in patients with rosacea [13]. In 2004 Baz et al. showed that in the rosacea population studied the seropositivity was higher for IgM and lower for IgG antibodies against *H. pylori* compared to controls, concurring with the previous findings that the *H. pylori* infection rate is higher in rosacea population [14]. The same study detected increased level of malondialdehyde (MDA) and decreased antioxidant potential (AOP) in the rosacea group, demonstrating that these patients have increased reactive oxygen species (ROS) activity. These findings did not correlate to the seropositivity to *H. pylori* and the authors conclude that rosacea is an oxidative stress condition related to deficient function of the antioxidant system, regardless of *H. pylori* infection [14]. This statement though needs to be supported by further studies.

Schneider et al. (1992) found no statistical difference in *H. pylori* infection prevalence in rosacea patients [15]. This was also the case in the study performed by Son et al. in Korean patients [16] and in the more recent study performed by Herr et al. the difference in anti-Hp antibodies was again not significant between the two groups [17]. Bonamingo et al. suggested that no differences appear in the frequency of *H. pylori* exposure in rosacea patients. However, they speculated that the previous systemic use of antibiotics could lead to incorrect conclusions regarding the differences in disease prevalence [18]. Our study also demonstrated no significant differences in the prevalence of anti-Hp antibodies, but, after stratification according to the prior use of antibiotics, the results were modified suggesting a strong association between *H. pylori* and rosacea in the population not previously treated with antibiotics [6, 19]. Gurer et al. found that although in the population they studied the seropositivity of anti-Hp antibodies was higher in the rosacea group, nitric oxide serum levels were normal [20].

Despite exhaustive studies the seroprevalence of anti-*H. pylori* antibodies remains a point of controversy. Helicobacter pylori infection is one of the most common infections in humans [21] and thus it is our belief that all the variables that have been proven to control its prevalence would need to be taken into consideration in order to identify the association with rosacea. The same controversy also lies with the association of the eradication of *H. pylori* and rosacea's clinical improvement [19, 22–24]. There are studies supporting the therapeutic effect in rosacea after *H. pylori* eradication [23–25] and other studies that demonstrate no relation of the eradication of *H. pylori* with the clinical improvement of skin lesions [22, 26]. A factor that needs to be taken into consideration is the efficacy of metronidazole in rosacea as well as in *H. pylori* eradication.

In conclusion we believe that based on all the studies to date, due to the high prevalence of anti-Hp antibodies in humans in conjunction with the fact that the antibiotics are effective for both disease entities, it would be very difficult to stratify the population studied against all factors that influence both rosacea and *H. pylori* infection. Thus, these studies remain inconclusive and do not help towards the development of the best therapeutic approach for these patients.

Demodex folliculorum

Demodex folliculorum is also implicated in the disease pathogenesis by several publications. *Demodex* is found in a very large number of the general population; with recent sensitive techniques the prevalence approaches almost 100 % [5]. Therefore only the identification of the mite in rosacea patients adds no value towards the proof of its pathogenetic role. *Demodex*-specific antibodies were detected only in 22 % of 31 rosacea patients in a study performed by Grosshans et al. [27]. Several studies suggest that the mean density of mites in the pilosebaceous units as well as their extrafollicular deposition are correlated with the pathogenesis of rosacea [1, 5, 6, 28, 29]. In our study, performed in the northern Greek population, we identified significantly higher density of *Demodex* in the rosacea patients, in comparison not only to healthy controls but also to patients with discoid lupus erythematosus and acne group [6]. Other studies also have demonstrated that the density of the mites in the rosacea population is higher than in the age-matched healthy individuals, although this observation is not valid for the telangiectatic disease, but only for the papulopustular form [5]. A

density of more than 5 mites per follicle or 5 mites per cm^2 has been considered to be pathogenic [28]. Perifollicular lymphohistiocytic inflammation linked with *Demodex* was observed by Forton in 69 rosacea specimens [30]. In another study Forton et al. suggest that in patients with papulopustular rosacea the density of *Demodex* is very rarely normal and this density is higher as visible immune reaction is lower [29]. Aroni et al. detected increased numbers of *Demodex* density in 35 % of rosacea patients, even though 54 % of these had neither perifollicular inflammation nor penetration into the dermis [7].
The pathogenic mechanisms involved include stimulation of the immune response, hair follicle blockage and foreign body granulomatous reaction to the mites and their products [28]. Based on all these studies, we can therefore speculate that *Demodex* represents a contributing cofactor to the inflammatory reaction seen in rosacea.

Mite-related Bacteria

Another theory suggests that *Demodex* mites can act as vectors for other pathogenetic microorganisms [28, 31]. Bacterial endosymbionts could indeed play an important role and this can explain the therapeutic effects of antibiotics in these patients [1]. The study performed by Borgo et al. to assess the occurrence of *Wolbachia* in *Demodex* mites, failed to demonstrate any association of this endosymbiont with the human mites [31]. *Bacillus olenorium*, another bacterium found in *Demodex*, has been linked with the initiation of the inflammatory response in rosacea patients through the production of antigenic proteins [32]. The inflammatory process about the centrofacial pilosebaceous units seen in papulopustular rosacea can be explained by the fact that the density of *Demodex* mites and thus of the associated bacterial agents such as *B. olenorium* is higher in these areas [1, 28, 29, 31]. It is hypothesized that the accumulation of the mites in the follicles causes their distension and damage allowing diffusion of bacterial agents through the follicular wall, thus resulting in the immune response around the pilosebaceous units [32]. Further research is required towards this direction.

Staphylococcus epidermidis

Staphylococcus epidermidis has also been described as a potential causative microorganism in a study performed by Dahl et al. in 2004 [33]. Still, cultures performed from rosacea pustules failed to isolate bacteria and *S. epidermidis* can be considered a contaminant since it is a normal inhabitant of human skin.

Bacterial Toxins

Bacteria grow at different rates in different temperatures producing different toxins [34]. As Dahl et al. described, the temperature in rosacea patients is higher than the healthy population [33]. Difference in the bacterial behavior in higher temperatures could lead to the production of the papules and pustules seen in rosacea. *S. epidermidis* strains isolated from rosacea patients were consistently β-hemolytic in contrast with the control group; the proteins produced by this strain are different at 37° C. Lipase levels have been higher in rosacea patients and it is postulated that not only the nature but also the amount of these proteins play a role in the disease development. As suggested by the authors, other strains of the facial skin microflora, such as *Demodex* and symbionts or yeasts such as *Malassezia ovalis* might be involved in the inflammatory process through this mechanism. However, this study only lays the grounds for further research into this direction.

Chlamydia pneumoniae

Chlamydia pneumoniae have been suggested as potential causative agents of rosacea by a study performed by Fernandez-Obregon and Patton [35]. *C. pneumoniae*-antigen was detected in 4 out of 10 and serum antibodies against *C. pneumoniae* were detected in 8 out of 10 rosacea patients. Patients were treated successfully with azithromycin. This is only a preliminary study and the possible involvement of *C. pneumoniae* in rosacea needs to be investigated more.

Intestinal bacteria

Small intestinal bacterial overgrowth (SIBO) was demonstrated to have greater prevalence in rosacea patients and its eradication led to skin lesion improvement [36, 37]. Additionally, in rosacea patients who were SIBO negative the antibiotic therapy had no effect on the skin lesions [36]. The clinical effectiveness of SIBO eradication in rosacea suggests that these bacteria might play a role in the pathogenesis of rosacea lesions as well, but not enough evidence has been provided yet.
Intestinal bacteria that are involved in the pathogenesis of inflammatory bowel disease (IBD) are also hypothesized to play a role in rosacea through the development of neurogenic inflammation [38]. Kendall has described a case of a patient without digestive tract disease who experienced complete remission of his rosacea after treatment for reduction of the gut transit time below 30 hours [39]. Intestinal bacteria can activate plasma kallikrein-kinin system (PKKS) and it is of interest that rosacea patients consistently demonstrate an activation of PKKS [38]. The possible involvement of intestinal bacteria in the pathogenesis of rosacea would also explain why metronidazole is efficacious in both rosacea and IBD, but the data available are currently inadequate to prove this hypothesis.

Antimicrobial peptides

Changes of the proteolytic balance of the skin lead to a reduced epidermal barrier function [40]. Proteases, their inhibitors and target proteins may contribute to the inflammatory responses seen in rosacea. Increased serine protease activity and cathelicidin promote skin inflammation in these patients [39]. The proteolytic imbalance can be caused by exogenous proteases, such as dust mite or microbial proteases, leading to the hypothesis that these proteins could play a role in rosacea pathogenesis [40]. Antimicrobial peptides (AMPs) constitute a primary system for protection against microbial invasion [41]. Cathelicidins belong to this group and their dysfunction could be one of the factors leading to the rosacea inflammatory response [41]. One of the cathelicidin peptides (LL-37) induces the production of cytokines in keratinocytes, chemotaxis, and angiogenesis [41]. Rosacea patients have abnormally high levels of cathelicidin (LL-37) and thus the increased AMP production along with their dysfunction is thought to lead to disease genesis [41]. Therefore agents that would be blocking cathelicidin could be beneficial in rosacea but this statement needs to be proved.

Discussion

The causes of rosacea remain unknown. Based on the controversial studies and opinions expressed in the literature it seems that we are rather far from identifying

the underlying pathology that leads to the disease development. The mechanisms described are based on different hypotheses and have yet been inconclusive, lacking the desired scientific data to provide evidence towards the pathogenesis of all the different forms of the disease. Microorganisms have been mainly implicated in the papulopustular form of rosacea. The question that arises is whether the disease is indeed multifactorial; a single pathophysiological theory could not therefore explain all the different disease manifestations. The possible role of microbes has been thoroughly discussed over many years, since the identification of the possible association of *Demodex folliculorum* and rosacea. Although we cannot draw any conclusions about the degree of *Demodex* contribution to the disease development, the rosacea population has indeed greater density of the mite on their skin while its prevalence is described as higher in many studies and equal to the general population in others [1, 5, 6, 28, 29].

An association between *H. pylori* infection and rosacea development has not been proven, despite many studies been performed in different populations. The controversial results previously described are not easy to interpret. Based on our study, where a higher prevalence of *H. pylori* in rosacea patients was not found [6], we conclude that this bacterium is unlikely to play a role in rosacea. Although S. epidermidis, *C. pneumoniae*, intestinal bacteria and proteolytic imbalance caused by microbial pathogens have been implicated in the disease development, they have not been connected definitely to the pathogenesis of rosacea in the pilot studies. Further research is required in this direction.

In their clinicopathological study Aroni et al. observed that there is no histological pattern unique to rosacea and suggested that this reaction pattern reflects the fact that a variety of pathogenetic routes may be involved [7].

Since only selected antibiotics are effective in rosacea, a bacterium sensitive to these agents could be involved in the pathogenesis of the disease [32]. Although investigators have not been able to identify any new microbial strains that could be deemed responsible for rosacea, the dramatic improvement seen after therapy with antibiotics supports the theory that microbes could be implicated [33]. The fact though that sub-antimicrobial anti-inflammatory doses of doxycycline demonstrated clinical efficacy in the papulopustular form of the disease suggests that microbes alone cannot explain the disease manifestations [42]. Moreover, photodynamic therapy using methylated 5-aminolevunate MAL-PDT that demonstrated a similar effect to long-term antibiotics in rosacea patients did not seem to significantly affect the skin flora [43].

In conclusion, the role of microorganisms in the development of rosacea has not been clearly defined. The data available to date suggest that they may have a potential role, which seems to be rather synergistic with other factors, unless the real causative microorganism has not been identified yet. <<<

Conflict of interest

None.

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