Heliyon 8 (2022) e10874

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Current research and clinical trends in rosacea pathogenesis

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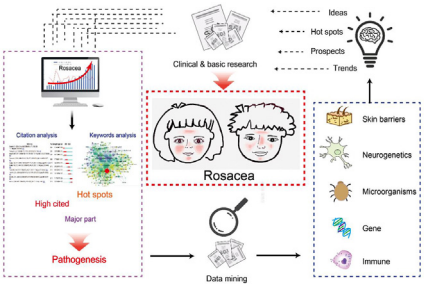
GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Rosacea
Pathogenesis
Bibliometric analysis
Data mining study
Risk factors
Comorbidity
Treatment

ABSTRACT

Background: Rosacea is a common and complex chronic inflammatory skin disorder, the pathophysiology and etiology of which remain unclear. Recently, significant new insights into rosacea pathogenesis have enriched and reshaped our understanding of the disorder. A systematic analysis based on current studies will facilitate further research on rosacea pathogenesis.

Objective: To establish an international core outcome and knowledge system of rosacea pathogenesis and develop a challenge, trend and hot spot analysis set for research and clinical studies on rosacea using bibliometric analysis and data mining.

Methods: A search of the WoS, and PubMed, MEDLINE, Embase and Cochrane collaboration databases was conducted to perform visual bibliometric and data analysis.

Results: A total of 2,654 studies were used for the visualization and 302 of the 6,769 outcomes for data analysis. It reveals an increased trend line in the field of rosacea, in which its fast-growing pathogenesis attracted attention closely related to risk, comorbidity and therapeutic strategies. The rosacea pathogenesis has undergone the great development on immunology, microorganisms, genes, skin barriers and neurogenetics. The major of studies have

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https://doi.org/10.1016/j.heliyon.2022.e10874
Received 25 May 2022; Received in revised form 30 July 2022; Accepted 27 September 2022
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focused on immune and microorganisms. And keyword visualization and data analyses demonstrated the cross-talk between cells or each aspect of pathogenesis, such as gene-gene or gene-environment interactions, and neurological mechanisms associated with the rosacea phenotype warrant further research.
Limitations: Inherent limitations of bibliometrics; and reliance on research and retrospective studies.
Conclusions: The understanding of rosacea's pathogenesis has been significantly enhanced with the improved technology and multidisciplinary integration, but high-quality, strong evidence in favor of genomic and neurogenic requires further research combined with a better understanding of risks and comorbidities to guide clinical practice.

1. Introduction

Rosacea is a complex chronic inflammatory facial skin disease that can have an adverse effect on the life quality of people worldwide. The prevalence of rosacea among people worldwide incidences peaks as high as 18% [1, 2], with estimates as high as 40 million cases, mostly in people aged between 30 and 50 [3,4]. Rosacea primarily affects the cheeks, nose, chin, and forehead with transient or persistent facial erythema, telangiectasia, papules, pustules, and recurrent flushing [5]. These pathological changes can lead to significant physical and mental discomfort, such as disfiguring manifestations, loss of sight in ocular rosacea, embarrassment, low self-esteem, and social phobia. Therefore, there is an urgent need for global research to develop better and more comprehensive management of rosacea, including its pathogenesis, risk factors, comorbidities, and treatment.

Although the etiology of rosacea is poorly understood, genetic factors, neurogenic dysregulation, immune systems dysregulation, microorganisms, barrier function impairment, and inflammatory response may play a major role in the development of rosacea [6, 7, 8]. In addition, a series of risk factors, comorbidities and specific treatments have also provided supplementary evidence for rosacea pathogenesis. For example, triggers that exacerbate the disorder (*e.g.,* heat, stress) may suggest a neurogenic relationship with rosacea [7]. And a significant association with psychiatric, neurological, metabolic and gastrointestinal diseases of rosacea are closely related to neurogenic dysregulation and microorganisms [9, 10]. Based on these findings, various advancements in the rosacea pathogenesis system have been made.

Recognizing and addressing the pathogenesis system are critical to improve the outcomes of rosacea management [11]. However, updated and systematic data on the rosacea's pathogenesis are still relatively sparse, which has not been thoroughly evaluated through comprehensive evidence or even through information on risks, comorbidities and treatments. Moreover, the development, research emphasis, challenges and prospects of rosacea research have been poor to date. Thus, the aim of this article was to establish a knowledge system of rosacea's pathogenesis system through a series of comprehensive studies. Notably, we also performed a trend analysis and insight setting for the guidelines on rosacea research and clinical study according to the pathogenesis system. Meanwhile, the noted management is highlighted for patients with rosacea.

2. Data and methods

2.1. Data strategy and selection criteria for bibliometric study

Literature data for this bibliometrics study were retrieved from the Web of Science (WoS) Core Collection. The WoS Core Collection contains several important index types, including Science Citation Index Expanded (SCIE), Social Science Citation Index (SSCI) and Emerging Sources Citation Index (ESCI). For a more comprehensive search of evidence on rosacea pathogenesis, we performed a thorough search and then manual classification to avoid missing information.

To perform a systematic analysis of rosacea, we chose articles, reviews and letters for inclusion in a visualization analysis. The terms 'Rosacea' and 'Pathogenesis' were used in the MeSH (https://www.ncbi.nlm.nih.gov/mesh) search, whereas 'Rosacea' and 'Pathogenesis' were represented by other expressions, such as 'Rhinophyma' and 'etiology', respectively. The search strategy used was as follows (TS=(rosacea) OR TS=(Rhinophyma)) AND (LA=("ENGLISH")) AND (DT= ("ARTICLE" OR "REVIEW" OR "LETTER")); AND WEB OF SCIENCE INDEX (WOS. SCI), and time span of 1992–01-01 to 2022-01-01 (Figure 1).

2.2. Data strategy and inclusion/exclusion criteria for data mining

We used a systematic approach to search the following databases: PubMed, MEDLINE, Embase and Cochrane collaboration databases with the search terms 'Rosacea' or 'Rhinophyma'. The article type was limited to English-language studies dated to 2022-01-01, with no limits on participant age, sex or type. The retrieval strategy of each database was customized according to the usage standard of the database and the scale of the retrieved documents. After the exclusion of repeated articles, a manual review of the citations from these articles was performed to identify additional articles by screening titles, abstracts and manuscripts. The literature screening process is shown in Figure 1, including search strategy and inclusion/exclusion criteria.

2.3. Data extraction and methodology

As for data extraction, the following information for rosacea pathogenesis was extracted by two investigators (XMH and ZXL) independently: first author's last name, year of publication, geographical region, study design, sample type, sample size, subtyping of rosacea, cell/bacteria culture/mice used in research, the key conclusion. while these information for risk factors/comorbidity/therapy was added as follow: mean age, gender, number of patient/exposure population-controls, adjusted risk estimate, variables adjusted in the multivariable analysis, *etc*. Moreover, publication bias was assessed using the Egger's test and visual inspection of funnel plots (Supplemental Figure 1). These statistical analyses were carried out with the 'meta' package of R.

The visualization analysis of the retrieval characteristics of rosacea included the distribution of publication years, countries and regions, organizations, journals, core authors, keywords and key references. Bibliometric analysis and network visualization were performed with VOSviewer (Version 1.6.14; https://www.vosviewer.com/download#downloadvosviewer) and CiteSpace (Version 6.1. R2; https://sourceforge. net/projects/citespace/files/latest/download). Microsoft Excel 2010 was used to assess the distribution of publication years. The Gunn map (http://lert.co.nz/map/) online world map was used to evaluate the distribution of countries and regions. Ranking was performed using the standard competition ranking method. Microsoft Excel software was utilized for data collection and analysis, and Adobe Illustrator CS6 was used for figure summary as Figures 5, 6, and 7.

3. Results

3.1. Bibliometric analysis

3.1.1. An increased trend line of publications in the field of rosacea

There were 1,980 (74.604%) articles, 350 (13.188%) reviews and 324 (12.208%) letters among the 2,654 publications. The chronological distribution of published documents is shown in Figure 2. The trend line

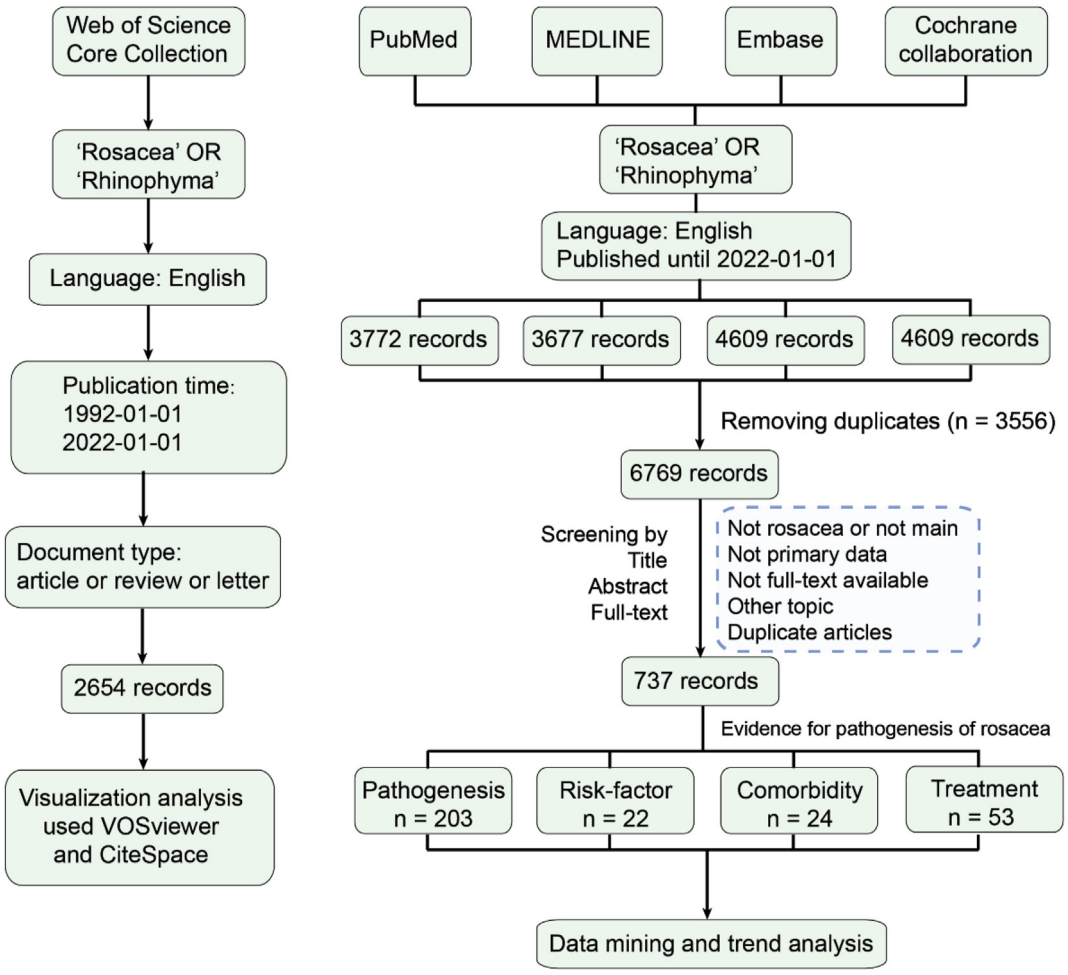

Figure 1. Systematic literature search and outcome identification.

demonstrates that the number of documents increased exponentially. The line chart illustrates that the number of documents increased relatively slowly from 1902 (n = 1, 0.038%) to 2002 (n = 33, 1.247%). Overall, the number of publications showed a sharply increasing trend from 2002 (with the largest sequential growth rate, 73%) onward, and the National Rosacea Society Expert Committee has developed a classification system and diagnostic standard to guiding clinicians and researchers. By 2020 (n = 262, 9.902%), the number of publications reached a peak. With a more standardized diagnosis as well as the improvement of aesthetics and quality of life, rosacea has attracted increasing attention worldwide, indicating that it will gradually become a research hotspot.

3.1.2. Rosacea is regarded as a universal and global topic according to its spatial distribution

According to the statistical analysis, 2,654 documents were published by research groups from 86 countries and regions using full counting analysis. The top 10 most prolific countries and regions have been shown in Table 1. The country with the largest number of documents was the United States (n = 927, 34.93%), followed by Turkey (n = 211, 7.95%), China (n = 210, 7.91%), and Germany (n = 205, 8.48%). Besides the number of publications, the United States also ranked the first according to the citation and centrality. The countries and regions with the strongest citation bursts are also shown in Table 1. Among them, China had the highest burst strength of 23.76. The duration of burst began in 2019 and ended in 2022, indicating that there were many researchers studying rosacea in China during 2019–2022. Many of countries have raised attention to rosacea from 1999 and recently more and more countries have also emerged, such as China and France. This spatial distribution maybe closely to the reported a varied prevalence of rosacea in people with skin of color from 1%- 22% [4]. Detailly, the research on the racial/ethnic distribution of patients with rosacea has been reported that 3.9% of rosacea patients were Hispanic or Latino, 2.3% were Asian or Pacific Islander, and 2% were black according to the US National Ambulatory Medical Care Survey (1993–2010) [12]. And other reasons may also contribute to this phenomenon, such as economy, technologic development, humanities and so on.

3.1.3. The pathogenesis of rosacea has attracted attention according to the citations

Among the total documents (n = 2,654), 40 met the threshold for vitalization analysis. According to the citation analysis of documents (n = 2,581), which reflects the number of times the documents were cited, we listed the top 10 most highly cited documents in Table 2. The range of the number of citations was 218–531. The top highly cited references were Hengge (2006), Wilkin (2002), Solomon (2001a), Yamasaki (2007), Sapadin (2006), Crawford (2004), and Bamford (2004), which had the highest number of citations, indicating that they were the most influential studies associated with rosacea. In addition, a systematic review and updating of international conferences on rosacea were likely cited many times.

Half of these studies were related to pathogenetic mechanisms, such as "*Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry eye disease*", which was ranked third and cited 500 times; "*Increased serine protease activity and cathelicidin promote skin inflammation in rosacea*", ranked fourth and cited 488 times; and

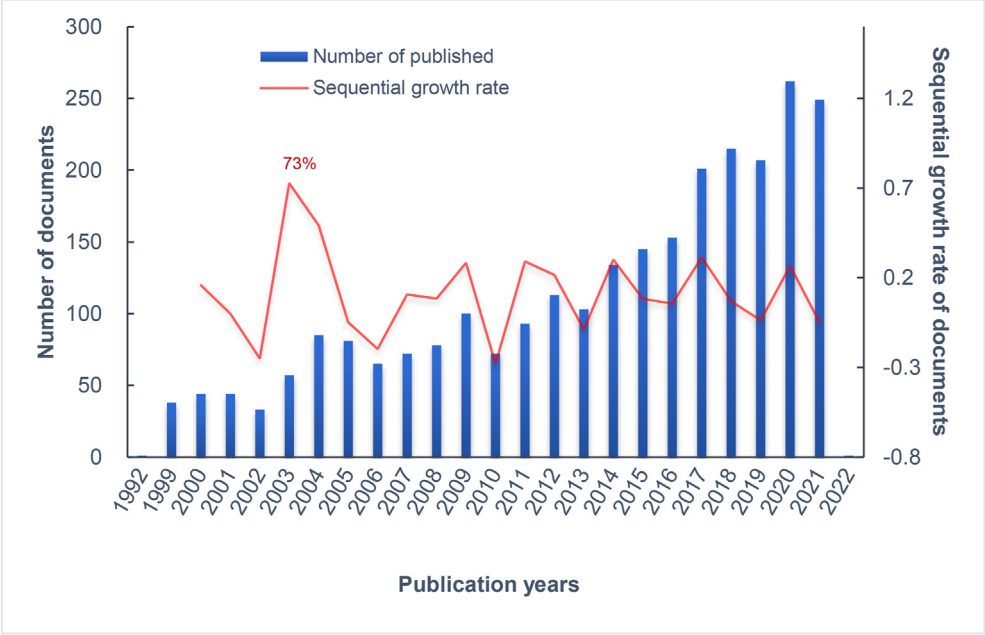

Figure 2. Distribution of publications on rosacea according to year. The number of publications increased slowly from 1902 to 2002. Overall, the number of publications showed an increasing trend in volatility from 2002 onward to a peak in 2020 (primary data for this analysis are shown in Table S7).

Table 1. Top 10 most productive countries and regions with publications on rosacea (2022-01-01).

Rank	Country/region	Documents	Citations	Total link strength	Strength of citation bursts	Begin (year)	End (year)
1st	USA	927	24,757	17,078	3.59	2006	2007
2nd	TURKEY	211	2,499	3,422	22.59	1999	2007
3rd	CHINA	210	2,903	3,905	23.76	2019	2022
4th	GERMANY	205	6,978	6,537	15.64	1999	2007
5th	ITALY	140	2,678	2,205	11.36	1999	2007
6th	FRANCE	132	4,046	4,949	11.02	1999	2007
7th	ENGLAND	120	2,986	3,029	11.53	1999	2007
8th	SOUTH KOREA	120	1,340	2,185	2.49	2017	2017
9th	CANADA	95	2,443	3,892	1.62	2002	2003
10th	SPAIN	88	1,588	1,072	1.57	2000	2000

Note: a strong citation burst indicates that a variable undergoes a great change in a short period of time.

"*Rosacea: I. Etiology, pathogenesis, and subtype classification*", ranked sixth and cited 334 times. Notably, the six research articles have focused on the pathogenetic mechanism [13, 14, 15, 16, 17, 18]. All of this evidence suggests that pathogenesis plays a vital role in the field of rosacea and has attracted attention for years as a hotspot [13, 14, 15, 16, 17, 18].

3.1.4. Pathogenesis as a new fast-growing rosacea subject according to the keywords

A total of 6,948 keywords were retrieved from 2,654 documents, and 100 met the threshold. The network visualization map shows the co-occurrence relations of keywords (Figure 3). The size of the circle indicates the occurrence of keywords. As shown in Figure 3, the high-frequency keywords include rosacea, skin, and pathogenesis. The average publication year of these three keywords is from 2012 to 2014. Furthermore, it also shows a fast-growing part that has developed in recent years, as the node in yellow indicates in Figure 3. As can be seen, in the last 5 years, an increasing number of researchers have given attention to cathelicidin, cytokines, immunity, mites, inflammation, pathophysiology, risk, and comorbidity in rosacea, indicating that pathophysiological factors have attracted attention as the focus of future research. Additionally, the management of rosacea, such as therapy, telangiectasia, and pulsed dye laser therapy, is a conspicuous aspect of rosacea research. All of this evidence suggests that it is a hotspot, and many scholars have devoted themselves to researching it.

4. Results of data mining on rosacea

4.1. Each of the core components of pathogenesis tends to increase

An increasing amount of evidence on rosacea etiology suggests that microorganisms (75, 31.9%), immune system (63, 26.8%), abnormal barrier function (33, 14.0%), gene (16, 6.8%), neurogenic (17, 7.2%), and other (30, 12.8%) factors may be genetic components. Additionally, the annual incidence of each factor is shown in Figure 4. The etiologic research on the immune system factors related to rosacea started in 1984, fluctuated rapidly in the last decade, and reached a peak in 2021. Additionally, research on microorganism etiology was conducted earlier, which is a major component (shown in orange in Figure 4) along with immune etiology (shown in blue in Figure 4). "Neurogenetic etiology" has been termed earlier but remains slow in progress. Abnormal barrier

Table 2. List of the top 10 most cited articles in rosacea (2022-01-01).

Rank by Total Citations	Title	Year/type	Corresponding Author	Country	Journal of Publication	Total Citations
1st	Adverse effects of topical glucocorticosteroids	2006 (review)	Hengge UR	Germany.	*J Am Acad Dermatol.*	531
2nd	Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea	2002 (guideline)	Wilkin J	USA	*J Am Acad Dermatol.*	508
*3rd	Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease	2001 (article)	Solomon, A	USA	*Invest Ophthalmol Vis Sci.*	500
*4th	Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea	2007 (article)	Yamasaki K	USA	*Nat Med.*	488
5th	Tetracyclines: Nonantibiotic properties and their clinical implications	2006 (review)	Sapadin AN	USA	*J Am Acad Dermatol.*	456
*6th	Rosacea: I. Etiology, pathogenesis, and subtype classification	2004 (review)	Crawford GH	USA	*J Am Acad Dermatol.*	334
7th	Standard grading system for Rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea	2004 (guideline)	Wilkin J	USA	*J Am Acad Dermatol.*	260
8th	Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature	2010 (review)	Griffin MO	USA	*Am J Physiol Cell Physiol.*	236
*9th	Azithromycin: mechanisms of action and their relevance for clinical applications	2014 (review)	Parnham MJ	Germany	*Pharmacol Ther.*	230
*10th	Antimicrobial peptides and the skin immune defense system	2008 (review)	Schauber J	Germany	*J Allergy Clin Immunol.*	218

* marked the document related to pathogenesis of rosacea. IL-1alpha, Interleukin 1alpha; TLR2, Toll-like receptor 2.

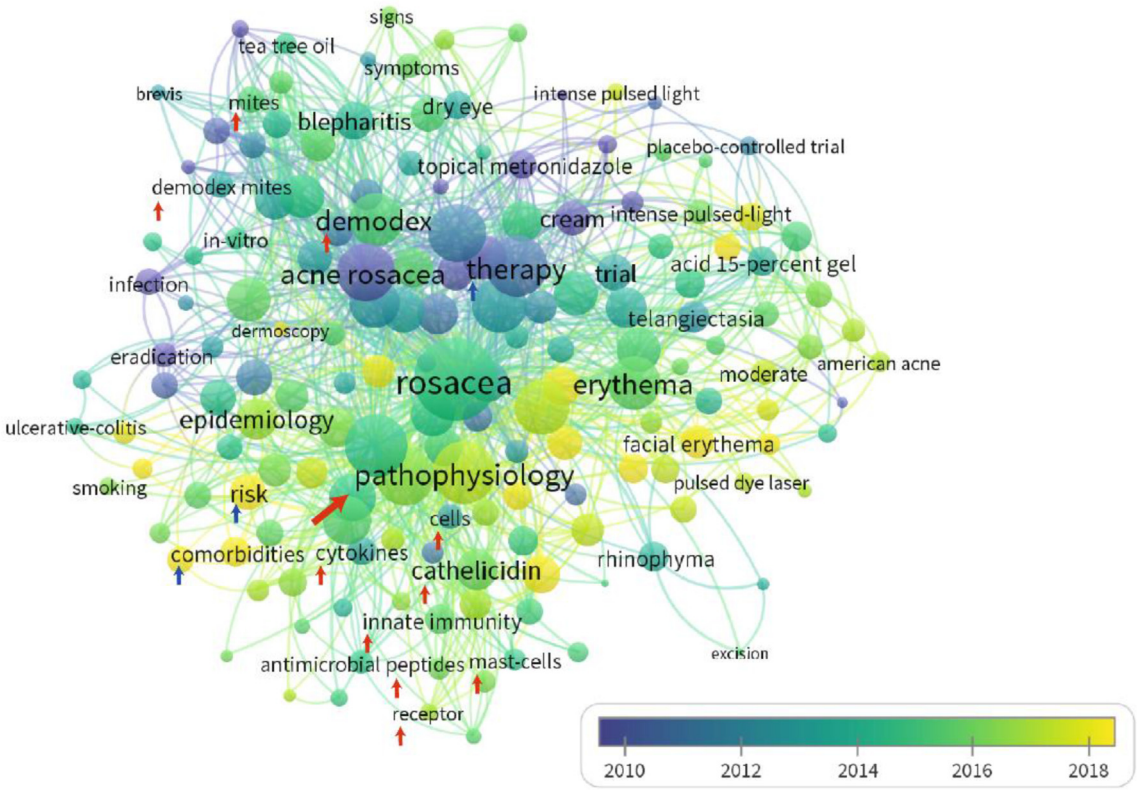

Figure 3. Co-occurrence analysis of keywords the keywords. The analysis method was Linlog/modularity. The weight was recorded. The color of the circle represents the average publication year. The red arrows are pathologically relevant, while the blue arrows are pathogenetic supporting evidence.

function and gene parts seem to be emerging aspects of rosacea pathogenesis and have increased in the literature in recent years.

Moreover, detailed information on the studies on each component has shown in Table S1-6 and detailly explained in discussion part, the subgroups including (*e.g.*, the roles of *Demodex* and H. pylori in microorganisms), study design, key outcomes, and publication year (neurogenetic and genetic etiologies, and immune, microorganism, barrier and other components).

4.2. Risk factors show an interface mechanism in rosacea pathogenesis

We screened out the parts as supporting material for rosacea pathogenesis. The main related risk factors include habits (*e.g.,* facial cleansing, shower, make-up, sun exposure), which suggest an impaired barrier function may be related to rosacea; natural factors (*e.g.,* H. pylori, E. coli) associated with immunity and microorganisms; genetic factors (*e.g.,* skin type, family history and genetic mutations) associated with genes; and

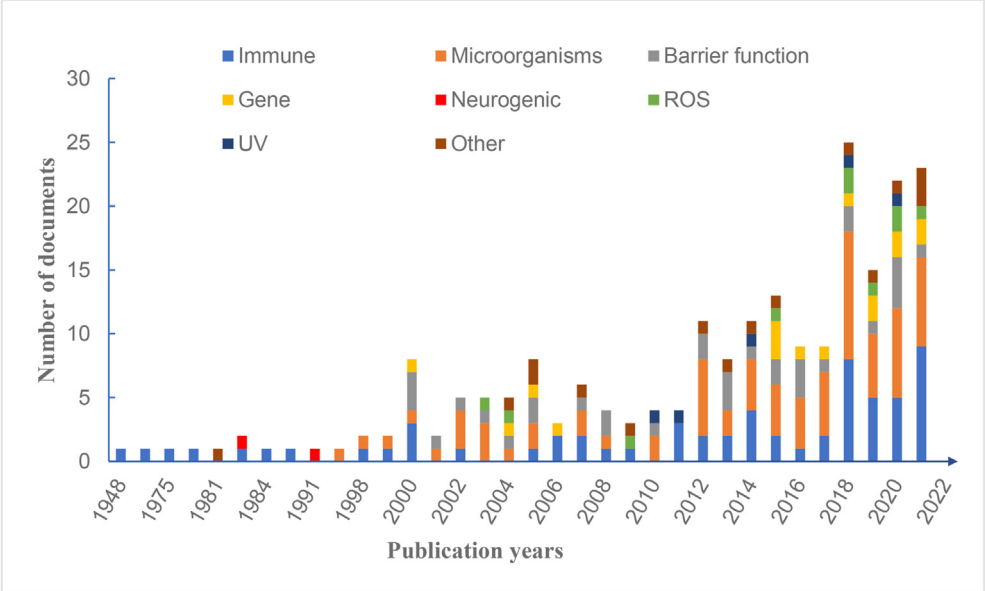

Figure 4. Distribution of publications on the pathogenesis of rosacea according to year, and each contribution is also shown (primary data for this analysis are shown in Table S8).

neuropsychiatric factors (*e.g.*, stress) associated with neurogenic parts. The detailed study design, individuals and statistical indicators are shown in Table 3.

4.3. Comorbidities and treatment also as vital supporting material for rosacea pathogenesis

Several studies have shown that rosacea is related to systemic disease, which could also contribute to rosacea pathogenesis. The prevailing literature has reported comorbidity associations between rosacea and gastrointestinal disorders (*e.g.*, irritable bowel syndrome (IBS), Crohn's disease), which proved the association with dysbacteriosis laterally. Notably, psychiatric diagnoses (*e.g.,* anxiety, depression) and neurological disorders (*e.g.,* Parkinson's disease, migraine, Alzheimer's disease) suggest a strong association between rosacea and neurogenic pathogenesis. More detailed information (study design, individuals and statistical indicators) is shown in Table 4. Moreover, some of the treatments based on pathogenesis are also regarded as supporting evidence for the etiology of rosacea (Table 5).

5. Discussion

Over the more than one hundred years of rosacea studies, the number of annual publications showed a sharply increasing trend from 2002, with the largest sequential growth rate onward and gradual increase in the last decade, reaching a peak in 2020 and 2021. The turning point in 2002 and 2004 may be related to the established standard for the classification system and diagnostic criteria by the National Rosacea Society Expert Committee [19, 20]. To date, the complex pathogenesis of rosacea has been elucidated. The timeline of some key discoveries has summered in Figure 5. Microorganisms have been found to be present early in rosacea pathogenesis, which develops with an increase in B. protein [18] and is associated with immunity and neurogenesis [21, 22]. Immune dysregulation continues to increase as a result of various immune cells and cytokines [23, 24]. An increasingly valued part, neurogenic dysregulation, has provided novel insight into rosacea pathogenesis [25, 26]. Family history suggests the presence of a genetic factor in the pathogenesis of rosacea [27, 28] and is enriched and elaborated to support other parts, such as immunity [29]. Several documents in the last two years may refer to emerging technologies (gene sequencing or single-cell sequencing, spatial transcriptomics, and other bioinformatics) and groups. Regardless, the increased curve trend of studies on rosacea suggests that an increasing number of researchers have become interested in rosacea, which indicates that there are still unsolved problems, such as pathogenesis.

Among the research on rosacea, pathogenesis seems to be a key part and a research hotspot. Among the top 10 highly cited documents, more than half of the documents addressed pathology-related studies, such as increased IL-1 expression [13], cathelicidin in skin inflammatory responses [14]. According to the keyword data, an increasing number of researchers have focused on pathogenesis-related items in the last 5 years. Further, we have summarized a systematic mechanistic pathway known to contribute to the pathophysiology of rosacea in Figure 6.

5.1. Genetic factors

The increased evidence in individuals with rosacea suggests that there may be a genetic component of the disorder. Earlier, a family history of rosacea, skin type (Fitzpatrick IV), and specific genetic mutations (ApaI G/T) were reported as risk factors, which strongly suggests a genetic component of the disorder. Various genomic association studies have already identified some genes pointing to various pathogenetic terms, such as the intercellular adhesion molecule-1 (*ICAM-1*) gene related to barrier function [30], glutathione S-transferase theta 1 (*GSTT1*) and/or glutathione-S-transferase μ-1 (*GSTM1*) and nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 (*NLRP3*) gene related to immune and inflammation [31, 32, 33], human leukocyte antigen-DR alpha (*HLA-DRA*), butyrophilin-like 2 (*BTNL2*) and signal transducer of activators of transcription (*STAT*) gene related to the immune [8, 34, 35]. Studies based on family, twin and regional factors (Celtic and Northern European descent) also suggest a genetic component of rosacea [29, 36]. Moreover, genetic studies have been reported every year since 2015 and may continue to increase with emerging technologies (*e.g.*, gene sequencing [37], omics analysis [38], other bioinformatics tools utilized in rosacea [39]). Further investigation will continue to focus on the mechanistic link between the gene variants identified in the rosacea phenotype [40]. Additionally, gene–gene (*e.g.*, lncRNA-mRNA coexpression networks [41]) and gene–environment interactions (*e.g.*, gene-ultraviolet) would be one of the focuses of intensive research studies. Finally, more research needs to be

Table 3. Risk factors as supporting evidence for rosacea pathogenesis.

Related factors	Differentiation	P/N	Design	Rosacea/Reference	No. of rosacea (F/M)	No. of reference (F/M)	Events in rosacea	Events in reference	Statistical indicators	Statistic	Adjusted *P* Value	Ref.
Gene												
Family history	rosacea	P	CC	122/132	\	\	\	\	OR (95% CI)	4.31 (2.34–7.92)	<0.0001	Abram er al., 2010
Family history	nasal lesions	P	CC	87/688	86 (70/16)	688 (587/101)	11 (12.8%)	50 (7.3%)	OR (95% CI)	2.12 (1.01–4.46)	0.049	Wu er al., 2021
Family history	rhinophyma	P	CC	52/156	2/50	3/153	25 (46%)	2 (1.3%)	OR (95% CI)	160.7 (27.3–944.6)	\<0.001	Second er al., 2019
Family history	rosacea	P	CC	1195/621	914/281	461/160	293 (24.5%)	40 (6.4%)	OR (95% CI)	4.718 (3.337–6.672)	0.000	Aksoy er al., 2019
GSTM1 (−/−)	rosacea	P	CC	45/100	31/14	53/47	29 (64.4%)	39 (39%)	OR (95% CI)	2.84 (1.37–5.89)	0.005	Yazici er al., 2006
GSTT1 (−/−)	rosacea	P	CC	45/100	31/14	53/47	20 (44.4%)	23 (23%)	OR (95% CI)	2.68 (1.27–5.67)	0.009	Yazici er al., 2006
TaqI alleles Mutant	rosacea	N	DS	60/0	46/14	46/14	10 (17%)	22 (37%)	OR (95% CI)	0.23 (0.07–0.74)	0.01	Akdogan er al., 2019
TaqI C/T Mutant	rosacea	P	DS	60/0	46/14	46/14	17 (10%)	37 (22%)	OR (95% CI)	4.69 (1.37–16.67)	0.01	Akdogan er al., 2019
ApaI alleles WT	rosacea	N	DS	60/0	46/14	46/14	12 (20%)	24 (40%)	OR (95% CI)	0.29 (0.10–0.84)	<0.01	Akdogan er al., 2019
ApaI G/T Heterozygous	rosacea	P	DS	60/0	46/14	46/14	43 (26%)	28 (17%)	OR (95% CI)	5.26 (1.51–18.35)	<0.01	Akdogan er al., 2019
ApaI G/T Mutant	rosacea	P	DS	60/0	46/14	46/14	37 (22%)	32 (19%)	OR (95% CI)	3.69 (1.19–11.48)	0.02	Akdogan er al., 2019
Cdx2 alleles Heterozygous	rosacea	P	DS	60/0	46/14	46/14	22 (37%)	15 (25%)	OR (95% CI)	2.51 (1.03–6.12)	0.04	Akdogan er al., 2019
Neurogenic												
Emotional change	rosacea	P	DS	168/0	117/51	\	12 (7.1%)	\	\	\	\	Bae er al., 2009
Nervousness and anxiety	rosacea	N	DS	40/0	\	\	25 (62.5%)	\	\	\	\	WATSON er al., 1965
Stress	rosacea	P	CR	14/0	12/2	\	10 (71%)	\	\	\	\	Scharschmidt er al., 2011
Stress	rosacea	P	DS	254/0	254 rosacea	\	188 (74.02%)	\	\	\	\	Chang er al., 2021
Rest and relaxation	rosacea	N	DS	168/0	117/51	\	18 (10.7)	\	\	\	\	Bae er al., 2009
Exercise	rosacea	P	CR	14/0	12/2	\	9 (64%)	\	\	\	\	Scharschmidt er al., 2011
Exercise/hot bath	rosacea	P	DS	168/0	117/51	\	41 (24.4%)	\	\	\	\	Bae er al., 2009
Sleep quality	rosacea	P	CSS	608/608	608 (526/82)	608 (526/82)	Measured by PSQI	PSQI	OR (96% CI)	3.525 (2.759–4.519)	no	Wang er al., 2020
Sleep quality	rosacea	P	CSS	608/608	608 (526/82)	608 (526/82)	Measured by PSQI	PSQI	OR (97% CI)	1.847 (1.332–2.570)	no	Wang er al., 2020
Spicy food	rosacea	P	DS	254/0	254 rosacea	\	153 (60.23%)	\	\	\	\	Chang er al., 2021
Spicy food (≥7 times per week)	rosacea	P	CC	1347/1290	1178/169	1096/194	572 (42.5%)	190 (14.7%)	OR (95% CI)	1.38 (0.87–2.18)	\	Yuan er al., 2019
Spicy food or hot food	rosacea	P	DS	168/0	117/51	\	4 (2.4%)	\	\	\	\	Bae er al., 2009
Temperature change	rosacea	P	DS	254	254 rosacea	\	222 (87.4%)	\	\	\	\	Chang er al., 2021
Cool	rosacea	N	DS	168/0	117/51	\	18 (10.7)	\	\	\	\	Bae er al., 2009
Heat	rosacea	P	CR	14/0	12/2	\	13 (93%)	\	\	\	\	Scharschmidt er al., 2011
Heat or sun	rosacea	P	DS	108/0	53/55	\	34 (31.5%)	\	\	\	\	Sibenge er al., 1992
Hot drinks	rosacea	N	DS	40/0	\	\	2 (5%)	\	\	\	\	WATSON er al., 1965
Hot showers	rosacea	P	CR	14/0	12/2	\	11 (79%)	\	\	\	\	Scharschmidt er al., 2011
Season changes	rosacea	P	DS	254	254 rosacea	\	144 (56.69%)	\	\	\	\	Chang er al., 2021
Thermal stimuli	rosacea	P	DS	224/0	M/F = 0.4	\	25%	\	\	\	\	Khaled er al., 2010
Warm environment	rosacea	P	DS	168/0	117/51	\	14 (8.3%)	\	\	\	\	Bae er al., 2009

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Table 3 (*continued*)

Related factors	Differentiation	P/N	Design	Rosacea/Reference	No. of rosacea (F/M)	No. of reference (F/M)	Events in rosacea	Events in reference	Statistical indicators	Statistic	Adjusted *P* Value	Ref.
Warmth	rosacea	P	DS	40/0	\	\	2 (5%)	\	\	\	\	WATSON er al., 1965
GCs												
GCs, Corticosteroids	rosacea	P	DS	108/0	53/55	\	32 (29.6%)	\	\	\	\	Sibenge er al., 1992
GCs, Fluorinated GCs	rosacea	P	CR	14/0	9/5	\	14 (100%)	\	\	\	\	Sneddon er al., 1969
Sun exposure												
Using sunscreen cream (≥6/week)	rosacea	P	CC	1245/1538	1245 (1124/121)	1538 (1388/150)	173 (13.9%)	327 (21.3%)	OR (95% CI)	0.303 (0.209–0.44)	<0.001	Huang er al., 2020
Using sunscreen cream (1–2/week)	rosacea	N	CC	1245/1538	1245 (1124/121)	1538 (1388/150)	125 (10.0%)	247 (16.1%)	OR (95% CI)	0.507 (0.353–0.727)	<0.001	Huang er al., 2020
Using sunscreen cream (3–5/week)	rosacea	N	CC	1245/1538	1245 (1124/121)	1538 (1388/150)	67 (5.4%)	116 (7.5%)	OR (95% CI)	0.533 (0.328–0.867)	0.017	Huang er al., 2020
Sun exposure	rosacea	P	DS	168/0	117/51	\	42 (25.0%)	\	\	\	\	Bae er al., 2009
Sun exposure	rosacea	N	DS	168/0	117/51	\	1 (0.6)	\	\	\	\	Bae er al., 2009
Sun exposure	rosacea	P	DS	224/0	M/F = 0.4	\	64%	\	\	\	\	Khaled er al., 2010
Sun exposure	rosacea	P	DS	254/0	254 rosacea	\	231 (90.94%)	\	\	\	\	Chang er al., 2021
Sun exposure	rosacea	P	CC	1195/621	914/281	461/160	249 (20.8%) High, 383 (32.1%) Moderate, 563 (47.1%) Little	82 (13.2%) High, 203 (32.7%) Moderate, 336 (54.1%) Little	OR (95% CI)	1.2951 (136–1.477)	0.000	Aksoy er al., 2019
Sun-based job	rosacea severity	P	DS	\	\	\	\	\	t ratio	-1.70	0.04	Alinia er al., 2018
Sunlight	rosacea	P	DS	40/0	\	\	3 (7.5%)	\	\	\	\	WATSON er al., 1965
Sunlight	rosacea	P	CR	14/0	12/2	\	13 (93%)	\	\	\	\	Scharschmidt er al., 2011

Risk factors will include in $P < 0.01$. GSTM1, Glutathione-S-transferase μ-1; GSTT1, Glutathione S-transferase theta 1; WT, Wild type; GCs, Glucocorticoids; P/N, positive/negetive; DS, Description study; CC, Case control; CSS, Cross-sectional study; CR, Case report; F/M, Female/Male; PSQI, Pittsburgh sleep quality index; OR, Odds ratio; CI, Confidence intervals.

Table 4. Comorbidities as supporting evidence for rosacea pathogenesis.

Comorbidity	P/N	Design	No. of rosacea (F/M)	No. of control (F/M)	Age (rosacea/control)	Events in rosacea patients	Events in control	Statistical indicators	Statistic	P Value	Ref.
Autoimmune disease											
Ankylosing spondylitis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	72 (0.56%)	21 (0.16%)	OR (95% CI)	2.34 (1.42–3.84)	0.001	Woo et al., 2020
Autoimmune thyroiditis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	121 (0.94%)	49 (0.38%)	OR (95% CI)	1.96 (1.40–2.73)	<0.001	Woo et al., 2020
Multiple sclerosis	P	CC	6759 (4270/2489)	33795 (21350/12445)	40.2/40.2	49 (0.7%)	149 (0.4%)	OR (95% CI)	1.65 (1.20–2.28)	0.003	Hua et al., 2015
Rheumatoid arthritis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	596 (4.6%)	272 (2.1%)	OR (95% CI)	1.72 (1.50–1.98)	<0.001	Woo et al., 2020
Rheumatoid arthritis	P	CC	6759 (4270/2489)	33795 (21350/12445)	40.2/40.2	217 (3.2%)	522 (1.5%)	OR (95% CI)	2.14 (1.82–2.52)	<0.001	Hua et al., 2015
Rheumatoid arthritis	P	CC	25 (14/11)	25 (14/11)	48/48	1 (4%)	0	\	\	\	Manna et al., 1982
Sjögren syndrome	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	94 (0.73%)	37 (0.29%)	OR (95% CI)	2.05 (1.40–3.00)	<0.001	Woo et al., 2020
Systemic sclerosis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	17 (0.13%)	2 (0.02%)	OR (95% CI)	6.57 (1.50–28.7)	0.012	Woo et al., 2020
Allergic conjunctivitis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	259 (2.0%)	121 (0.94%)	OR (95% CI)	1.57 (1.27–1.94)	<0.001	Woo et al., 2020
Allergic rhinitis	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	2064 (16.0%)	938 (7.3%)	OR (95% CI)	1.65 (1.54–1.76)	<0.001	Woo et al., 2020
Neurologic											
Alzheimer disease	P	CC	82439 (55161/27278)	5509279 (2775014/2734265)	42.1/40.4	465 (0.56%)	28728 (0.52%)	HR (95% CI)	1.25 (1.14–1.37)	<0.001	Egeberg et al., 2016
Fibromyalgia syndrome (FMS)	P	CSS	100 (100/0)	100 (100/0)	43.2/41.2	37 (37%)	21 (21%)	Prevalence (rosacea/control)	37% VS 21%	0.019	Acar et al., 2021
Glioma	P	CS	68372 (45994/22378)	5416538 (2732029/2684509)	42.2/40.8	184 (0.27%)	20934 (0.39%)	IRR (95% CI)	1.36 (1.18–1.58)	<0.001	Egeberg et al., 2016
Migraine	N	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	54 (0.42%)	58 (0.45%)	OR (95% CI)	0.66 (0.45–0.96)	0.053	Woo et al., 2020
Migraine	P	CS	49475 (33659/15816)	4312213 (2182262/2129951)	53.7/48.6	1095 (2.21%)	41606 (0.96%)	HR (95% CI)	1.23 (1.16–1.30)	<0.001	Egeberg et al., 2017
Migraine	P	CSS	53927 (33879/20048)	53927 (33879/20048)	\	4803 (8.9%)	4137 (7.7%)	OR (95% CI)	1.18 (1.13–1.24)	\	Spoendlin et al., 2013
Migraine	P	CC	137 (89/48)	161 (114/47)	46/42	66 (44%)	21 (13%)	\	\	<0.0005	Tan et al., 1976
Parkinson disease	P	CSS	68053 (45712/22341)	5404692 (2722615/2682077)	42.2/40.8	280 (0.41%)	22107 (0.41%)	IRR (95% CI)	1.71 (1.52–1.92)	\	Egeberg et al., 2016
Parkinson's disease	P	CSS	14696 (10278/4417/1)	399383 (246777/152542/64)	\	49 (0.33%)	985 (0.25%)	OR (95% CI)	1.39 (1.04–1.85)	0.02	Mathieu et al., 2018
Gastrointestinal disorders											
Barrett's oesophagus	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	88 (2.5%)	223 (1.6%)	OR (95% CI)	1.69 (1.20–2.37)	<0.01	Yi et al., 2021
Barrett's oesophagus	P	CC	3485/13,942	\	\	88 (2.5%)	223 (1.6%)	\	\	<0.001	Yi et al., 2021
Celiac disease	P	CC	49475 (33659/15816)	4312213 (2182262/2129951)	53.7/48.6	52 (0.11%)	2643 (0.06%)	HR (95% CI)	1.46 (1.11–1.93)	0.007	Egeberg et al., 2017
Celiac disease	P	CC	6759 (4270/2489)	33795 (21350/12445)	40.2/40.2	32 (0.5%)	80 (0.2%)	OR (95% CI)	2.03 (1.35–3.07)	<0.001	Hua et al., 2015
Crohn's disease	P	CC	1127 (1127/0)	95187 (95187/0)	37.6/36.2	11 (0.98%)	138 (0.14%)	HR (95% CI)	2.20 (1.15–4.18)	\	Li et al., 2016

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Table 4 (*continued*)

Comorbidity	P/N	Design	No. of rosacea (F/M)	No. of control (F/M)	Age (rosacea/control)	Events in rosacea patients	Events in control	Statistical indicators	Statistic	P Value	Ref.
Crohn's disease	P	CC	80957 (63.1%/36.9%)	80957 (Not specified)	\	326 (0.4%)	226 (0.3%)	OR (95% CI)	1.49 (1.25–1.77)	\	Spoendlin et al., 2016
Crohn's disease	P	CC	3485/13,947	\	\	92 (2.6%)	291 (2.1%)	\	\	0.047	Yi et al., 2021
Crohn's disease	P	CS	49475 (33659/15816)	4312213 (2182262/2129951)	53.7/48.6	98 (0.20%)	5684 (0.13%)	HR (95% CI)	1.45 (1.19–1.77)	<0.001	Egeberg et al., 2017
Diverticulitis	P	CC	3485/13,948	\	\	713 (20.5%)	2465 (17.7%)	\	\	<0.001	Yi et al., 2021
Diverticulitis	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	713 (20.5%)	2465 (17.7%)	OR (95% CI)	1.16 (1.05–1.28)	<0.01	Yi et al., 2021
Dyspepsia	P	CC	60 (31/29)	\	45.7/0	34	\	\	\	\	WATSON et al., 1965
Gastritis	P	CC	3485/13,943	\	\	446 (12.8%)	1366 (9.8%)	\	\	<0.001	Yi et al., 2021
GERD	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	1275 (36.6%)	4261 (30.6%)	OR (95% CI)	1.27 (1.17–1.38)	<0.001	Yi et al., 2021
GERD	P	CC	3485/13,941	\	\	1275 (36.6%)	4261 (30.6%)	\	\	<0.001	Yi et al., 2021
GERD	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	3118 (24%)	2487 (19%)	OR (95% CI)	1.05 (0.91–1.19)	0.052	Woo et al., 2020
GERD	P	CSS	1195 (914/281)	621 (461/160)	44.6 ± 13.8/42.5 ± 13.4	158 (13.2%)	61 (9.8%)	OR (95% CI)	1.399 (1.023–1.912)	0.036	Aksoy et al., 2019
Hepatobiliary system disorders	P	CSS	1195 (914/281)	621 (461/160)	44.6 ± 13.8/42.5 ± 13.4	12 (1.0%)	1 (0.2%)	OR (95% CI)	6.289 (1.010–48.479)	0.048	Aksoy et al., 2019
Inflammatory bowel disease	P	CS	89356 (68051/21305)	178712 (136102/42610)	32.58/32.58	16 (0.018%)	37 (0.020%)	HR (95% CI)	1.94 (1.04–3.63)	0.04	Wu et al., 2017
Irritable bowel syndrome	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	333 (9.6%)	1032 (7.4%)	OR (95% CI)	1.62 (1.02–2.58)	<0.05	Yi et al., 2021
Irritable bowel syndrome	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	1472 (11%)	1226 (9.5%)	OR (95% CI)	1.18 (0.62–1.42)	<0.001	Woo et al., 2020
Irritable bowel syndrome	P	CC	49475 (33659/15816)	4312213 (2182262/2129951)	53.7/48.6	291 (0.59%)	17047 (0.40%)	HR (95% CI)	1.34 (1.19–1.50)	<0.001	Egeberg et al., 2017
Irritable bowel syndrome	P	CC	3485/13,946	\	\	333 (9.6%)	1032 (7.4%)	\	\	<0.001	Yi et al., 2021
Non-diabetic gastroparesis	P	CC	3485/13,944	\	\	42 (1.2%)	107 (0.8%)	\	\	0.012	Yi et al., 2021
Non-diabetic gastroparesis	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	42 (1.2%)	107 (0.8%)	OR (95% CI)	1.49 (1.03–2.14)	<0.05	Yi et al., 2021
Oesophagitis	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	323 (9.3%)	920 (6.6%)	OR (95% CI)	1.30 (1.07–1.57)	<0.01	Yi et al., 2021
Peptic ulcer	P	CSS	61 (0/61)	193 (0/193)	42.8/not mentioned	8 (13.1%)	2 (1.0%)	OR (95% CI)	!	0.021	Li et al., 2020
SIBO	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	26 (0.7%)	63 (0.5%)	OR (95% CI)	1.29 (1.13–1.47)	<0.001	Yi et al., 2021
SIBO	P	CC	113 (82/31)	60 (40/20)	52/49	52 (46%)	3 (5%)	\	\	<0.001	Parodi et al., 2008
SIBO	P	CC	3485/13,945	\	\	26 (0.7%)	63 (0.5%)	\	\	0.029	Yi et al., 2021
Ulcerative colitis	P	CC	49475 (33659/15816)	4312213 (2182262/2129951)	53.7/48.6	163 (0.33%)	11588 (0.27%)	HR (95% CI)	1.19 (1.02–1.39)	0.028	Egeberg et al., 2017
Ulcerative colitis	P	CC	80957 (63.1%/36.9%)	80957 (Not specified)	\	556 (0.7%)	322 (0.4%)	OR (95% CI)	1.65 (1.43–1.90)	\	Spoendlin et al., 2016
Psychiatric diagnoses											
Adjustment disorder	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	179 (5.1%)	431 (3.1%)	OR (95% CI)	1.22 (1.03–1.47)	<0.05	Yi et al., 2021

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Table 4 (*continued*)

Comorbidity	P/N	Design	No. of rosacea (F/M)	No. of control (F/M)	Age (rosacea/control)	Events in rosacea patients	Events in control	Statistical indicators	Statistic	P Value	Ref.
Anxiety	P	CSS	774 (669/75)	\	\	417 (53.9%)	\	Prevalence (95% CI)	53.9% (50.4–57.4%)		Chen et al., 2021
Anxiety	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	844 (10.71%)	3031 (9.61%)	HR (95% CI)	2.911 (2.794–3.033)	<0.001	Hung et al., 2019
Anxiety (Anxiety score ≥9)	P	CC	201 (137/64)	196 (119/77)	38.8 ± 13.7/38.2 ± 14.1	41 (20.40%)	23 (11.70%)	Morbidity	0.204	\	Wu et al., 2018
Anxiety disorder	P	CC	194 (147/47)	194 (147/47)	47 (40–56)/46 (39–54.25)	21 (10.8%)	5 (2.6%)	OR (95% CI)	4.59 (1.69–12.43)	0.003	Incel et al., 2019
Anxiety disorder	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	757 (5.9%)	582 (4.5%)	OR (95% CI)	1.03 (0.92–1.13)	<0.001	Woo et al., 2020
Anxiety disorders	P	CC	55439 (36672/18767)	4576904 (2183601/2393303)	39.9/37.7	7413 (13.4%)	946025 (20.7%)	IRR (95% CI)	1.89 (1.72–2.07)	<0.001	Egeberg et al., 2016
Anxiety, generalized anxiety disorder	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	415 (11.9%)	1051 (7.5%)	OR (95% CI)	1.25 (1.10–1.42)	<0.001	Yi et al., 2021
Attention deficit hyperactivity disorder	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	1 (0.01%)	10 (0.03%)	HR (95% CI)	1.045 (1.003–1.089)	0.042	Hung et al., 2019
Bipolar disorder	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	22 (0.28%)	72 (0.23%)	HR (95% CI)	3.194 (3.066–3.329)	<0.001	Hung et al., 2019
Dementia	N	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	168 (1.2%)	197 (1.5%)	OR (95% CI)	0.80 (0.65–0.97)	0.051	Woo et al., 2020
Depression	P	CSS	774 (669/75)	\	\	450 (58.1%)	\	Prevalence (95% CI)	58.1% (54.7–61.6%)		Chen et al., 2021
Depression	P	CC	194 (147/47)	194 (147/47)	47 (40–56)/46 (39–54.25)	27 (12.9%)	9 (4.1%)	OR (95% CI)	3.041 (1.38–6.07)	0.006	Incel et al., 2019
Depression	P	CSS	12936 (8540/4396)	12936 (8540/4396)	47.4 ± 0.13/48.4 ± 0.13	890 (6.9%)	691 (5.34%)	OR (95% CI)	1.03 (0.93–1.12)	<0.001	Woo et al., 2020
Depression	P	CS	55439 (36672/18767)	4576904 (2183601/2393303)	39.9/37.7	5527 (10.0%)	672096 (14.7%)	IRR (95% CI)	1.96 (1.82–2.12)	<0.001	Egeberg et al., 2016
Depression	P	CC	53927 (33879/20048)	53927 (33879/20048)	\	8883 (16.5%)	7907 (14.7%)	OR (95% CI)	1.20 (1.16–1.24)	\	Spoendlin et al., 2014
Depression	P	CC	201 (137/64)	196 (119/77)	38.8 ± 13.7/38.2 ± 14.1	33 (16.40%)	16 (8.20%)	Morbidity	0.164	\	Wu et al., 2018
Depression symptoms	P	CC	120 (107/13)	497 (369/128)	42.3/40.3	36 (30%)	34 (6.8%)	OR (95% CI)	7.22 (4.12–12.63)	<0.001	Lukaviciute et al., 2020
Depression, MDD	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	219 (6.3%)	724 (5.2%)	OR (95% CI)	1.31 (1.14–1.51)	<0.001	Yi et al., 2021
Depression	P	CC	13026 (9884/3142)	\	\	\	\	Prevalence (95% CI)	20.0 (19.3–20.7)	\	Lin et al., 2013
Depression, MDD	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	360 (4.57%)	995 (3.16%)	HR (95% CI)	3.783 (3.630–3.941)	<0.001	Hung et al., 2019
Manic disorder	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	1981 (25.14 %)	7873 (24.97%)	HR (95% CI)	2.631 (2.525–2.741)	<0.001	Hung et al., 2019
Obsessive–compulsive disorder (OCD)	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	11 (0.14%)	18 (0.06%)	HR (95% CI)	6.389 (6.132–6.657)	<0.001	Hung et al., 2019
Persistent mood disorders	P	CC	3485 (2384/1101)	13940 (9536/4404)	59.6/59.4	37 (1.1%)	73 (0.5%)	OR (95% CI)	1.59 (1.06–2.37)	<0.05	Yi et al., 2021
Personality disorder	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	6 (0.08%)	22 (0.07%)	HR (95% CI)	2.851 (2.737–2.971)	<0.001	Hung et al., 2019

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Table 4 (*continued*)

Comorbidity	P/N	Design	No. of rosacea (F/M)	No. of control (F/M)	Age (rosacea/control)	Events in rosacea patients	Events in control	Statistical indicators	Statistic	P Value	Ref.
Phobic disorder	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	12 (0.15%)	16 (0.05%)	HR (95% CI)	7.841 (7.526–8.170)	<0.001	Hung et al., 2019
Schizophrenia	P	CS	7881 (5336/2545)	31524 (21344/10180)	40.60 ± 15.37/40.89 ± 15.30	28 (0.36%)	128 (0.41%)	HR (95% CI)	2.287 (2.195–2.383)	<0.001	Hung et al., 2019
Schizophrenia	N	CC	53927 (33879/20048)	53927 (33879/20048)	\	225 (0.4%)	318 (0.6%)	OR (95% CI)	0.71 (0.60–0.85)	\	Spoendlin et al., 2014

Comorbidity will include in $P < 0.01$. FMS: Fibromyalgia syndrome; GERD: Gastroesophageal reflux disease; SIBO: Small intestinal bacterial overgrowth; MDD: Major depressive disorder; OCD: Obsessive–compulsive disorder; P/N: positive/negetive; CC: Case control; CSS: Cross-sectional study; F/M: Female/Male; OR: Odds ratio; CI: Confidence intervals; HR: Hazard ratio; IRR: incidence rate ratio.

conducted on the causative genes, including their detailed functional feedback, for clinical applications.

5.2. Microorganisms

The percentages of studies related to microorganisms is extraordinarily large in the area of rosacea pathogenesis. According to our data, microbial pathogenesis can be divided into two parts: 1. Infection: *Demodex/mite* and H. pylori infection; 2. Dysbacteriosis: microorganisms in the skin, blood and gut.

The earlier study focused on descriptive research, has reported *mite* was only a highlighted risks [42]. Multiple studies have focused on the strong association of *Demodex* in deep pathogenesis, such as inflammatory stimulation [43, 44], tissue degradation [45], targeted therapies [46]. Detailly, the mechanism may be related to *Demodex*-associated Bacillus proteins, which could involve in inositol 1,4,5-trisphosphate (IP3) pathway [21], leading to corneal scarring [47] or erythema [48]. However, the topic regarding the causality between *Demodex/mite* and rosacea is still controversial. Immune and skin barrier dysregulation in rosacea patients may also lead to pathological growth of *Demodex/mite* [49]. So, more recent studies have reported *Demodex/mite* as aggravated factors of rosacea [50]. Overall, causality needs to be further studied through close observation of rosacea patients through the entire development combined with basic studies and accurate testing methods.

The role of H. pylori in the rosacea's pathogenesis remains controversial, which is mostly reported as an aggravating factor in rosacea and the target therapy is beneficial [51]. Other dysbacteriosis or targeted therapies have also attracted attention as they relate to skin microorganisms (S epidermidis [52]) and intestinal flora (E. coli Nissle therapy [53]). However, some studies have conducted superficial difference analyses. Therefore, how to explain a deeper microorganism mechanism contributing to the progression of rosacea and how to address it remain challenges. Whether inner linkage is involved in systematic dysbacteriosis occurring in the blood, gut, and skin as axis also requires further investigation to guide systematic and maintenance treatment on rosacea and reduce recurrence [54].

5.3. Immune system dysregulation

Research on the immunology related to the rosacea pathogenesis has rapidly increased in recent years. In addition to the technologies, research models have been established to aid this effort (LL-37 induced rosacea-like traits in mice and various cells) [55]. LL-37 (Cathelicidin antimicrobial peptide) and kallikrein 5 (KLK5) may serve as the key contributors to the proinflammatory and proangiogenic effects, which are highly expressed in the skin of patients with rosacea. Recent studies may pay more attention to the integrated mechanism of their up/downstream molecules (e.g., NLRP3 inflammasome [56], IL-36γ [57], protease-activated receptor 2 (PAR-2) [58], mechanistic target of rapamycin complex 1 (mTORC1) [59]). Additionally, it has also reported high expression of toll-like receptor (TLR) family and matrix metalloproteinases (MMPs) in patients with rosacea. Specifically, TLR1/2 and TLR4 activation promoted inflammation [60], *TLR2* gene expression was enhanced in glucocorticoid-induced rosacea [61], and the TLR signaling pathway was modulated by *Demodex mites* in rosacea progression [17].

Recent work has also focused on immune cells. An increased baseline number, activation and polarization of immune cells have been found in patients with rosacea (*e.g.*, mast cells, dendritic cells, T cells, Langerhans cells, plasma cells, macrophages, neutrophils) [62]. For example, N2-polarized neutrophils reduce inflammation in rosacea by regulating vascular factors and proliferation of $CD4^+$ cells [63]. A continued increasing trend may focus on more detailed and causative mechanisms, and a more complex co-network. Notably, these molecules have also contributed to diagnosis and treatment (e.g., doxycycline inhibited MMP [64], azelaic acid (AzA) inhibited KLK5 and TLR2 [65]). Thus, the

Table 5. Treatment as supporting evidence for rosacea pathogenesis.

Subtitle	Treatment	Design	Differentiation	Human sample	Cell/ mice	Mechanism	Ref.
Immune							
KLK 5, MMP-3	Oral doxycycline	RA	Rosacea	\	\	An inhibited activation of tryptic KLKs by inhibiting of matrix metalloproteinases (MMPs) in keratinocytes.	Kanada et al., 2012
KLK5	Gold nanoparticles (GNP	RA	Rosacea	\	Cell	antiKLK5 inhibited intracellular KLK5 activity in HaCaT cells and diminished secretion of IL-8 under inflammatory conditions triggered by TLR-2 ligands.	Limón et al., 2018
KLK5	Oral riterpenoids, from natural sources	RA	Dermatoses (rosacea, *etc.*)	\	Cell + mice	An inhibition of KLK5 protease activity and cathelicidin peptide production.	Matsubara et al., 2017
KLK5, MMP-9, VEGF	Compounds	RA	Rosacea	\	Cell	Dextran could inhibit KLK5 and MMP-9 mRNA expression, and IL-8, IL-1α and VEGF production.	Hernandez et al., 2018
LL-37	Chlamydial Plasmid-Encoded Virulence Factor Pgp3	RA	Rosacea	\	Cell	The middle region of Pgp3 (Pgp3m) was responsible for both the binding to and neutralization of LL-37.	Hou et al., 2016
LL-37	Cinnamtannin B1 (CB1)	RA	Rosacea	\	Mice	CB1 attenuated LL-37-induced inflammation, specifically IL-8 production, through inhibiting the phosphorylation of ERK.	Kan et al., 2020
LL-37	Hydroxychloroquine (HCQ)	RA	Rosacea	\	Mice + cell	HCQ attenuated LL37-mediated MCs activation partly via inhibiting KCa3.1-mediated calcium signaling.	Li et al., 2020
LL-37	Oral artesunate, doxycycline	RA	Rosacea	\	\	A decrease of inflammatory response	Li et al., 2018
LL-37	RNA Aptamer Apt 21-2	RA	Rosacea	\	Cell	Prevalence of LL-37 in these inflammatory skin conditions, as an anti-IL-17A RNA aptamer, Apt 21–2. LL-37	Macleod et al., 2019
LL-37	Single-stranded oligonucleotide (ssON)	RA	Rosacea	\	Mice + cell	Its ability to inhibit the basic secretagogues compound 48/80 (C48/80)-and LL-37 in vitro and in vivo.	Dondalska et al., 2020
LL-37	Topical AzA 15% Gel	RCT	Rosacea	20 PPR	\	Azelaic acid has been found to inhibit the pathologic expression of cathelicidin, as well as the hyperactive protease activity that cleaves cathelicidin into LL-37.	Wirth et al., 2017
LL-37	Topical SAGEs	RA	Rosacea	\	Mice + cell	A decrease of erythema and PMN infiltration from intradermal LL-37.	Zhang et al., 2011
LL-37, KLK5	Citron Essential Oils	RA	Rosacea	\	Cell	KLK5 and LL-37 induced by VD3 were suppressed by citron seed and unripe citron essential oils	Jeon et al., 2018
LL-37, KLK5	Superoxide dismutase 3 (SOD3)	RA	Rosacea	\	Mice + cell	SOD3 on LL-37- or KLK-5-induced skin inflammation in vitro and in vivo and its underlying anti-inflammatory mechanisms.	Agrahari et al., 2020
LL-37, KLK5, PAR2, VEGF	Topical Dermasence Refining Gel (DRG)	RA	Rosacea	\	Cell	The protein expression of all four inflammatory markers KLK5, LL-37, PAR2, VEGF was markedly reduced after treatment	Borelli et al., 2017
LL-37, mTORC1	Rapamycin (mTORC1 inhibition)	RA	Rosacea	32 rosacea	Mice + cell	Excess cathelicidin LL37 induces both NF-κB activation and disease-characteristic cytokine and chemokine production possibly via mTORC1 signaling.	Deng et al., 2021
LL-37. MCs	Onabotulinum toxin A and B	RA	Rosacea	\	Mice + cell	In mice, injection of onabotulinum toxin A significantly reduced LL-37-induced skin erythema, mast cell degranulation.	Choi et al., 2019
LL-37. TNF-α	Metformin	RA	Rosacea	\	Mice + cell	Metformin suppressed LL37- and TNF-α-induced the ROS production and MAPK–NF–κB signal activation in keratinocytes cells.	Li et al., 2021
MMP	Long-pulsed 1064-nm Nd: YAG laser	RA	Rosacea	\	Mice	LPND improve rosacea by ameliorating dermal connective tissue disorganization and elastosis through MMPs.	Kim et al., 2018
MMP-8	Oral Doxycycline	RCT	OcR	22 OcR, 22 HCs	\	Doxycycline effectively reduces these pathologically excessive levels and activation of MMP-8.	Määttä et al., 2006
MMP-9	Oral Doxycycline	RCT	OcR	21 OcR	\	MMP-9 did so after doxycycline treatment.	Lam et al., 2018
MMP9, cytokines	Tranexamic acid (TXA)	RA	Rosacea	\	Mice + cell	Rosacea-like symptoms including skin erythema and histopathological alterations, as well as the elevated pro-inflammatory cytokines (IL-6 and TNFα) and MMP9 expression were significantly ameliorated by TXA treatment.	Li et al., 2019
MMPs	Oral Doxycycline	RA	Rosacea	\	Cell	Doxycycline inhibits MMP activity in human skin and cultured keratinocytes	Kanada et al., 2012

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Table 5 (*continued*)

Subtitle	Treatment	Design	Differentiation	Human sample	Cell/ mice	Mechanism	Ref.
TLR2	Oral carvedilol administration	RA	Rosacea	\	Mice + cell	Inhibiting of macrophage TLR2 expression as a novel anti-inflammatory mechanism.	Zhang et al., 2021
TLR2	siRNA dispersion in topical emulsions	RA	Rosacea	\	Mice + cell	the interaction of siRNA with combination of excipients, such as urea and glycerol, is likely to favour the siRNA delivery, inducing genetic silencing of TLR2.	Colombo et al., 2019
TLR2, cytokine	Artemisinin (ART)	RA	Rosacea	\	Mice + cell	A decrease of pro-inflammatory factors (IL-1β, IL6, TNFα) and TLR2 after ART treatment in LL37-induced rosacea-like mice.	Yuan et al., 2019
TLR2, KLK5, LL-37	Topical AzA	RA	Rosacea	\	Mice + cell	AzA directly inhibited KLK5 and TLR2, and cathelicidin in mouse skin.	Coda et al., 2015
Macrophage	Paeoniflorin	RA	Rosacea	\	Cell	inhibits the macrophage-related rosacea-like inflammatory reaction through the SOCS3-ASK1-p38 pathway	Liu et al., 2021
MCs	Topical cromolyn	RCT, RA	PPR	10 PPR	Cell + mice	A decrease in matrix metalloproteinase activity after treatment.	Muto et al., 2014
Monocytes	Oral carvedilol 5 mg twice daily	RCT	Rosacea	18 rosacea	\	A decrease in plasma levels of CCL2, HMGB-1, IL-1β and TNF-α after treatment.	Gao et al., 2021
Neutrophils	Sodium bituminosulfonate	RA	Rosacea	\	Cell	SBDS reduces the generation of inflammatory mediators from human neutrophils possibly accounting for its anti-inflammatory effects in rosacea.	Schiffmann et al., 2021
T cell	Thalidomide	RA	Rosacea	\	Mice + cell	thalidomide reduced CD4+ T helper cell infiltration and downregulated Th1- and Th17-polarizing genes.	Chen et al., 2019
Cytokine	Melatonin (MLT)	RA	Rosacea	\	Cell	MLT treatment significantly improved rosacea-like skin lesion by reducing keratinocyte-mediated inflammatory cytokine secretion.	Zhang et al., 2021
Cytokines	Pioglitazone (PGZ)	RA	Rosacea	\	\	PGZ-NE showed good anti-inflammatory efficacy by decreasing the expression of inflammatory cytokines IL-6, IL-1β and TNF-α.	Espinoza et al., 2019
Cytokines	Thermal waters	RA	Rosacea	\	Cell	thermal waters suppress pro-inflammatory cytokines and angiogenic growth factor.	Karagülle et al., 2018
VEGF	Devices RF irradiation	DS, RA	Rosacea	2 rosacea	Cell + mice	RF irradiation attenuated VEGF-induced angiogenesis-associated processes such as tube formation, cell migration and endothelial cell proliferation.	Son et al., 2020
IL-1α	oral Azithromycin	RCT	OcR	21 OcR	\	IL-1α levels decreased after azithromycin therapy.	Lam et al., 2018
Immune response	Coptis chinensis Franch	RA	Rosacea	\	Cell	Coptis chinensis improved rosacea by regulating the immune response and angiogenesis, and revealed its mechanism of action	Roh et al., 2020
Lnc RNA NEAT1	Lnc RNA NEAT1	RA	Rosacea	6 rosacea	Cell	NEAT1 may have functioned as a competing endogenous RNA which regulated inflammatory responses in rosacea by sponging miR-196a-5p and upregulating S100A9 expression.	Wang et al., 2021
Microorganisms							
H. pylori	Anti-H. pylori therapy	RCT	H. pylori positive patients	872 H pylori positive patients (167 within rosacea)	\	H. pylori eradication leads to improvement of rosacea.	Saleh et al., 2017
H. pylori	Anti-H. pylori therapy	RCT	Rosacea	44 rosacea	\	H pylori infection can benefit from eradication therapy, mainly in PPR.	Boixeda et al., 2006
H. pylori	Anti-H. pylori therapy	PS, RCT	Rosacea	320 rosacea with H pylori	\	Treating H pylori infection has no short-term beneficial effect on the symptoms of rosacea to support the suggested causal association between H pylori infection and rosacea.	Bamford et al., 1999
H. pylori	Anti-H. pylori therapy	PS, RCT	Rosacea	25 rosacea, 87 HCs	\	H. pylori may be involved in rosacea and that eradication treatment may be beneficial.	Utaş et al., 1999
H. pylori	Anti-H. pylori therapy	PS, RCT	Rosacea	60 rosacea, 60 HCs	\	Rosacea may be considered as one of the major extragastric symptoms of Hp infection probably mediated by Hp-related cytotoxins and cytokines.	Szlachcic et al., 1999
SIBO	oral rifaximin	CC	Rosacea	60 rosacea, 40 HCs	\	SIBO may trigger rosacea by increasing circulating cytokines, especially tumor necrosis factor-alpha.	Drago et al., 2016
SIBO	Treat SIBO	DS	Rosacea within SIBO	40 Caucasian rosacea within SIBO	\	Treatment for SIBO is crucial in improvement and maintaining the clinical remission of rosacea.	Drago et al., 2017

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Table 5 (*continued*)

Subtitle	Treatment	Design	Differentiation	Human sample	Cell/ mice	Mechanism	Ref.
Demodex	Anti-Demodex therapy	RCT	Rosacea	25 rosacea	\	A reduction in the density of Demodex mites in facial skin of patients with rosacea under therapy.	Sattler et al., 2015
Gut microbiota	Oral E. coli Nissle	RCT	Intestinal-borne facial dermatoses	57 acne, PPR, seborrhoic dermatitis	\	Patients responded to E. coli Nissle therapy with significant amelioration or complete recovery.	Manzhalii et al., 2016
Neurogenetic							
TRPV1	Topical cream with trans-4-t-butylcyclohexanol and licochalcone A	RCT	Sensitive skin and rosacea	1221 sensitive skin and rosacea	\	Anti-inflammatory licochalcone A and the TRPV1 antagonist trans-t-butylcyclohexanol in subjects with sensitive skin prone to redness and rosacea.	Jovanovic et al., 2017
PPAR γ	Oral Doxycycline	RA	Rosacea	\	Cell	Reduced the cell number and increased the lipid content of SZ95 sebocytes in vitro byupregulatng of PPAR γ mRNA levels	Zouboulis et al., 2021
PPARγ	PPARγ	RA	Inflammatory skin diseases	\	Cell	AzA effect involves PPARγ modulation in inflammation and aging.	Briganti et al., 2013
PPAR γ	PGZ	RA	Rosacea	\	\	An agonist of PPARs, a nuclear receptor that regulates important cellular functions, including inflammatory responses.	Silvaet al., 2017
PDE5i	PDE5i	CC	Rosacea	7 ETR, 3 PPR	\	The NO liberated, following administration of PDE5i, lead to vessel alterations and induction in rosacea.	Ioannides et al., 2009
Oxidative stress							
ROS	Oral Azithromycin	RCT, RA	PPR	17 PPR, 25 HCs	\	This study supports the antioxidant properties of azithromycin in rosacea.	Bakar et al., 2007
Oxidative stress	Topical metronidazole	RA	Rosacea	\	\	Metronidazole in the treatment of rosacea is probably due to its ability to decrease ROS.	Narayanan et al., 2007

(KLK5, Kallikrein 5; MMP-3, Matrix metalloproteinase-3; VEGF, Vascular endothelial growth factor; mTORC1, Mechanistic target of rapamycin complex 1; TXA, Tranexamic acid; ART, Artemisinin; MLT, Melatonin; PGZ, Pioglitazone; MCs, Mast cells; TNF-α, Tumor necrosis factor α; TLR2, Toll-like receptor 2; IL-1α, Interleukin 1α; NEAT1, Nuclear-enriched abundant transcript 1; SIBO, Small intestinal bacterial overgrowth; TRPV1, Transient receptor potential vanilloid; PPARγ, Peroxisome proliferator-activated receptor γ; PDE5i, Phosphodiesterase-5 inhibitors; ROS, Reactive oxygen species; GNP, Gold nanoparticles; CB1, Cinnamtannin B; HCQ, Hydroxychloroquine; ssON, Single-stranded oligonucleotide; SAGEs, Semi-synthetic glycosaminoglycan ethers; SOD3, Superoxide dismutase 3; DRG, Dermasence refining gel; mTORC1, Mechanistic target of rapamycin complex 1; AzA, Azelaic acid; DS, Description study; CC, Case control; RA, Research article; RCT, Randomized controlled trial; PPR, Papulopustular rosacea; OcR, Ocular rosacea; ETR, Erythematotelangiectatic rosacea; HCs, Human controls; ERK, Extracellular signal-regulated kinase; VD3, Vitamin D; NF-κB, Nuclear factor kappa-B; MAPK, Mitogen-activated protein kinase; LPND, yttrium-aluminum-garnet laser; SOCS3-ASK1-p38, Suppressor of cytokine signaling 3-apoptosis signal-regulating kinase 1-p38; HMGB-1, High mobility group box-1; RF, Radiofrequency; NO, nitric oxide.).

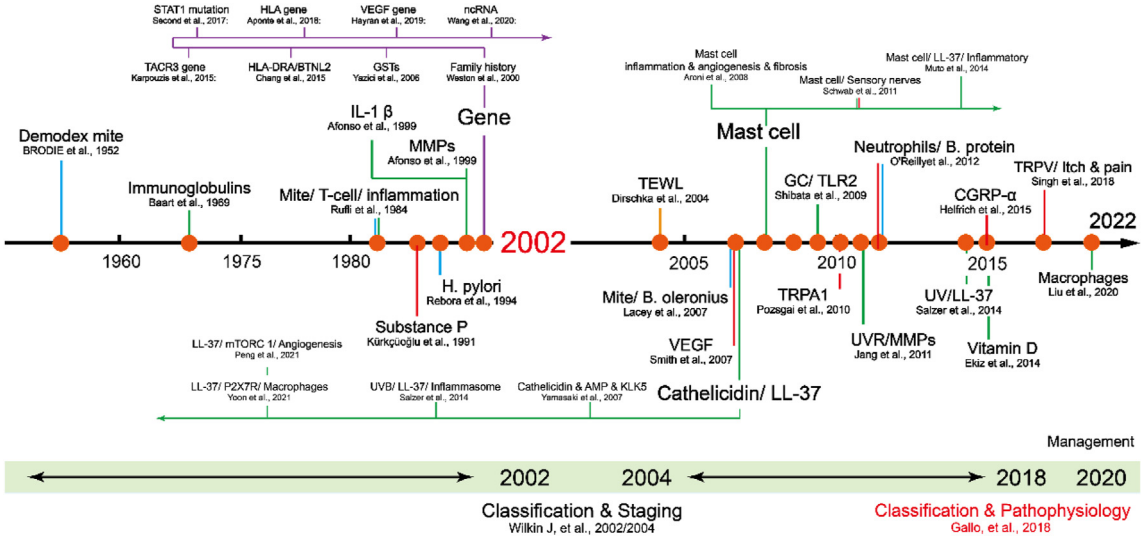

Figure 5. The timeline of some key discoveries in the field of the pathogenesis of rosacea. The timeline shows different aspects of pathogenesis in different colors as follows: green—immune, red—neurogenic, orange—barrier, purple—gene, blue—microorganisms. Part of the detailed development has occurred in topics such as cathelicidine/LL-37, mast cells and genes. A guideline with a vital role in the development of rosacea is shown in the second timeline below. MMPs, matrix metalloproteinases; IL-1 β, interleukin-1 beta; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor; HLA, human leukocyte antigen; ncRNA, noncoding RNA; mTOR, mammalian target of rapamycin; STAT, signal transducers and activators of transcription; H. pylori: Helicobacter pylori; TACR3, tachykinin receptor 3; TEWL: transepidermal water loss; TRPV, transient receptor potential ion channels of vanilloid type; B. oleronius, Bacillus oleronius; CGRP, calcitonin gene-related protein; GC, glucocorticoids; UVR, ultraviolet radiation. (The primary data for this analysis are shown in Tables S 1–6.)

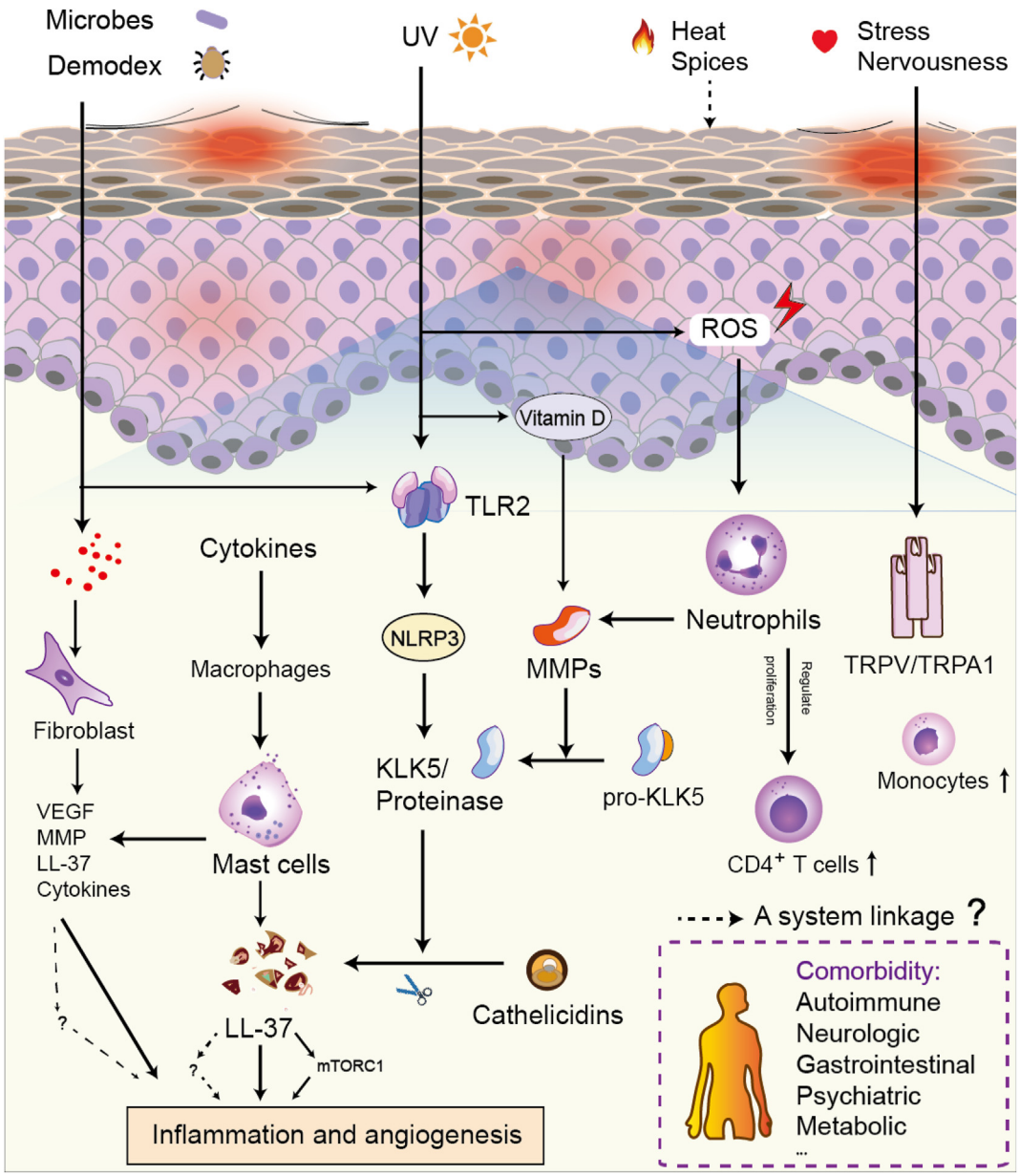

Figure 6. Mechanisms known to contribute to the pathophysiology of rosacea. The cathelicidin could be cleaved into its active peptide form, LL-37, by KLK5 or protease 3. These mutant forms of LL-37 play a role in inflammation and angiogenesis, which contribute to the clinical manifestations seen in rosacea. KLK5 is transformed from a proenzyme to an active enzyme by MMPs. TLR2 signaling could be triggered via multiple factors, such as ultraviolet (UV) light, reactive oxygen species or microbes and *Demodex/mite*, which again leads to increased levels of LL-37. Moreover, UV could activate VEGF, further contributing to the clinical manifestations of rosacea. Additionally, mast cells could produce LL-37 and other cytokines to promote inflammation in rosacea. Other triggers, such as spicy food, stress, exercise, and heat, have been shown to activate TRPV/TRPA1. Rosacea seems to be a disease with systemic implications rather than a localized skin disease as previously thought. Whether these mechanisms are involved in the systemic implications needs further study. Abbreviations: KLK5: Kallikrein 5; MMPs: Matrix metalloproteinases; TLR2: Toll-like receptor 2; UV: Ultraviolet; VEGF: Vascular endothelial growth factor; TRPV: Transient receptor potential vanilloid; TRPA1: Transient receptor potential ankyrin 1.

pathogenesis of rosacea will also continue to be studied in relation to clinical applications.

5.4. Neurogenic dysregulation

Strong and universally accepted evidence suggests a potential pathogenesis of neurogenic dysregulation. For example, triggers (stress, spicy food and heat [66]) could be aggravating factors for rosacea. Comorbidity research also suggests a close relationship between neurogenic dysregulation and rosacea, such as psychosis (e.g., anxiety, depression) and neurological disorders (e.g., Parkinson's disease, Alzheimer's disease). Additionally, symptoms (*e.g.*, erythema, itch, and pain) also refer to neurogenic disorders of rosacea. Although the term "neurogenic dysregulation" has been developed in relation to rosacea in the 20th century, the pathogenesis mechanism has been difficult to elucidate, possibly due to limitations in technologies or the heterogeneity of the disease presentation. It has been found that some neurogenic events are regarded as vital components in patients with rosacea (*e.g.*, sympathetic/axon reflex-mediated alterations [67], the neuropeptide calcitonin gene-related peptide (CGRP-α) [68], substance P [69], transient receptor potential vanilloid (TRPV) [70] and the vascular endothelial-derived growth factor (VEGF) family [71]). The

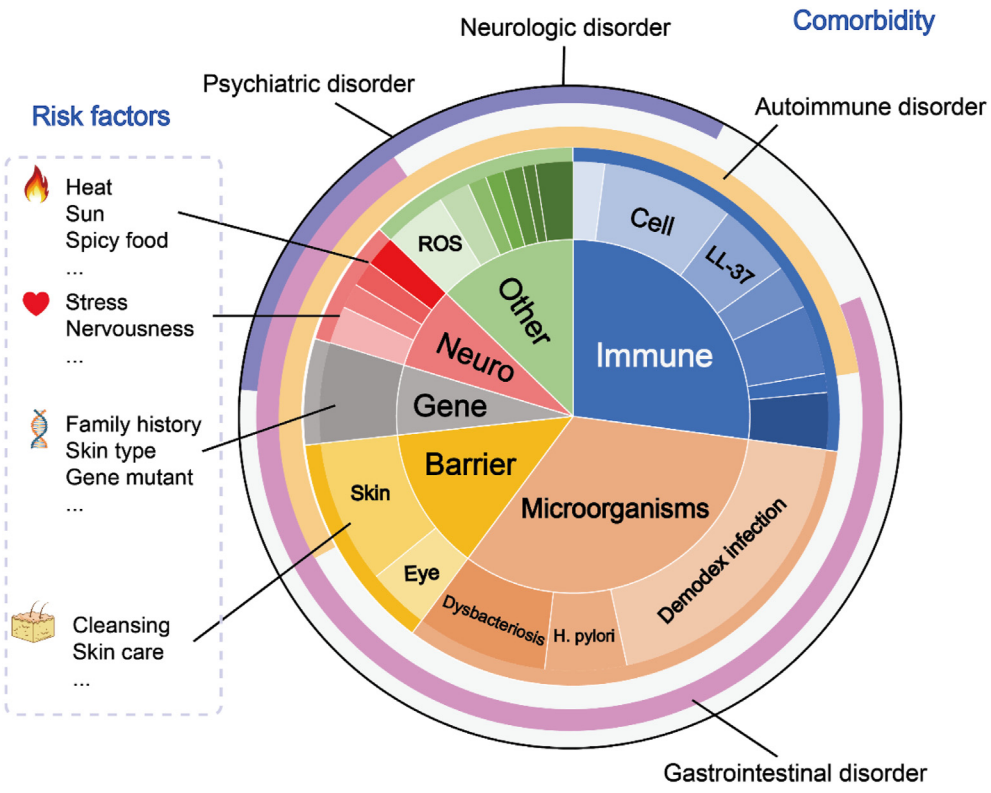

Figure 7. Establishment of the systemic pathogenesis of rosacea. The distribution of each subitem in the studies of rosacea pathogenesis according to publications is also shown (primary data for this analysis is shown in Table S9). Comorbidities and risk factors share distinct pathogenetic associations with rosacea. For example, rosacea comorbidities, such as autoimmune disorders, may be related to immune, genetic, barrier and other factors. The risk factors, such as heat, sun, and spicy food, suggest a relationship between rosacea and neurogenetic pathogenesis.

detection of TRP channel activation is related to inflammatory skin conditions, itching, and pain [25]. TRPV2 and TRPV4 were found to colocalize with mast cells in rosacea patients [26]. It has also reported that ETR has shown a significantly increased immunolabeling of TRPV2/3 and gene expression of TRPV1, while an enhanced immunoreactivity for TRPV2/TRPV4 has been found in PPR, and TRPV3/4 phymatous rosacea [26]. Additionally, it has been found that the upregulation of TRPV4 induced by LL-37 depends on mas-related gene X2 (*MRGX2*) activity related to inflammation in rosacea [72]. TRPV channels are regarded as a key role in a variety of sensory pathologies. It is closely related to the release of neuropeptides from sensory nerve by a rise in the cytosolic Ca^{2+} concentration [73]. Various lines of evidence point to neurogenic dysregulation, but further studies are needed to elucidate the mechanisms underlying this association using novel technologies, such as optogenetics, which leads to specific gene expression and gene product trafficking with subcellular precision [74], used in skin pathogens [75].

5.5. Inflammation and/or oxidative stress

Interestingly, a large number of studies are related to inflammation and/or ROS, which may be an indispensable event of rosacea. A high rate of inflammatory response has been found in subjects with rosacea (*e.g.,* follicular inflammatory reactions [76], the high-expressed cytokines IL-17 [77] and IL-1β [38]). It seems to be a response or a trigger to immune, microorganisms, and neurogenic dysregulation progression. Thus, these studies have further illuminated the detailed mechanism or triggers of inflammation related to serine protease activity and cathelicidin [14], immune cell infiltration [78], and *Demodex mite* infection [79]. For instance, mast cell proteases can recruit other immune cells through an inflammatory response, causing vasodilation and angiogenesis [80]. As for first-line strategy, AzA involves the specific activation of peroxisome proliferator-activated receptor γ (PPARγ), which plays a relevant role in inflammation and even in aging processes [81].

5.6. Abnormal barrier function

After suffering from those pathogenetic factors, skin may be dysfunctional featuring increased TEWL, decreased stratum corneum hydration [82], and collagen content [83], which is closely related to ICAM-1 and claudins (CLDNs, the main components of tight junctions constituting the major barrier) [84]. Thus, various creams and cleaners, such as Cetaphil PRO Redness Control Night Repair Cream, focus on repairing the skin barrier [85]. More related factors have been identified (*e.g.*, UV/sun exposure, Vitamin D, and hormones) and are aiding for therapeutic guidelines.

5.7. Risk factors for pathogenesis

Based on the common triggers for rosacea induction or exacerbation, it may be regarded as an intuitive theory of its macrolevel role in the pathogenesis of rosacea. Current research on risk factors contributing to the disease etiology is focusing on molecular mechanisms. Based on our data, cleansing habits and skin care support barrier function. However, cleansing at a high frequency or with a machine could mechanically break the walls of stem cells [86]. Many studies have been conducted on each of these topics. Risk factors may serve as a guideline and initial factor for pathogenesis studies.

As shown in Table 3, some of the outcomes of risk factors are controversial, such as whether spicy food is a positive risk factor for rosacea. In other words, there may be no specific risk factors associated with rosacea, and a large population-based study is needed to confirm this hypothesis. Additionally, it is important to recognize the control populations included in the study, which should be properly matched in terms of other factors. These factors may be known to influence each other or the rosacea phenotype, such as age, sex, body mass index (BMI), skin type, family history, related food, drug use, and sun exposure. Additionally, the risk factors for rosacea may vary with the phenotypic subtype, so we emphasize the importance of clear subtype inclusion and

the related mechanisms in future studies. Further studies are needed to elucidate the mechanisms underlying this association.

5.8. Comorbidities of pathogenesis

In recent years (especially in 2021), some observational evidence has shown that patients with rosacea have a higher risk of developing various comorbidities, which also highlights the pathogenesis progression in rosacea (Table 4). Regarding gastrointestinal disorders, almost all studies reported a positive relationship with rosacea, such as celiac disease, Crohn's disease, and irritable bowel syndrome (IBS). This can be understood in the context of the microbial pathogenesis of rosacea, which contributes to gastrointestinal disorders, such as H. pylori infection and dysbiosis of intestinal flora (i.e., small intestinal bacterial overgrowth (SIBO)). Psychiatric and neurological disorders have also been reported as positive comorbidities of rosacea (except dementia schizophrenia and migraine), which provides supplementary evidence for neurogenic dysregulation of pathogenesis in rosacea. Studies on rosacea comorbidities may continue to increase, combined with their pathogenetic pathways. However, many more concerns remain for continued research: 1) To date, association studies have failed to identify causal relationships between rosacea and other diseases. For example, rosacea could exert an adverse effect on quality of life, leading to psychiatric disorders. Meanwhile, anxiety disorders and depression may trigger or worsen rosacea. 2) The relationship between some diseases involving a particular system, such as Parkinson's disease in neurological system disorder, could not prove an overall association between the system disease and rosacea. 3) Whether identified comorbidities are positive or negative still needs to be further studied, such as migraine and schizophrenia.

6. Conclusion

Overall, the pathogenesis of rosacea has attracted increasing attention due to the complex interplay and/or co-network of genetic, microorganism, immunological, neurogenic, and barrier factors, further illustrating the chronic rather than acute nature of this inflammatory disease. We have provided a summary of the establishment of the systemic pathogenesis of rosacea in Figure 7. Various factors, such as risk factors and comorbidities, also contribute to the pathogenesis of rosacea. Notably, a growing body of evidence suggests that the pathogenesis of rosacea may play a vital role in systematic pathological changes, as well as in a systemic origin, or be a marker for increased/decreased risk of systemic disease.

7. Limitations

Limited research models of rosacea; diagnostic testing of patients; patient selection protocols; possible confounding factors; non-standardized research data collection and reporting across studies; reliance on research and retrospective studies in the WoS, PubMed, MEDLINE, Embase and Cochrane collaboration databases. Inherent limitations of bibliometrics were reported in others [87, 88, 89, 90, 91, 92, 93].

Declarations

Author contribution statement

Xi-min Hu, Li Ji, Rong-hua Yang and Kun Xiong: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Zhi-xin Li, Dan-yi Zhang, Yi-chao Yang, Sheng-yuan Zheng, Qi Zhang and Xin-xing Wan: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Funding statement

Ji Li was supported by National Key Research and Development Program of China [2021YFF1201200].

Kun Xiong was supported by National Natural Science Foundation of China [81971891; 82172196; 81772134].

Rong-hua Yang was supported by Applied Basic Research Key Project of Yunnan [2021A1515011453], Basic and Applied Basic Research Foundation of Guangdong Province [2022A1515012160], Key Laboratory of Medical Electrophysiology of Ministry of Education [KLET-202108].

Dr. Xi-min Hu was supported by National College Students Innovation and Entrepreneurship Training Program [S20210026020013].

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e10874.

Acknowledgements

We would like to thank American Journal Experts (AJE) (http://www.aje.com) for English language editing.

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