SIERADOCHA, Kamila, JEDLIKOWSKA, Wiktoria and FURLEPA, Natalia. The Role of Inflammatory Pathways in the Development of Rosacea. Journal of Education, Health and Sport. 2024;71:56142. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.71.56142
https://apcz.umk.pl/JEHS/article/view/56142

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

The Role of Inflammatory Pathways in the Development of Rosacea

Kamila Sieradocha
University Clinical Hospital in Poznań, Przybyszewskiego Str. 49, 60-355 Poznań, Poland
https://orcid.org/0009-0006-1952-0139
sieradochakamila@gmail.com

Wiktoria Jedlikowska
Heliodor Swiecicki Clinical Hospital, Poznań, Poland
https://orcid.org/0009-0002-7874-9911
wiktoria.jedlikowska1998@gmail.com

Natalia Furlepa
Heliodor Swiecicki Clinical Hospital: Poznań, PL
https://orcid.org/0009-0002-8163-2087
nataliafurlepa@gmail.com

Aim of the Study:
The aim of this article was to review the role of inflammatory pathways in the development of rosacea, focusing on key mechanisms such as immune system dysregulation, neurogenic inflammation, and microbial influences, as well as potential therapeutic strategies to target these pathways.
Materials and Methods:
A comprehensive literature review was conducted using the PubMed, Google Scholar, and Medline databases with keywords including “inflammatory pathways,” “rosacea,” “immune response,” and “skin inflammation.”

Results and Conclusions:
The findings highlight the central role of inflammatory pathways in the onset and progression of rosacea. Key mechanisms identified include the overactivation of innate immune responses, neuroinflammatory processes, and alterations in the skin microbiome, all contributing to the chronic inflammation seen in rosacea. These insights underline the potential for targeted therapies that modulate inflammatory pathways, offering promise for more effective management of the condition.

Abstract:
Rosacea is a prevalent yet poorly understood chronic inflammatory skin condition, characterized by symptoms such as flushing, erythema, papules, and telangiectasia. Although the precise causes of rosacea remain unclear, its pathogenesis involves complex interactions between genetic, environmental, microbial, and immune factors. Recent studies highlight a crucial role for both the innate and adaptive immune systems, implicating Toll-like receptors, neutrophils, macrophages, and cytokines as central to the inflammatory cascade seen in rosacea. Additionally, the overexpression of molecules like cathelicidin and vascular endothelial growth factor (VEGF) contributes to the disease's hallmark features, such as vasodilation and angiogenesis. Trigger factors including UV radiation, dietary components, and microbial influences further exacerbate inflammation, underscoring the multi-factorial nature of the condition. Traditional treatment options, like topical metronidazole, azelaic acid, and oral tetracyclines, have demonstrated efficacy in controlling mild to moderate cases of rosacea. However, more severe cases remain challenging to treat, prompting exploration into novel therapies like IL-17 inhibitors, laser therapy, and probiotics. This review investigates the inflammatory pathways central to rosacea pathogenesis and evaluates emerging therapeutic approaches aimed at addressing the underlying mechanisms of this condition. Understanding these pathways may lead to more effective treatment strategies, improving patient outcomes and quality of life.

Keywords: rosacea, inflammatory pathways, immune response, toll-like receptors (TLRs), UV radiation

1. Introduction

Rosacea, a chronic inflammatory skin condition, is both common and poorly understood in terms of its origin. The combination of symptoms, including flushing, chronic inflammation, fibrosis, and various trigger factors [1].

The development of rosacea is driven by mechanisms such as innate immune responses, vascular changes, reactive oxygen species, exposure to UV radiation, and microbial activity. Our present understanding of innate immunity allows us to link these molecular events more cohesively [2]. The condition is diagnosed through clinical assessment and treatment primarily emphasizes educating the patient, steering clear of factors that might aggravate symptoms, maintaining proper skin care and exploring various therapeutic strategies [3].

The aim of this study is to investigate the role of inflammatory processes in the pathogenesis of rosacea and to identify therapeutic interventions that effectively target these mechanisms.

By understanding the complex interactions of immune and inflammatory responses involved in rosacea development, this research seeks to inform the selection of optimized treatment strategies that reduce symptom severity and improve patient outcomes.

2. Pathogenesis and Clinical Presentation of Rosacea: Genetic, Environmental, and Microbial Influences

Rosacea frequently appears in middle-aged individuals. Recognizing its subtypes is essential for properly assessing the patient [4]. This condition has a global prevalence ranging between 1% and 20% [5]. Rosacea is commonly observed in individuals with fair skin, yet it is not uncommon among people with darker skin tones. In fact, it may be underdiagnosed in these populations due to challenges in detecting erythema and telangiectasia on darker skin [6].

It presents in four primary forms: (1) erythematotelangiectatic, with constant redness, flushing, and visible blood vessels; (2) papulopustular, with ongoing redness and occasional bumps; (3) phymatous, marked by thickened skin and potential nose enlargement; and (4) ocular, affecting the eyes with dryness, burning, swollen eyelids, and in severe cases vision issues [7].

Rosacea, affecting the central face symmetrically, varies by age and gender: rhinophyma is most common in men, while younger individuals often show early redness and flushing, and older adults typically develop telangiectasia [8]. Secondary symptoms of rosacea can occasionally include sensations like itching, burning, or stinging [9]. Rosacea symptoms can appear from multiple subtypes simultaneously or as isolated signs that don't match any specific category. These symptoms typically fluctuate, with periods of intense flare-ups followed by remission phases [10].

While the exact cause of rosacea remains uncertain, research highlights multiple pathogenic pathways involving immune system irregularities, mast cells, and neurovascular issues. Key aspects include disruptions in skin barrier function and permeability, affecting hydration, pH balance, microbiome, and molecular structure [11]. The underlying mechanisms of rosacea result from a complex interaction of genetic, microbial, immune, neurogenic, and barrier factors, emphasizing its chronic inflammatory character rather than an acute one [12]. Activating an inflammatory cascade, bacterial ligands bind to epidermal receptors, causing vasodilation and drawing white blood cells to the site. This alteration in the skin's environment allows microorganisms such as *Demodex folliculorum*, *Helicobacter pylori* to proliferate, playing a critical role in rosacea's pathogenesis [13]. One study indicates that the disease's development is roughly half influenced by genetic factors and half by environmental ones [14]. The link between rosacea and certain single nucleotide polymorphisms in major histocompatibility complex genes suggests a strong genetic susceptibility paired with altered immune response [15]. Another perspective is the dermal matrix degeneration theory, which proposes that rosacea symptoms stem from inadequate connective tissue support surrounding facial blood vessels [16]. Rosacea can be triggered or intensified by several factors, including exposure to UV rays, high temperatures, consumption of spicy foods or alcohol, emotional stress, and microbial imbalances on the skin or within the digestive system, like bacterial overgrowth [17].

3. Inflammatory Pathways Involved in Rosacea Development

Molecular studies have shown a relationship between the triggers of rosacea and the cellular response, suggesting that an altered innate immune response is one of the factors contributing to the development of the disease [18]. The innate immune system includes families of Toll-like receptors (TLRs), which detect external environmental stimuli such as UV radiation, microbes, and physical and chemical injuries. The activation of the innate immune system results in a controlled increase in cytokines and antimicrobial molecules in the skin [19].

Recent studies have shown that the adaptive immune system is also responsible for inflammatory processes in skin diseases such as acne, psoriasis, and atopic dermatitis. The cellular infiltrate of the adaptive immune system in rosacea includes T cells and B cells [20].

Among the cells of the innate immune system, effector cells such as neutrophils are distinguished. The infiltration of a large number of neutrophils in biopsies of patients with rosacea was the first time a connection between these cells and rosacea was observed [21]. Recent studies demonstrate the significant role of macrophages in the pathophysiology of rosacea. Macrophages are responsible for the overproduction of proinflammatory cytokines and angiogenic factors, which contribute to inflammation and the formation of blood vessels [22]. CD4+ T-cells are observed in large numbers in the skin of patients with rosacea, and an enhanced response from Th1/Th17 lymphocytes may significantly contribute to the development of rosacea [23]. The group of antimicrobial molecules whose levels increase during the activation of the innate immune system includes the cathelicidin peptide. [24] Cathelicidin can be found in small amounts in the granular and cornified layers of the skin, but its levels significantly increase in cases of skin damage or infection, which helps protect the damaged epidermis from infection. Studies on cathelicidin peptides have shown that some forms exhibit both vasoactive and proinflammatory effects [19].

Toll-like receptors (TLRs) recognize specific microbial components or products of host tissue damage, thereby initiating inflammatory and immune responses [25]. Activation of TLR2 leads to increased levels of rosacea-associated kallikrein 5, which then results in the production of pro-inflammatory forms of the antimicrobial peptide LL37. LL37 interacts with TLR2, activating the mTOR signaling pathway, which consequently contributes to the development of rosacea [26]. Recent studies have shown that TLR7 is overexpressed in patients with rosacea. Overactivation of TLR7 in keratinocytes activates the NFκB signaling pathway, which in turn activates the mTORC1 pathway. As a result, the TLR7/NFκB/mTORC1 axis promotes the production of cytokines and chemokines associated with rosacea, leading to the migration of CD4+ T cells involved in the development of the disease [27].

Many mediators, such as nitric oxide, cathelicidins and vascular endothelial growth factor (VEGF), are involved in vasodilation and angiogenesis [28].VEGF has a key function as a master regulator of pathological angiogenesis and increased vascular permeability in patients with inflammatory and malignant diseases [28]. Skin biopsies from patients with rosacea show increased VEGF expression in both epidermal and infiltrating cells [29].

4. Triggers of Inflammatory Responses in Rosacea

The causes of rosacea are still unclear however, it is known that the development of rosacea consists of the interaction of many predisposing factors [30]. Genetics, microorganisms, the immune system, reactive oxygen species, an impaired skin barrier and neuronal and vascular dysfunction, among others, play an important role in its formation [31]. In the process of its formation, a key role is played by environmental factors such as air pollution, sun exposure, nutrition, alcohol, tobacco, and mental stress [32].

The Morgado-Carrasco team pays particular attention to the role of UV radiation in the pathogenesis of rosacea [31]. Long-term exposure to UV radiation has been proven to be a major environmental factor in its development [31]. UVB radiation stimulates the formation of new blood vessels and telangiectasia, including through the expression of vascular endothelial growth factor [30]. On the other hand UVA radiation can lead to collagen degeneration and skin damage by inducing overexpression of metalloproteinases [33]. UV disrupts the oxidative balance, raising levels of reactive oxygen species (ROS), which cause inflammation. In addition, UV radiation activates TLR2 mechanisms, which can initiate innate immune system responses in rosacea [33]. Increased activation of TLR2 receptors induces the release of cathelicidins and kallikrein 5 (KLK5) [34]. Cathelicidins are transformed into LL-37 [34]. The cathelicidin LL-37 enhances light sensitivity, increasing the inflammatory and angiogenic effects of UV radiation, which can exacerbate rosacea symptoms [35].

It is suspected that microorganisms such as Demodex folliculorum, Bacillus oleronius, Cutibacteium acnes and Staphylococcus epidermidis may be involved in the development of the disease [34]. According to the study, the population of Demodex folliculorum in a group of people with rosacea was 5.7% higher than in a group of healthy people [36]. Demodex participates in the development of rosacea through multiple mechanisms. By proliferating in the sebaceous glands, it causes their mechanical blockage and inflammation, leading to the formation of papules and pustules, as the glands' mouths become obstructed. Such lesions are characteristic of the papulopustular and popular forms of rosacea [37]. These parasites activate TLR-2 receptors, resulting in the secretion of LL-37, an inflammatory factor that stimulates angiogenesis and the formation of new blood vessels [34]. Moreover, an association between D. folliculorum and markers of inflammation has been found, suggesting adverse activation of the innate immune system. Cytokines such as interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α) have been observed to promote angiogenesis, resulting in erythema [38].

In recent years, the Helicobacter Pylori bacterium has been suspected of involvement in the development of rosacea. The bacterium contributes to chronic gastritis, peptic ulcers, MALT lymphoma and gastric cancer [34]. The role of the bacteria in the development of the disease is not fully known . Carrying H. pylori is more common in rosacea patients than in healthy individuals [38]. Some studies indicate that eradication of this bacterium leads to relief of

rosacea symptoms, suggesting that H. pylori may have a role in the development of the disease [39]. H. pylori infection is thought to lead to facial erythema through the release of vasodilators such as histamine, gastrin, nitric oxide, cytokines and leukotrienes, as well as increased mucosal permeability, an autoimmune response or disruption of vascular integrity [38].

Many studies have linked disruption of the gut microbiome to inflammatory skin diseases such as rosacea [38].

People with rosacea have been found to have an altered microbiome composition, characterized by a lower presence of Peptococcaceae and Methanobrevibacter, and a higher abundance of Acidaminococcus and Megasphaera [36]. A study was conducted in which it was proven that patients with rosacea were 13 times more likely to suffer from small intestinal bacterial overgrowth (SIBO) compared to the control group [30]. Those with the papulopustular form were 12 times more likely to experience SIBO [30]. A diagnosis of SIBO may contribute to the development of rosacea, possibly through increased production of pro-inflammatory cytokines [30].

Another of the factors influencing the pathogenesis of rosacea is diet [40]. Among the foods that cause the disease, are products high in cinnamaldehyde and histamine [40]. In a National Rosacea Society (NRS) survey of 1,066 rosacea sufferers, participants reported alcohol (52%), spicy foods (45%), certain fruits (13%), pickled meats (10%) and some vegetables (9%) as triggers [41]. Participants also reported that changing their diet resulted in an improvement in rosacea symptoms [40]. Histamine, formed by the metabolism of acetaldehyde and acetone, can affect the dilation of skin capillaries, which manifests as erythema. In addition, cinnamaldehyde, histamine, alcohol and capsaicin (present in spicy foods) are believed to activate TRPV1 (vanilloid potential receptor type 1) receptors, which are responsible for flushing, burning and increased skin sensitivity leading to the initiation or exacerbation of rosacea [40,42].Hot drinks and foods can often act as triggers for symptoms in patients with rosacea [42]. Heat leads to vasodilation of blood vessels and activates TRPV1 channels [42]. In a study by Tilwani and colleagues, it was proven that exposure to air pollution can cause the development and exacerbation of rosacea [43].

5. Novel Anti-inflammatory Therapies

Standard treatment for rosacea usually allows for effective control of symptoms in mild and moderate forms of the disease, but in cases of severe and treatment-resistant rosacea, the effectiveness of therapy is limited [44]. The facial skin of people suffering from rosacea exhibits significantly higher levels of cathelicidin compared to the skin of healthy individuals [45]. Azelaic acid belongs to a group of naturally occurring saturated dicarboxylic acids that exhibit anti-inflammatory, antioxidant, and antibacterial properties. Preparations containing 15% azelaic acid are recommended by the AARS (American Academy of Dermatology) for topical treatment of inflammatory papules and pustules in rosacea. The mechanism of action of azelaic acid involves lowering cathelicidin levels by inhibiting the activity of serine protease KLK5 [46]. Metronidazole, used in the form of a gel or ointment, has a comparable effectiveness to azelaic acid gel. It acts as an oxygen scavenger, reducing the amount of reactive oxygen species (ROS) and inhibiting neutrophil activity [47]. Studies have shown

elevated levels of IL-17 in the serum of patients with rosacea [48]. It is hypothesized that IL-17 inhibitors, used in the treatment of psoriasis and psoriatic arthritis, could potentially be used in the future for treating severe and treatment-resistant papulopustular rosacea [44].
Oral medications, including tetracyclines, are also used in the treatment of rosacea, primarily for their anti-inflammatory properties, as well as for inhibiting angiogenesis, leukocyte chemotaxis, and inflammatory cytokines.

Tetracycline, doxycycline, and minocycline are commonly used. It has been proven that the simultaneous use of oral doxycycline with 15% azelaic acid gel or 1% metronidazole is a well-tolerated treatment method for papulopustular rosacea [49]. Among macrolide antibiotics, second-generation macrolides such as clarithromycin and azithromycin are preferred. They have faster action and better tolerance concerning gastrointestinal side effects compared to oral tetracyclines, metronidazole, and ketoconazole [50].
An updated systematic review of rosacea treatment methods recommends the use of laser therapy and intense pulsed light (IPL) therapy for treating erythema and, particularly, telangiectasia, although the evidence for the effectiveness of these methods is of low to moderate certainty [51]. A retrospective study conducted by Zhang and colleagues, involving 807 patients, demonstrated that various sequential light/laser devices can be safely used in the treatment of nasal rosacea [52]. A study involving 68 patients showed the effectiveness of sequential use of Nd 532/1064 nm laser and IPL in treating facial telangiectasia and erythema [53]. Another study compared the effects of sequential application of IPL and Nd laser on one side of the face with a regimen where IPL was used separately, followed by the Nd laser three days later. The results showed that simultaneous sequential use of both methods yields better outcomes than separate treatments [54].
The skin and gut microbiota may become an interesting therapeutic target for rosacea treatment due to their probable influence on the development of the disease. However, the effectiveness of probiotics for rosacea has not been confirmed by a sufficient number of clinical studies [55].
Manzhalii and colleagues conducted a randomized clinical trial involving 57 patients with erythema and papulopustular lesions, 36% of whom had papulopustular rosacea. The patients were divided into two groups, with the first group receiving topical therapy that included tetracyclines, corticosteroids, and retinoids. The second group was treated according to the same regimen with the addition of the oral probiotic *Escherichia Coli* Nissle 1918. After a month of treatment, 32% of patients in the probiotic group were cured, and 57% showed significant improvement, compared to 17% and 39% of patients in the control group [56].
Further research on rosacea therapy is essential, particularly in exploring new treatment methods and understanding the role of skin and gut microbiota in disease development. The development of targeted therapies, such as IL-17 inhibitors, and studies on the use of probiotics may contribute to creating more effective and personalized treatment options in the future. As knowledge of rosacea pathophysiology deepens, innovative therapeutic approaches may be developed, improving the quality of life for patients with severe forms of the disease.

6. Conclusions

Rosacea is a complex, chronic inflammatory disorder involving multiple genetic, immune, microbial, and environmental factors. The disease's pathogenesis highlights significant interactions among these factors, leading to characteristic features such as erythema, telangiectasia, and inflammation. The role of innate immunity, particularly through Toll-like receptor activation, and the involvement of antimicrobial peptides like cathelicidin, emphasize the importance of inflammatory pathways in disease development. Moreover, UV exposure, microbial imbalances, and dietary triggers further contribute to exacerbating rosacea symptoms.

While traditional treatments, such as topical azelaic acid, metronidazole, and oral tetracyclines, have proven effective in many patients, severe cases of rosacea often resist these approaches. The need for more effective treatments has driven research into novel therapies targeting underlying inflammatory mechanisms. Promising options include IL-17 inhibitors, which may help address the inflammatory responses in rosacea, as well as light-based therapies that target erythema and vascular changes. The potential benefits of probiotics also open new possibilities for modulating gut-skin interactions in rosacea patients.

Future research should focus on further clarifying the immune pathways involved in rosacea and evaluating the long-term effectiveness of emerging treatments. By gaining a deeper understanding of the disease’s inflammatory and immune-driven mechanisms, it may be possible to develop targeted therapies that provide improved outcomes, especially for those with severe or refractory rosacea. Enhanced patient education on trigger management and lifestyle adjustments also remains a critical component in optimizing care for rosacea sufferers.

Author Contributions:
Analysis and Preliminary Research:
Kamila Sieradocha
Planning and Designing:
Kamila Sieradocha
Writing and Editing:
Kamila Sieradocha, Natalia Furlepa, Wiktoria Jedlikowska
Data Analysis:
Kamila Sieradocha, Natalia Furlepa, Wiktoria Jedlikowska
Scientific Verification:
Natalia Furlepa, Wiktoria Jedlikowska
Summary and Conclusions:
Kamila Sieradocha, Natalia Furlepa, Wiktoria Jedlikowska

All authors have read and agreed with the published version of the manuscript.

Financing statement:
This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

Conflict of interest:
The authors deny any conflict of interest.

References:
1. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. Journal of the American Academy of Dermatology. 2013 Dec 1;69(6):S15-26.
2. Yamasaki K, Gallo RL. The molecular pathology of rosacea. Journal of dermatological science. 2009 Aug 1;55(2):77-81.
3. van Zuuren EJ. Rosacea. New England Journal of Medicine. 2017 Nov 2;377(18):1754-64.
4. Van Onselen J. Rosacea: symptoms and support. British Journal of Nursing. 2012 Nov 22;21(21):1252-5.
5. Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of rosacea: a systematic review and meta-analysis. British Journal of Dermatology. 2018 Aug 1;179(2):282-9.
6. Alexis AF, Callender VD, Baldwin HE, Desai SR, Rendon MI, Taylor SC. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: review and clinical practice experience. Journal of the American Academy of Dermatology. 2019 Jun 1;80(6):1722-9.
7. Abokwidir M, Feldman SR. Rosacea management. Skin appendage disorders. 2016 May 18;2(1-2):26-34.
8. Buddenkotte, Joerg, and Martin Steinhoff. "Recent advances in understanding and managing rosacea." *F1000Research* 7 (2018).
9. Johnson SM, Berg A, Barr C. Managing Rosacea in the clinic: from pathophysiology to treatment—a review of the literature. The Journal of Clinical and Aesthetic Dermatology. 2020 Apr;13(4 Suppl 1):S17.
10. Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of rosacea. Dermatology practical & conceptual. 2017 Oct;7(4):31.
11. Fisher GW, Travers JB, Rohan CA. Rosacea pathogenesis and therapeutics: current treatments and a look at future targets. Frontiers in Medicine. 2023 Dec 13;10:1292722.
12. Hu XM, Li ZX, Zhang DY, Yang YC, Zheng SY, Zhang Q, Wan XX, Li J, Yang RH, Xiong K. Current research and clinical trends in rosacea pathogenesis. Heliyon. 2022 Oct 1;8(10).

13. Mehrholz DM, Nowicki R, Barańska-Rybak WM. Infectious factors in the etiopathogenesis of rosacea. Dermatology Review. 2016 Jul 1;103(4).
14. Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, Gotow E, Cooper KD, Mann M, Popkin DL. Genetic vs environmental factors that correlate with rosacea: a cohort-based survey of twins. JAMA dermatology. 2015 Nov 1;151(11):1213-9.
15. Chang AL, Raber I, Xu J, Li R, Spitale R, Chen J, Kiefer AK, Tian C, Eriksson NK, Hinds DA, Tung JY. Assessment of the genetic basis of rosacea by genome-wide association study. Journal of Investigative Dermatology. 2015 Jun 1;135(6):1548-55.
16. Del Rosso JQ. Update on rosacea pathogenesis and correlation with medical therapeutic agents. CUTIS-NEW YORK-. 2006 Aug 1;78(2):97.
17. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. Journal of the American Academy of Dermatology. 2013 Dec 1;69(6):S15-26.
18. Yamasaki K. Rosacea in skin innate immunity. In: Immunology of the Skin: Basic and Clinical Sciences in Skin Immune Responses. 2016. p. 451-62.
19. Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity. J Investig Dermatol Symp Proc. 2011 Dec;15(1):12-5.
20. Buhl T, Sulk M, Nowak P, Buddenkotte J, McDonald I, Aubert J, et al. Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways. J Investig Dermatol. 2015;135(9):2198-208.
21. Zhao Z, Liu T, Liang Y, Cui W, Li D, Zhang G, et al. N2-polarized neutrophils reduce inflammation in rosacea by regulating vascular factors and proliferation of CD4+ T cells. J Investig Dermatol. 2022;142(7):1835-44.
22. Liu Y, Zhou Y, Chu C, Jiang X. The role of macrophages in rosacea: implications for targeted therapies. Front Immunol. 2023;14:1211953.
23. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol. 2017;26(8):659-67.
24. Dorschner RA, Pestonjamasp VK, Tamakuwala S, Ohtake T, Rudisill J, Nizet V, et al. Cutaneous injury induces the release of cathelicidin antimicrobial peptides active against group A Streptococcus. J Investig Dermatol. 2001;117(1):91-7.
25. Barton GM, Kagan JC. A cell biological view of Toll-like receptor function: regulation through compartmentalization. Nature Reviews Immunology . 2009 Aug 1 [cited 2020 Oct 1];9(8):535–42.
26. Deng Z, Chen M, Liu Y, Xu S, Ouyang Y, Shi W, et al. A positive feedback loop between mTORC1 and cathelicidin promotes skin inflammation in rosacea. EMBO Molecular Medicine. 2021 Mar 18;
27. Huang Y, Liu D, Chen M, Xu S, Peng Q, Zhu Y, et al. TLR7 promotes skin inflammation via activating NFκB-mTORC1 axis in rosacea. PeerJ. 2023 Sep 26 [cited 2024 Nov 6];11:e15976.
28. Hayran Y, Lay I, Mocan MC, Bozduman T, Ersoy-Evans S. Vascular endothelial growth factor gene polymorphisms in patients with rosacea: A case-control study. Journal of the American Academy of Dermatology [Internet]. 2019 Jun 8;81(2):348–54.

29. Rodrigues-Braz D, Zhao M, Nilufer Yesilirmak, Selim Aractingi, Behar-Cohen F, Jean-Louis Bourges. Cutaneous and ocular rosacea: Common and specific physiopathogenic mechanisms and study models. Molecular Vision [Internet]. 2021 May 13;27:323.
30. Ahn CS, Huang WW. Rosacea Pathogenesis. Dermatologic Clinics. 2018 Apr;36(2):81–6.
31. Morgado-Carrasco D, Granger C, Trullas C, Piquero-Casals J. Impact of ultraviolet radiation and exposome on rosacea: Key role of photoprotection in optimizing treatment. Journal of Cosmetic Dermatology. 2021 Mar 4;20(11).
32. Alinia H, Tuchayi SM, Patel NU, Patel N, Awosika O, Bahrami N, et al. Rosacea Triggers. Dermatologic Clinics. 2018 Apr;36(2):123–6.
33. Woo Y, Lim J, Cho D, Park H. Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition. International Journal of Molecular Sciences. 2016 Sep 15;17(9):1562.
34. Barczak I, Bondos B, Kochan R, Barczuk P, Bara S, Dzięgielewski J, Bączek K, Barć J, Gałajda E, Antonik J. Current views on pathogenesis of rosacea. J Educ Health Sport [Internet]. 2023 Jul. 18 [cited 2024 Nov. 6];18(1):109-22.
35. Salzer S, Kresse S, Hirai Y, Koglin S, Reinholz M, Ruzicka T, et al. Cathelicidin peptide LL-37 increases UVB-triggered inflammasome activation: Possible implications for rosacea. Journal of Dermatological Science. 2014 Dec;76(3):173–9.
36. Marson JW, Baldwin HE. Rosacea: a wholistic review and update from pathogenesis to diagnosis and therapy. International Journal of Dermatology. 2019 Dec 27;59(6).
37. Placek W, Wolska H. Rosacea – new data on pathogenesis and treatment. Dermatology Review. 2016;5:387–99.
38. Daou H, Paradiso M, Hennessy K, Seminario-Vidal L. Rosacea and the Microbiome: A Systematic Review. Dermatology and Therapy. 2020 Nov 10;11(1):1–12.
39. Wang FY, Chi CC. Rosacea, Germs, and Bowels: A Review on Gastrointestinal Comorbidities and Gut–Skin Axis of Rosacea. Advances in Therapy. 2021 Jan 28;
40. Searle T, Ali FR, Carolides S, Firas Al-Niaimi. Rosacea and Diet: What is New in 2021? The Journal of Clinical and Aesthetic Dermatology. 2021 Dec;14(12):49.
41. New Survey Pinpoints Leading Factors that Trigger Symptoms | Rosacea.org . www.rosacea.org.
42. Alia E, Feng H. Rosacea pathogenesis, common triggers, and dietary role: The cause, the trigger, and the positive effects of different foods. Clinics in Dermatology. 2021 Oct;40(2).
43. Nations U. Marine litter, an analytical overview. Uneporg . 2022 [cited 2022 Jul 28]
44. Amir Ali A, Vender R, Vender R. The role of IL-17 in papulopustular rosacea and future directions. J Cutan Med Surg. 2019;23(6):635-41.
45. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med. 2007;13:975-80.
46. Feldman SR, Huang WW, Huynh TT. Current drug therapies for rosacea: a chronic vascular and inflammatory skin disease. J Manag Care Pharm. 2014;20(6):623-9.
47. Narayanan S, Hünerbein A, Getie M, Jäckel A, Neubert RH. Scavenging properties of metronidazole on free oxygen radicals in a skin lipid model system. J Pharm Pharmacol. 2007;59:1125-30. doi: 10.1211/jpp.59.8.0010.

48. Hayran Y, Şen O, Fırat Oğuz E, Yücel Ç, Eren F, Külcü Çakmak S, et al. Serum IL-17 levels in patients with rosacea. J Cosmet Dermatol. 2022;21(3):1147-53.
49. Sharma A, Kroumpouzos G, Kassir M, Galadari H, Goren A, Grabbe S, et al. Rosacea management: a comprehensive review. J Cosmet Dermatol. 2022;21(5):1895-904.
50. Korting HC, Schöllmann C. Current topical and systemic approaches to treatment of rosacea. J Eur Acad Dermatol Venereol. 2009;23(8):876-82.
51. van Zuuren EJ, Fedorowicz Z, Tan J, van der Linden MM, Arents BW, Carter B, et al. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. Br J Dermatol. 2019;181(1):65-79.
52. Zhang Y, Jiang S, Lu Y, Yan W, Yan H, Xu Y, et al. A decade retrospective study of light/laser devices in treating nasal rosacea. J Dermatol Treat. 2020.
53. Bennardo L, Patruno C, Zappia E, Tamburi F, Sannino M, Negosanti F, et al. Combination of specific vascular lasers and vascular intense pulsed light improves facial telangiectasias and redness. Medicina. 2022;58(5):651.

54. Liu J, Zhou BR, Wu D, Xu Y, Luo D. Sequential delivery of intense pulsed light and long-pulse 1.064-nm neodymium-doped yttrium aluminum garnet laser shows better effect in the treatment of facial telangiectasias than using them separately. G Ital Dermatol Venereol. 2016;152(1):1-7.
55. Sánchez-Pellicer P, Eguren-Michelena C, García-Gavín J, Llamas-Velasco M, Navarro-Moratalla L, Núñez-Delegido E, et al. Rosacea, microbiome and probiotics: The gut-skin axis. Front Microbiol. 2024;14:1323644.
56. Manzhalii E, Hornuss D, Stremmel W. Intestinal-borne dermatoses significantly improved by oral application of Escherichia coli Nissle 1917. World J Gastroenterol. 2016;22(23):5415.