

The potential role of *Demodex folliculorum* mites and bacteria in the induction of rosacea.

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Microbes and rosacea

Rosacea is a common dermatological condition that predominantly affects the central regions of the face. Rosacea affects up to 3% of the world's population and a number of subtypes are recognized. Rosacea can be treated with a variety of antibiotics (e.g. tetracycline or metronidazole) yet no role for bacteria or microbes in its aetiology has been conclusively established. The density of *Demodex* mites in the skin of rosacea patients is higher than in controls, suggesting a possible role for these mites in the induction of this condition. In addition, *Bacillus oleronius*, known to be sensitive to the antibiotics used to treat rosacea, has been isolated from a *Demodex* mite from a patient with papulopustular rosacea and a potential role for this bacterium in the induction of rosacea has been proposed. *Staphylococcus epidermidis* has been isolated predominantly from the pustules of rosacea patients but not from unaffected skin and may be transported around the face by *Demodex* mites. These findings raise the possibility that rosacea is fundamentally a bacterial disease resulting from the over proliferation of *Demodex* mites living in skin damaged as a result of adverse weathering, age or the production of sebum with an altered fatty acid content. This review surveys the literature relating to the role of *Demodex* mites and their associated bacteria in the induction and persistence of rosacea and highlights possible therapeutic options.

Rosacea: definition and epidemiology

Rosacea is a common chronic inflammatory dermatosis of the face that affects up to 3% of the world's population (Buechner, 2005). Skin lesions are usually located in the central regions of the face, involving mostly the cheeks, nose and chin. Occasionally, lesions may be found on sun-exposed areas such as the neckline, the neck and ears; however, the periorcular region often remains lesion-free (Powell, 2005). The rash is usually symmetrical and may be described according to

associated or underlying symptoms of vascular origin (flushing or permanent erythema, telangiectasias or oedema), as well as the presence of papules and pustules, which can develop secondarily. In some patients, hypertrophy of connective tissue and hyperplasia of the sebaceous glands may occur, resulting in the development of phyma. Rosacea usually affects people between the ages of 30 and 50 and is rare in children. Rosacea affects mostly fair-skinned people with Fitzpatrick skin phototypes I and II (Del Rosso, 2006) and is three times more common in women than in men (Butterwick *et al.*, 2006). In men, the disease has a more severe course and men with rosacea have an increased tendency to develop phyma lesions (Buechner, 2005). The standard classification system for rosacea identified four basic stages of the disease: erythematotelangiectatic rosacea (ETR) (Fig. 1), papulopustular rosacea (PPR) (Fig. 2), phymatous rosacea, ocular rosacea (Fig. 3) and one variant rosacea, granulomatous rosacea (GR) (Wilkin *et al.*, 2002).

Diagnostic criteria of rosacea include primary features, such as flushing erythema, permanent erythema, papules, pustules and telangiectasias, the presence of which on the convexities of the face justifies the diagnosis of rosacea, and secondary features, such as the feeling of burning or tingling of the skin, oedema, the presence of tarsus, dryness of the skin, ocular symptoms, lesions outside the face and hyperplastic changes, which aid the diagnostic process (Wilkin *et al.*, 2002)

Etiopathogenesis

The etiopathogenesis of rosacea remains unexplained, as the pathogenic mechanisms that lead to the development of the skin lesions have not yet been fully elucidated. Possible factors responsible for rosacea may include autoimmune dysregulation, vascular disorders, external factors, degeneration of connective tissue elements, functional disorders of the pilosebaceous unit, nutritional and chemical factors and infectious factors (Crawford *et al.*, 2004, Yamasaki & Gallo, 2009). Over a significant period of time, there have been numerous attempts to connect the etiopathogenesis of rosacea with the presence of some micro-organisms on or within the skin (Lazaridou *et al.*, 2011), including *Demodex* mites and bacteria. It is well established that there is a higher density of *Demodex* mites in the skin of rosacea patients than control patients but the significance of this has been disputed (Vance, 1986; Bonnar *et al.*, 1993; Erbağcı & Ozgöztaşı, 1998). This review will explore the current understanding of the role of these organisms in the induction of rosacea.

Demodex folliculorum

There are more than 100 species of *Demodex* mites (class *Arachnida*, subclass *Acarina*) and all are highly specialized, host-specific obligatory commensals of mammals. Various kinds of *Demodex* mites may infest the skin of the host, depending on the preferred area on the skin (Lacey *et al.*, 2009). In many cases, mite infestation is asymptomatic and their role remains unclear (Lacey *et al.*, 2011). The pathogenic role of *Demodex* mites is well-documented in dogs where *Demodex canis* causes demodicosis – a serious, potentially fatal disease connected with numerous skin and ocular symptoms (Gortel, 2006).

Human skin may be inhabited by two species of *Demodex* mites and both have a worm-like shape and are covered by a thin cuticle (Fig. 4). The larger species, *Demodex folliculorum*, is about 0.3–

0.4 mm long, has an elongated shape and resides in hair follicles in a cluster consisting of several mites. The smaller species, *Demodex brevis*, is about 0.2–0.3 mm long, has a spindle shape, shorter legs and resides solitarily in the sebaceous or meibomian glands (Raszeja-Kotelba *et al.*, 2004). As *D. brevis* inhabits the deep parts of the skin, it is difficult to extract it without tearing of tissue. Due to the fact that the main food sources for mites in all phases of the development are epidermal cells and sebum components, they reside in skin areas particularly rich in sebaceous glands, such as the face – especially the nose, cheeks, forehead and chin. They may also be found in the external auditory canal, on the chest and in the genital area (Raszeja-Kotelba *et al.*, 2004).

The ultrastructure of *Demodex* mites

The gnathosoma, comprising the mouth and feeding parts, is located in the anterior portion of the *Demodex* body, the rest of the body consists of prosoma and opisthosoma (Fig. 4). The gnathosoma of *D. folliculorum* has sharp, stylet-like chelicerae, more developed than those of *D. brevis*, which are used to cut and take food, and pedipalps, which are used to hold the food. Both species have four pairs of legs in the prosoma (Jing *et al.*, 2005). *Demodex* mites use the chelicerae to cut the epithelial cells of the host skin, secrete lytic enzymes for pre-oral digestion and evacuate liquid cytoplasm components (Desch & Nutting, 1972). In the process of destroying the epithelial cells, the epithelial barrier is often disturbed and the mite penetrates into the dermis stimulating Toll-like receptors (TLR) (Schauber *et al.*, 2007). Proteolytic enzymes (proteases) are among the digestive enzymes secreted by *Demodex* mites. Concrements of serum immunoglobulin IgD and two inhibitors of serum proteases (α -1-antitrypsin and α -1-antichymotrypsin), which might be a specific defensive reaction of the host against mites, have been detected on the surface of *Demodex* mites (Tsutsumi, 2004). In atopic dermatitis, proteases produced by house dust mites have been identified as the factor responsible for local skin irritation (Deleuran *et al.*, 1998).

***Demodex* life cycle**

In all phases of their life cycle, *Demodex* mites avoid sunlight. They emerge from the pilosebaceous units at night and migrate across the surface of the skin to find a mating partner, travelling at a speed of about 16 mm h⁻¹ (Lacey *et al.*, 2011). The life cycle of *Demodex* mites consists of five phases of development and lasts from 14 to 18 days. The copulation takes place near the entry of the hair follicle. Afterwards, the gravid female moves to the inside of the sebaceous gland, where she deposits eggs, from which the larvae will emerge about 60 h later. Protonymphs and nymphs are the next phases of the *Demodex* life cycle (Lacey *et al.*, 2009; Spickett, 1961)

Due to the fact that *Demodex* mites are obligate parasites of the pilosebaceous units and highly susceptible to desiccation, they are not capable of surviving for long periods outside the host. Routes of transmission are not fully known but it may occur by direct contact as well as through dust. While the skin of new-borns is free of *Demodex folliculorum*, colonization of the skin in humans takes place in childhood or early adulthood. *Demodex* mites are found in representatives of all human races and in all geographical areas (Lacey *et al.*, 2009).

Role of *Demodex* mites in human skin disease

Demodex mites were originally perceived to be commensals, having a symbiotic relationship with the human host. However the opinion about the role of *Demodex* in pathogenesis of many diseases, including rosacea has been changing (Lacey *et al.*, 2009). In some specific conditions in the host system, *Demodex* mites may become potential pathogens. This may happen when the immunological conditions of the host change and new environmental conditions on the skin facilitate the development of *Demodex* mites (Dahl *et al.*, 2004; Whitfeld *et al.*, 2011).

There are certain differences in distribution on the skin between the two species of *Demodex* mites found in the human population. *D. folliculorum* counts are notably higher but *D. brevis* inhabits a larger area of the human body. The proportion of *D. brevis* to *D. folliculorum* also differs among men (1:4, respectively) and women (1:10) (Bohdanowicz & Raszeja-Kotelba, 2001). *D. folliculorum* is more often associated with erythema and epithelial desquamation, whereas *D. brevis* is linked with papulopustular eruption, symmetrical rashes and conditions arising on the background of a pre-existing disease (Akilov *et al.*, 2005).

The extent of *Demodex* colonization in the human population is high (20–80%), reaching 100% in elderly people (Elston, 2010). Mite density starts to rise in the sixth decade of life and stays at the same level until the eight decade of life. 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 (Ozdemir *et al.*, 2005; Aylesworth & Vance, 1982). 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 (Ní Raghallaigh *et al.*, 2012). This finding raises the possibility that non-antibiotic therapies to restore the normal fatty acid composition of sebum may improve skin integrity and inhibit the proliferation of *Demodex* mites.

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 is not enough to determine pathogenicity. An increase in mite density on facial skin is observed in perioral dermatitis, caused by long-term use of local steroids or other immunomodulating drugs (Fujiwara *et al.*, 2010). Higher numbers of *Demodex* mites have been noted in patients undergoing immunosuppressive therapy, for example children receiving chemotherapy for leukaemia (Ivy *et al.*, 1995), patients with HIV-infection or AIDS (Aquilina *et al.*, 2002; Dominey *et al.*, 1989) and chronic dialysis patients (Karincaoglu *et al.*, 2005).

A positive correlation between high density of *Demodex* mites and the presence of antigens affecting tissue compatibility, HLA Cw2 and Cw4, has been established (Akilov & Mumcuoglu, 2003). Furthermore, increased numbers of mites have been associated with a higher tendency of leukocytes to undergo apoptosis. Such a genetically conditioned decreased immune performance may result in local immuno-suppression and so facilitate survival and replication of *Demodex* mites (Akilov & Mumcuoglu, 2004).

Ayres & Anderson (1932) first suggested a correlation between the presence of *Demodex* mites on the skin and development of various skin lesions (Ayres, 1930). They described a disease entity which they named 'pityriasis folliculorum' and associated its development with the presence of *D. folliculorum* mites. Pityriasis folliculorum is characterized by small, follicular, scaling papules, the feeling of skin dryness and pruritus. Lesions in pityriasis folliculorum are usually unilateral, located mainly on the cheeks, but may also reach the eyelids (Ayres, 1930). Ayres & Ayres, (1961) identified a new disease entity, rosacea-like demodicosis, caused by the presence of abundant *D. folliculorum* mites and characterized by erythema, dryness and fine follicular scaling. Later research proved pityriasis folliculorum to be a form of demodicosis, and the most frequent one (54%), but so discrete and unfamiliar that it was often not diagnosed. Demodicosis is characterized by discrete symptoms of erythema, higher densities of *Demodex* mites per cm² (up to 61 mites per cm²) in comparison to papulopustular rosacea (up to 36 mites per cm²), and is primarily a disease of the elderly or immunocompromised. A compromised immune system is thought to enable such proliferation of *Demodex* mites in cases of pityriasis folliculorum (Forton *et al.*, 2005).

The mean density of *Demodex* mites on the skin of rosacea patients is 10.8 mites per cm² in comparison to 0.7 mites per cm² in healthy people. However, when all types of rosacea are taken into account, statistically larger mite densities per cm² are found in cases of papulopustular rosacea (Forton & Seys, 1993). Other diseases in which infestation with *Demodex* mites is believed to be the aetiological factor include blepharitis (Czepita *et al.*, 2007) and, in one case, hair loss described in a 6-year-old boy (García-Vargas *et al.*, 2007).

Histopathological examination of skin specimens obtained from control patients revealed the presence of *Demodex* mites in 10% of all facial skin biopsies and in 12% of all pilosebaceous units (Aylesworth & Vance, 1982). Skin specimens with histological features of folliculitis revealed that *D. folliculorum* mites were found in 42% of inflamed and only 10% of non-inflamed follicles. Overall, 83% of all affected follicles demonstrated features of inflammation. However, whether *D. folliculorum* causes folliculitis or simply inhabits inflamed follicles remains unclear (Vollmer, 1996). 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 (Georgala *et al.*, 2001).

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 (Ayres & Ayres, 1961). Most probably, when *Demodex* mites breach the epithelial barrier, their antigens influence the immune system of the host and induce a type IV hypersensitivity reaction. *Demodex* mites may then be attacked by giant cells giving rise to dermal granulomas, which are most often observed in granulomatous acne rosacea. Granulomas are also found in skin biopsies of patients with papulopustular rosacea and even in patients with erythematous rosacea (Hsu *et al.*, 2009).

The causal relationship of *Demodex* mites in skin lesions has been suspected to occur through several mechanisms. They may mechanically block the follicles, leading to distension and causing intra-follicular hyperkeratosis. The presence of mite's chitinous external skeleton may act like a foreign body and contribute to the formation of granulomas. 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 (Bevins & Liu, 2007).

Potential role of *Bacillus oleronius* in rosacea

One hypothesis concerning the role of *Demodex* mites in the induction of rosacea assumes that *Demodex* are vectors for micro-organisms that causes and exacerbates skin lesions (Hsu *et al.*, 2009). The theory has its roots in the fact that clinical improvement was noted in patients with rosacea who were administered tetracycline antibiotics, although these antibiotics neither demonstrate activity against *D. folliculorum* nor reduce their numbers on the skin. It has been suggested that the beneficial activity of antibiotics was due to their anti-inflammatory properties; however, other anti-inflammatory agents, such as steroids or tacrolimus, intensify the symptoms of rosacea or even induce its development (Antille *et al.*, 2004). The fact that only some drugs proved to be effective in the treatment of rosacea suggested that that an unknown bacterium may have a role in the pathogenesis of the disease. Attempts to prove the presence of DNA of Gram-negative intracellular bacterium *Wolbachia pipientis*, which has been detected in various species of mites and nematodes, proved futile in the case of *Demodex* mites (Borgo *et al.*, 2009). *Bacillus oleronius* was isolated from a *Demodex* mite, obtained from a patient with papulopustular rosacea (Lacey *et al.*, 2007). The species is an endosporic Gram-negative bacterium (genus *Bacillus*, family *Bacillaceae*) and was first described in 1995 when it was isolated from the hindgut of the termite *Reticulitermes santonensis*, where it most likely plays a symbiotic role (Kuhnigk *et al.*, 1995). The bacterium produces 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. The sera of six other patients with papulopustular rosacea reacted with two antigens isolated from the bacterium: two specific proteins of 62 kDa and 83 kDa, bearing similarity to the heat-shock proteins) (Lacey *et al.*, 2007). Another experiment investigated sera from 59 patients with diagnosed rosacea and a statistically significant correlation was demonstrated between positive reactions of the serum from these patients with *B. oleronius* antigens and the presence of *Demodex* mites on their eyelashes and facial skin lesions (Li *et al.*, 2010). Recent work has indicated that a range of *B. oleronius* proteins can activate neutrophils which migrate and produce inflammatory cytokines. It was speculated that the release of *B. oleronius* from dead *Demodex* mites within the pilosebaceous unit could lead to the release of a range of *Bacillus* proteins into the unit, which 'leak' into the surrounding tissue and so attract neutrophils (O'Reilly *et al.*, 2012). If this occurs *in vivo* it would lead to inflammation and tissue degradation in the vicinity of the pilosebaceous unit. Interestingly, inflammation in papulopustular rosacea is often orientated around the pilosebaceous unit, suggesting that the focus of the inflammation is within or adjacent to the unit (Lacey *et al.*, 2007). Exposure of corneal epithelial cells to *Bacillus* proteins results in an aberrant wound healing

response, suggesting a possible link between the action of these antigens on the corneal surface and the development of sterile ulcers which are a common feature of ocular rosacea (O'Reilly *et al.*, 2012).

Recent examination of patients with blepharitis has provided further evidence on the pathogenic role of *B. oleronius* (Szkardkiewicz *et al.*, 2011). The severity of the disease did not correspond with an increased number of *Demodex* mites per lash, with the exception of the five most severe cases, where a greater numbers of mites were observed. Statistically significant differences in *B. oleronius* incidence rates were found between patients with severe disease and healthy controls. This might indicate that *Demodex* mites constitute an independent pathogenic factor of blepharitis and the *B. oleronius* bacteria, carried by the mites, most probably play a role as a co-pathogen in the development of more severe forms of blepharitis.

Role of *Staphylococcus epidermidis* in rosacea

Staphylococcus epidermidis has been isolated from the pustules of 9 out of 15 patients with papulopustular rosacea, whereas this bacterium was not detected on unaffected areas of the skin (Whitfeld *et al.*, 2011). *S. epidermidis* was also isolated from the eyelid margins of 4 out of 15 patients with papulopustular rosacea, whereas no pure growth was isolated from the eyelids of age- and sex-matched control subjects. The same study also found that this bacterium was susceptible to antibiotics commonly used to treat rosacea. Facial erythema and increased blood flow in the skin of those with rosacea causes the temperature of the skin to become elevated. Dahl *et al.* (2004) found that *S. epidermidis* secreted more proteins when cultured at 37 °C than at 30 °C and that isolates from rosacea patients' skin were consistently β -haemolytic, whereas isolates from control subjects were non-haemolytic. *Demodex* mites have been shown to transport bacteria around the face (Lacey *et al.*, 2007) so the possibility remains that *S. epidermidis*, along with other bacteria, are moved to areas which favour their proliferation.

Conclusion

Rosacea is a complex disease entity of disputed aetiology. The literature offers numerous arguments supportive of the theory that rosacea is primarily connected with compromised immunity (Forton, 2012). According to this theory, on the skin of healthy, immune-competent individuals, the proliferation of *Demodex* mites is kept under control. In the first stage of rosacea, studied by investigators of the clinical form of pityriasis folliculorum, no inflammation is observed, despite the presence of a large number of *Demodex* mites. This is probably caused by an unidentified, genetic defect of the innate immunity (Akilov & Mumcuoglu, 2003) and/or the localized immunosuppressive influence of the mites (Akilov & Mumcuoglu, 2004). In the later stages of the disease, characterized by developed rosacea, there is an overstimulated reaction of the immune system, which includes elevated levels of serine proteases, kallikrein (KLK5), the presence of abnormal forms of cathelicidins (with lower anti-bacterial potential) (Yamasaki *et al.*, 2007; Schaubert & Gallo, 2008) and increased expression of Toll-like 2 receptors (TLR 2), which stimulate the calcium-dependent production of kallikrein (Yamasaki *et al.*, 2011).

Such immunological conditions favour the development of different types of micro-organisms, including *Demodex* mites. Other characteristic features of rosacea patients, such as increased vascularization and elevated temperature, may further promote the growth of the organisms (Whitfield *et al.*, 2011). Developing *Demodex* mites may be causative agents of rosacea through various mechanisms: they may mechanically block hair follicles, secrete digestive enzymes, destroy the epithelial barrier or trigger reactions of the immune system.

It is believed that *B. oleronius* forms a symbiotic relationship with *Demodex*, as it does in the termite (Kuhnigk *et al.*, 1995). On the skin of humans, this bacterium may occur in the endospore form, which enters the digestive tract of *Demodex* mites when they consume epithelial cells. The dead mites then decompose inside the hair follicles, where they release significant numbers of bacterial antigens, which have the potential to stimulate a strong immune response (O'Reilly *et al.*, 2012). Thus, the intensification of blepharitis and rosacea, especially the papulopustular variant, may not be induced so much by the presence of the mites alone but by the presence of *Demodex* mites that carry *B. oleronius* in their digestive tract. Empirically confirmed sensitivity of *B. oleronius* to different antibiotics, especially doxycycline, (Lacey *et al.*, 2007) might explain the favourable therapeutic effect of the drug in diseases such as rosacea and blepharitis.

The pathogenic role of *Demodex* mites, as well as *B. oleronius* and *S. epidermidis*, in the induction and persistence of rosacea remains an unresolved issue. The lack of an immunological response to *Demodex* mites in healthy skin raises the possibility of localized immunosuppression, facilitating the survival of the mite. Hopefully, the results of further research will bring us closer to understanding the role of microbes in the pathogenesis of rosacea and assist in the development of new and more effective therapies for the treatment of this disfiguring disease.

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Fig. 1. Erythematotelangiectatic rosacea. Note presence of inflammation on skin and increased vascularization on nose.



Fig. 2. Papulopustular rosacea. Characteristics papules and pustules are present on skin of cheek.

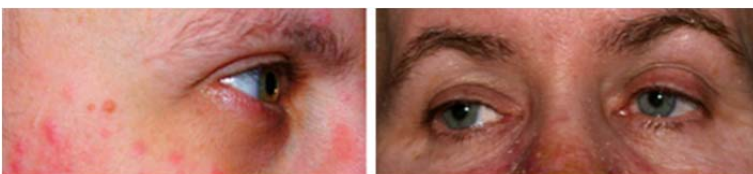


Fig. 3. Ocular rosacea. Note inflammation on eyelid margins.

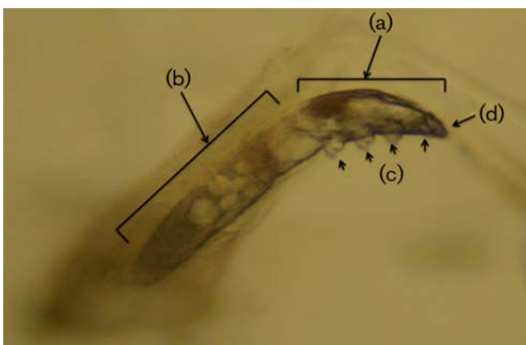


Fig. 4. *Demodex folliculorum* mite embedded in a hair follicle. The body parts of the mite, including the head–neck segment (a), the body–tail segment (b), the four pairs of short legs attached to the head–neck (c) and the mouth parts (d), are shown. Length, 0.4 mm.