Supplemental table 1 Gene mechanism of the rosacea pathogenesis

Main title	Design	Differentiation	Human sample	Cell/mice	Mechanism	Ref.
Immune						
STAT gene	Family study	Rosacea	3/5 children and mother	\	Associated with demodicosis, in all family members with STAT1 mutation in rosacea.	Second et al., 2017
STAT gene	Family study	Rosacea	8 families (6 rosacea)	\	Heterozygous STAT1-GOF mutations contribute to fungal, bacterial, mycobacterial and viral infections, and autoimmune and inflammatory.	Sáez-de-Ocariz et al., 2020
TLR2, cytokines	CC	Rosacea	19 rosacea, 10 HCs	\	The TLR signaling was the most significant pathway detected in rosacea.	Sun et al., 2021
VEGF genes	CC	Rosacea	100 rosacea, 100 HCs	\	405+ C/G polymorphism of the VEGF gene increases the risk of rosacea.	Hayran et al., 2019
Inflammation						
HLA gene	DS	Rosacea	73265 rosacea	\	The identified loci provide specificity of inflammatory mechanisms in rosacea	Aponte et al., 2018
HLA-DRA and BTNL2 gene	CC	Rosacea	2618 rosacea, 20334 HCs	\	The gene variants identified in this study support the concept of a genetic component for rosacea	Chang et al., 2015
NLRP3 gene	Family study	Rosacea	29 families (8 rosacea)	\	A skin rosacea with ocular involvement was in 8 patients, correlated with hearing loss.	Sobolewska et al., 2016
GSTT1 and/or GSTM1 gene	CC	Rosacea	45 rosacea, 100 HCs	\	GSTs contributes to cellular defense against electrophilic chemical species and radical oxygen species.	Yazici et al., 2006
VDR gene	CC	Rosacea fulminans	27 fulminans, 110 rosacea, 61 HCs	\	VDR/RXR pathway in this inflammatory disease.	Jansen et al., 2004
Abnormal barrier function						
Claudin gene	CC, RA	Rosacea	12 ETR, 12 PPR, 8 PhR, 12 HCs	Cell	Claudin, CLDN reduction may associate with an impaired skin barrier.	Deng et al., 2019
ICAM-1 gene	Family study	Rosacea, CMC	Mother and nonidentical twin sons	\	The associations recorded with ICAM-1 deficiency and hyper-Ig E syndrome.	Ee et al., 2005
Neurogenic						
TACR3 gene	CC	Rosacea	67 ETR, 61 PPR, 121 HCs	\	TACR3 rs3733631 G allele possibly predisposes the evolution of the initial phase of PPR.	Karpouzis et al., 2015
Other						
Family history, drug	DS	Steroid rosacea	106 steroid rosacea	\	Family history of rosacea refers to prepubertal children with steroid rosacea.	Weston et al., 2000
Genetic contribution	Twin study	Rosacea	275 twin pairs (550 individuals)	\	A higher association of NRS scores between identical vs fraternal twins.	Aldrich et al., 2015
lncRNA-mRNA co-expression networks	CC	Rosacea	38 rosacea, 20 HCs	\	Ferroptosis, PPAR, NOD-like, and NF-κB and JAK-STAT signaling pathways are involved in rosacea.	Wang et al., 2020
miRNA	CC	PPR	32 PPR, 8 HCs	\	e.g., miRNA 21-3p is related to promoting angiogenesis and fibroblast function	Seo et al., 2021

(STAT, Signal transducer of activators of transcription; TLR2, Toll-like receptor 2; VEGF, Vascular endothelial growth factor; HLA, Human lymphocyte antigen; BTNL2, Butyrophilin-like 2; NLRP3, Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3; GSTT1, Glutathione S-transferase theta 1; GSTM1, Glutathione-S-transferase μ-1; VDR, Vitamin D receptor; ICAM-1, Intercellular adhesion molecule-1; TACR3, Tachykinin receptor 3; RXR, Retinoic X receptor; CC, Case control; DS, Description study; CMC, Mucocutaneous candidiasis; PPR, Papulopustular rosacea; STAT1, Signal transducer of activators of transcription 1; GOF, Gain-of-function; GSTs, Glutathione S-transferases; CLDN, Claudins; PPAR, Peroxisome proliferator-activated receptor; NRS, Numerical rating scale; NOD-like, Nucleotide-binding and oligomerization domain like; NF-κB, Nuclear factor kappa-B; JAK, Janus kinase)

Supplemental table 2 Microorganisms mechanism of the rosacea pathogenesis

Main title	Design	Differentiation	Human sample	Cell /mice	Mechanism	Ref.
Microbial infection						
***Demodex* infection**						
B. oleronius	CC	Rosacea	22 rosacea, 17 HCs	\	*B. oleronius* could stimulate inflammatory response in PPR.	O'Reilly et al., 2012
B. oleronius	RA	Rosacea	\	Cell	*B. oleronius* proteins activate neutrophils via the IP3 pathway leading to inflammatory.	Yun et al., 2019
B. oleronius	CC	Ocular Dermatosis	38 ocular Dermatosis, 21 HCs	\	Ocular *Demodex* and serum immunoreactivity associated with Bacillus proteins.	Forton et al., 2019
B. oleronius	DS	ETR	75 ETR	\	Increased Demodex and reduced sebum levels were found in rosacea with *B. oleronius* response.	Kubanovet al., 2019
B. oleronius, MMP 9	RA	OcR	\	Cell	Bacillus protein associated with inflammatory cytokines and MMP-9 leading to tissue degradation and corneal scarring.	Sędzikowska et al., 2018
B. oleronius, mononuclear cells	CC	Rosacea	22 rosacea, 17 HCs	\	*B. oleronius* stimulate inflammatory response in PPR.	Falay et al., 2018
Demodex	CC	PPR	92 PPR, 92 HCs	\	Increased density of Demodex and delayed hypersensitivity were found in PPR.	Clanner et al., 2018
Demodex	DS	Rosacea	132 rosacea	\	Demodex is closely related to rosacea.	Gonzalez et al., 2018
Demodex	CSS	Rosacea, demodicosis	57 PPR, etc.	\	Demodicosis is closely related to rosacea.	Forton et al., 2018
Demodex	CC	Acne rosacea	75 acne rosacea, 75 discoid LE, 75 actinic lichen planus	\	Demodex were higher in rosacea.	Ciccarese et al., 2018
Demodex	CS	Dermatosis	539 dermatosis, 321 HCs	\	Demodex is closely related to rosacea.	Yun et al., 2017
Demodex	CC	Rosacea	25 rosacea, 25 HCs	\	Demodex were higher in rosacea.	Turan et al., 2017
Demodex	RA	OcR	\	Cell	Demodex were higher related to corneal ulcers in OcR.	Turgut et al., 2017
Demodex	CSS	Rosacea	52 ETR, 174 PPR	\	The dermal inflammatory infiltration was found in rosacea.	Lee et al., 2016
Demodex	CC	Rosacea	18 ETR, 32 PPR, 48 HCs	\	Demodex were higher in rosacea related to inflammation.	Lee et al., 2016
Demodex	CC	Rosacea	30 rosacea; 30 HCs	\	Demodex were higher in rosacea.	Talghini et al., 2015
Demodex	CC	Rosacea, etc.	34 rosacea, 34 HCs	\	Demodex were higher in rosacea.	Murillo et al., 2014
Demodex	DS	Rosacea	52 ETR, 174 PPR	\	ETR & PPR exhibit demodex within the follicular infundibulum.	Harmelin et al., 2014
Demodex	CS	Demodicosis	35 demodicosis (13 rosacea)	\	Demodex were higher in rosacea.	McMahon et al., 2014
Demodex	CC	Rosacea	30 PPR, 30 ETR, 40 HCs	\	Demodex were higher in PPR & ETR.	Jarmuda et al., 2014
Demodex	CSS	\	134 blepharitis, 67 rosacea, 69 rheumatoid arthritis.	\	Rosacea are risk factors for Demodex infection.	Ríos et al., 2013
Demodex	RA	\	\	\	Demodex were higher in rosacea.	Sattler et al., 2012
Demodex	CC	Rosacea	31 ETR, 10 PPR	\	Demodex were higher in PPR.	O'Reillyet al., 2012
Demodex	DS, CC	Rosacea	254 rosacea	\	Demodex is closely with PPR.	O'Reillyet al., 2012
Demodex	DS	\	60 rosacea	\	Demodex was the agent most frequently found in rosacea.	Casas et al., 2012
Demodex	CC	Rosacea	77 rosacea, 31 HCs	\	High positive Demodex infestation was found in rosacea.	Zhao et al., 2011
Demodex	CC	Rosacea, demodicosis	23 ETR, 254 PPR, 590 demodicosis, 180 other facial dermatoses, 20 HCs	\	ETR is related to Demodex proliferation, as a subclinical stage	Li et al., 2010
Demodex	DS	Rosacea	108 rosacea	\	Demodex may be present in rosacea.	Moravvej et al., 2007
Demodex	CC	Rosacea	60 rosacea, 40 HCs	\	SIBO was the most relevant factor in PPR.	Basta et al., 2002
Demodex	CC	Rosacea	43 rosacea, 77 HCs	\	Demodex is closely related to rosacea.	Georgala et al., 2001
Demodex	CC	Rosacea	58 rosacea, 31 HCs	\	Demodex were higher in rosacea.	Kara et al., 2021

Demodex	CC	Rosacea	40 rosacea, 40 HCs	\	Demodex were higher in rosacea, especially in PPR.	Forton et al., 2021
Demodex	CC	Rosacea	60 rosacea	\	Demodex were higher in PPR.	Trave et al., 2021
Demodex	DS	PPR	60 PPR	\	Demodex follicular openings were higher in moderate rosacea.	Aktaş et al., 2020
Demodex, *sebum secretion*	DS	Rosacea	17 ETR, 15 PPR, 8 FR	\	The changing sebaceous microenvironment in rosacea leads to increased *demodex*.	Falay et al., 2018
Demodex, MMP-2/9	CSS	Rosacea	34 rosacea	\	High level of *Demodex* and MMP-2/9 were found rosacea.	Lazaridou et al., 2010
Demodex, T-cell	CC	PPR	36 PPR, 24 HCs	\	High levels of TH 1 cell were found in rosacea; high frequencies of TH 9/22 cells in Rosacea/Demodex	Forton et al., 2005
Demodex, TLR	RA	\	\	Cell	Demodex secreted bioactive molecules affected TLR2 receptor by sebocytes inducing inflammation	Türkmen et al., 2019
Demodex, CD4 helper/inducer T	CC	Rosacea	38 rosacea, 38 HCs	\	CD4 helper/inducer T cell response related to mite in rosacea.	Sarac et al., 2020
Demodex, immune	CC	ETR	26 ETR, 21 HCs	\	Serum immunoreactivity is related to Bacillus proteins in ETR.	Ogrum et al., 2020
Demodex, immune	CS	Dermatosis	844 Dermatosis, 200 HCs	\	Age, immunosuppression, sebaceous gland hyperplasia, and hypervascularization lead to demodex proliferation.	Agnoletti et al., 2017
Demodex, inflammatory	CC	PPR	11 PPR, 10 HCs	\	Abnormal proliferation of Demodex is related to inflammatory in rosacea.	Sibenge et al., 1992
Demodex, inflammatory	CC	Rosacea	17 ETR, 15 PPR, 8 FR, 40 HCs	\	Demodex were higher in rosacea within high oxidative stress and inflammation in circulation.	Erbağci et al., 1998
Demodex, inflammatory	CC	Rosacea, demodicosis	60 rosacea &demodicosis, 60 rosacea only, 72 HCs	\	Demodex mites promote the acute-inflammatory, increase the recurrence.	Lacey et al., 2007
Demodex, microbiota	CC	Rosacea	15 ETR, 15 PPR, 17 HCs	\	Increased of *Proteobacteria* and *Firmicutes* and whereas proportion of decreased of *Actinobacteria*in PPR.	Bonamigo et al., 2005
Demodex, MMP-2/9	DS	Rosacea	34 rosacea	\	Demodex and MMP-2 and MMP-9 Demodex were found in rosacea.	Moreno et al., 2021
Demodex, neutrophils	RA	ETR	\	Cell	Mite-related Bacterium protein increase the migration, degranulation and cytokine production of neutrophils.	Weinstock et al., 2013
Demodex, skin type	CC	Rosacea, acne vulgaris	30 rosacea & acne vulgaris, 60 HCs	\	Oily, acidic, very dry skin could facilitate Demodex in rosacea.	AlBalbeesi et al., 2021
Demodex, sun exposure	DS	Rosacea	100 rosacea	\	Demodex leads a vascular to an inflammatory stage promotesd by UV.	Ciccarese et al., 2018
***H. pylori* infection**						
H. pylori	DS	Rosacea	20 rosacea	\	H. pylori is an aggravating factor especially in ETR.	Thompson et al., 2020
H. pylori	CC	Rosacea	62 rosacea, 124 HCs	\	H. pylori is a triggering factor for rosacea.	Wang et al., 2020
H. pylori	CC	Rosacea	24 rosacea, 17 HCs	\	H. pylori was higher found in rosacea.	Maher et al., 2018
H. pylori	DS	Rosacea	49 rosacea	\	H. pylori was higher found in rosacea.	Dahl et al., 2004
H. pylori	DS	Rosacea	48 rosacea	\	H. pylori is associated with rosacea.	Yuan et al., 2020
H. pylori	CC	Rosacea	26 rosacea, 26 gastritis, 52 HCs	\	H. pylori is associated with rosacea.	Bertolini et al., 2015
H. pylori	CC	Rosacea	90 rosacea, 90 HCs	\	H. pylori infection was significantly higher in rosacea.	Thompson et al., 2020
H. pylori	CC	Rosacea	60 rosacea, 40 HCs	\	H. pylori was the agent most frequently found in rosacea.	Rainer et al., 2020
H. pylori	DS	\	60 rosacea	\	H. pylori was the agent most frequently found in rosacea.	Nam et al., 2018
H. pylori, CSU	DS	Rosacea	41 rosacea, 73 urticaria	\	H. pylori with rosacea is significantly associated with CSU.	Zaidi et al., 2018
H. pylori, cytokines	CC	Rosacea	60 rosacea, 60 HCs	\	Higher H. pylori in rosacea may mediate by Hp-related cytotoxins and cytokines.	Thompson et al., 2020
H. pylori, inflammatory	CC	Rosacea	33 rosacea, 20 HCs	\	H. pylori increases oxygen radicals to stimulate inflammatory species NO.	Thompson et al., 2021
H. pylori, inflammatory	CC	Rosacea	68 rosacea, 54 HCs	\	H. pylori is closely related to PPR by virulent strains leading to inflammatory.	Whitfeld et al., 2011
Chlamydia trachomatis	DS	LGV	16 rosacea, etc.	\	*Chlamydia* appears to be an important cause of rosacea.	Lacey et al., 2007
Dysbacteriosis						
Bacteria- temperature	RA	Rosacea	\	\	Temperatures effects Bacteria proteins production.	Bhattarai et al., 2012
Bacterial dysbiosis	CSS	PPR	22 PPR	\	Skin dysbacteriosis was found in rosacea.	El-Khalawanyet al., 2012

Bacterial dysbiosis	CC	\	15 twin pairs with rosacea	\	A significant correlation was found between facial microbiome and severity of rosacea	Zandi et al., 2003
Bacterial dysbiosis	CC	Rosacea	25 rosacea (lesion, non-lesion)	\	Bacterial dysbiosis is related to skin barrier.	Diaz et al., 2003
Bacterial metabolism-temperature	RA	PPR	\	\	Increased temperature leads to immune response via altering *B. oleronius*.	Argenziano et al., 2003
Blood Microbiota	CC	Rosacea	10 rosacea, 30 HCs	\	Rosacea was related to an aberrant blood microbiota composition.	Szlachcic et al., 2002
Gut microbiota	CC	Rosacea	12 rosacea, 125 HCs	\	A link between rosacea and enteral microbiota was observed.	Son et al., 1999
Gut microbiota	CC	Rosacea	15 rosacea, 15 HCs	\	Microbiological composition is differed in rosacea.	Sawhney et al., 2008
Gut microbiota	CC	Rosacea	11 rosacea, 110 HCs	\	A significant reduction of fecal microbial richness was found in rosacea.	Chen et al., 2021
C. ureolyticus (up)	CC	PPR	not detailly	\	UC may increase to colonization with C. ureolyticus	Gürer et al., 2002
C. ureolyticus, etc	CC	Rosacea	19 rosacea, 19 HCs	\	The skin microbiota in rosacea displays changes.	Bonamigoet al., 2000
Acinetobacter (down)	DS	PPR	\	\	Acinetobacter negatively associated with anti-inflammatory molecules in rosacea.	Agnoletti et al., 2017
Actinobacteria, Firmicutes	DS	Rosacea	36 ETR, 33 PPR	\	Increased *Firmicutes* and decreased *Actinobacteria* were found in rosacea.	Gravina et al., 2015
Prevotella intermedia (up)	CC	PPR	not detailly	\	The skin microbiota is as a link between rosacea and its comorbidities.	Drago et al., 2016
Serratia marcescens/C acnes	CC	Acne, rosacea	19 rosacea, 8 acnes	\	Serratia marcescens and C acnes were significantly enriched in rosacea.	Gravina et al., 2015
Staphylococcus epidermidis	CC	Rosacea	15 PPR, 15 HCs	\	S epidermidis may play a role in pustular and OcR.	Agnoletti et al., 2017
SIBO	CC	Rosacea	90 rosacea, 90 HCs	\	SIBO was higher found in rosacea.	Gazi et al., 2019
SIBO	CC	Rosacea	60 rosacea, 40 HCs	\	SIBO trigger rosacea by increasing circulating cytokines-TNF-a.	McMahon et al., 2016
SIBO	CC	Rosacea	60 rosacea, 40 HCs	\	SIBO was the most relevant factor in papulopustular rosacea.	Lacey et al., 2018
SIBO	DS	\	60 rosacea	\	SIBO was higher found in rosacea.	Bonamigo et al., 2005
SIBO	CC	Rosacea	4 OcR, 9 PPR, 50 ETR; 30 HCs	\	SIBO trigger rosacea by increasing TNF-a, suppressing IL-17, and stimulating immune response.	Ciccarese et al., 2018

(MMP, Matrix metalloproteinase; TLR, Toll-like receptor; CSU, Chronic Spontaneous Urticaria; SIBO, Small intestinal bacterial overgrowth; DS, Description study; CC, Case control; RA, Research article; CS, cohort study; CSS, Cross-sectional study; PPR, Papulopustular rosacea; OcR, Ocular rosacea; ETR, Erythematotelangiectatic rosacea; LGV, Lymphogranuloma venereum; LE, Lupus erythematosus; FR, fimatous rosacea; HCs, Human controls; IP3, Inositol 1,4,5-trisphosphate; SIBO, Small intestinal bacterial overgrowth; UV, Utralviolet; NO, Nitric oxide; UC, Ulcerative colitis; TNF-a, Tumor necrosis factor a; IL-17, Interleukin 17.)

Supplemental table 3 Immune mechanism of the rosacea pathogenesis

Main title	Design	Differentiation	Human sample	Cell /mice	Mechanism	Ref.
Autoimmunity						
Antibodies	DS	PPR	7 PPR	\	Antinuclear antibodies are tested in PPR (lgG lgA lgM circulating anti-body; lgM, lgE (antinuclear antibodies).	Nunzi et al., 1980
IgG deposits	DS	Rosacea	4 rosacea	\	IgG deposits were found at the dermo-epidermal junction.	Gajewska et al., 1975
IgM, IgG, complement	CC	Rosacea	25 rosacea, 25 HCs (immune text); 23 rosacea (biopsies)	\	IgM, IgG, and complement deposits were found at the dermo-epidermal junction and/or in the dermal collagen.	Manna et al., 1982
Immunoglobulins	DS	Rosacea	30 rosacea	\	Ig was found at the dermo-epidermal junction rosacea.	Baart et al., 1969
Autoimmunity	CC	Rosacea	72 rosacea, 62 HCs	\	High levels of CRP, anti-M and prolactin were found in rosacea.	Berksoy et al., 2018
Cell						
Langerhans cells, PDC	CC	Rosacea	19 PPR, 7 non-PPR, 2 non-identified rosacea	\	PDC were found in skin samples of rosacea as isolated cells and forming small clusters.	Moura et al., 2018
Dendritic cells, T cells, cytokines	CC, RA	PPR	10 PPR, 18 HCs	Cell	Decreased TSLP level and influx of inflammatory dendritic cells and T cells with IL-17/IFN-γ were observed.	Dajnoki et al., 2017
Macrophages	CC, RA	Rosacea	35 rosacea, 14 HCs	Cell +mice	ADAM-DEC1 role in pro-inflammatory of rosacea via modulating the M1 polarization of macrophages.	Liu et al., 2020
Macrophages	RA	Rosacea	\	Cell +mice	P2X7 receptor on macrophages to trigger NLRP3 inflammasome promoted by LL-37.	Yoon et al., 2021
Mast cells	CC	Rosacea	69 rosacea (lesion/non lesion)	\	MCs number were significantly greater in lesion.	Aroni et al., 2008
Mast cells	DS	Rosacea	69 rosacea	\	MCs may contribute to inflammation, angiogenesis and tissue fibrosis.	Aroni et al., 2008
Mast cells	CS, RA	PPR	10 PPR	Cell +mice	Increased MCs were found in rosacea. MC proteases recruit other immune cells with inflammatory response causing vasodilation and angiogenesis. MCs could produce LL-37.	Muto et al., 2014
Mast cells	CC	Rosacea	1. 9 ETR, 9 PPR, 9 PhR, 10 HCs, 9 LE (morphometric); 2. 11 ETR, 11 PPR, 6 PhR, 12 HCs (gene)	\	MCs and fibroblasts was increased in rosacea closely with sensory nerves.	Schwab et al., 2011
Monocytes	CC	Rosacea	116 rosacea, 26 SLE, 28 acne, 42 HCs	\	High frequency of classical monocytes was found in rosacea.	Gao et al., 2021
Mononuclear cells	CC	Rosacea	22 rosacea, 17 HCs	\	Antigenic proteins related to a bacterium (*B. oleronius*), isolated from mite, could stimulate an inflammatory response PPR	Lacey et al., 2007
Neutrophil	RA	Rosacea	\	Cell	*B. oleronius* proteins activate neutrophils via the IP3 pathway leading to inflammatory.	McMahon et al., 2016
Neutrophils	RA	Rosacea	\	Mice	N2-polarized neutrophils reduce inflammation in rosacea by regulating vascular factors and proliferation of CD4+ cells	Zhao et al., 2021
Neutrophils (*Demodex*)	RA	ETR	\	Cell	Mite-related Bacterium protein increase the migration, degranulation and cytokine production of neutrophils.	O'Reillyet al., 2012
Plasma cells	DS	Rosacea	78 rosacea	\	Lymphocytic, leukocytes infiltration. Plasma cells increase.	LAYMON et al., 1948
T cell	CC	PPR	36 PPR, 24 HCs	\	High levels of TH 1 cell were found in rosacea; and high frequencies of TH 9/22 cells in Rosacea/Demodex	Gazi et al., 2019
T cell	CC	OcR	8 OcR, 13 HCs	\	Inflammatory cell infiltration is increased (CD4+, CD8+, CD25, CD1+, CD14+, Mac-l+)	Hoang et al., 1990
CD4 helper/inducer T cell	CC	Rosacea	38 rosacea, 38 HCs	\	CD4 helper/inducer T cell in granulomas and in perifollicular infiltrates leading to inflammatory.	Erbağci et al., 1998
Helper/inducer T cell	DS	Acne rosacea	4 acne rosacea	\	The predominance of helper/inducer T-cell relates to Demodex in rosacea.	Rufli et al., 1984
T/B cell, ADA	CC	ETR	30 ETR, 40 HCs	\	ADA enzyme deficiency results in the loss of functional properties of B and T lymphocytes.	Sener et al., 2020
Th1/Th17 pathway	CC	Rosacea	7 ETR, 6 PPR, 6 PhR, 10 HCs	\	Th 1/Th 17 polarized inflammation and macrophage infiltration were found in rosacea.	Buhl et al., 2015
Immune	CC	PPR	6 PPR, 9 HCs	\	Alterations of immune and geratinization gene expression in PPR. (Whole Transcriptome Analysis)	Shih et al., 2020
LL-37						
Cathelicidin, SCTE	CC, RA	Rosacea	3 rosacea, 3 HCs	Mice	Increased serine protease activity and cathelicidin promotes skin inflammation (result from SCTE)	Yamasaki et al., 2007
Cathelicidin	CC	Rosacea	6 rosacea, 6 HCs	\	Koebnerisin could regulate keratinocytes proliferation and function.	Batycka et al., 2019
LL-37, mTORC1	CC, RA	Rosacea	rosacea, HCs (not detailly)	Cell +mice	LL-37 could promote mTORC 1-mediated angiogenesis responding. (RNA-Seq)	Peng et al., 2021

LL-37	CC, RA	Rosacea	30 rosacea, 11 HCs	Cell	High level of IL-33 was found in rosacea, especially ETR. UVB and LL-37 could increase inflammatory cytokines.	Suhng et al., 2018
LL-37	RA	\	\	Cell	LL-37 induces chemokines related to inflammation and immune.	Li et al., 2014
LL-37, hBD-2, hBD-9	CC	OcR	32 OcR, 22 HCs	\	A high level of LL-37, hBD-2, and hBD-9 were found in OcR.	Gökçınar et al., 2019
LL-37, inflammasome	RA	Rosacea	\	Cell	Cathelicidin peptide LL-37 increases UVB-triggered inflammasome activation	Salzer et al., 2014
LL-37, inflammasome	RA	Rosacea	\	Cell +mice	P2X7 receptor on macrophages to trigger NLRP3 inflammasome promoted by LL-37.	Yoon et al., 2021
LL-37, inflammation	RA	\	\	Cell	Cathelicidin promotes inflammation by enabling binding of self-RNA to cell surface scavenger receptors	Takahashi et al., 2018
LL-37, JAK 2 and STAT 3 axis	RA	Rosacea	\	Cell	LL-37 increased apoptotic rate and cell cycle arrest in HaCaT leading to inflammatory response	Li et al., 2018
LL-37, PAR-2	CC, RA	Rosacea	12 ETR, 28 PPR, 20 HCs	Cell	PAR-2 could activate cathelicidin LL-37.	Kim et al., 2014
LL-37	CC, RA	Rosacea	5 rosacea, 5 HCs	Cell	UVB exposure promote both double-stranded RNA and LL-37 was responsible for the endothelial response to keratinocytes.	Kulkarni et al., 2020
MMPs						
MMP-2/9, *Demodex*	CSS	Rosacea	34 rosacea	\	High level of D. folliculorum and MMP-2/9 were found rosacea.	Bonamigo et al., 2005
MMP-3	CC	ETR	26 ETR, 20 TP, 11 HCs	\	High expression of MMP-3 was found in rosacea, especially ETR.	Helfrich et al., 2015
MMP-3/9	CC, RA	OcR	15 OcR, 8 HCs	Cell	MMP-9 and TIMP-1 were high in rosacea tear. MMP-3 was detected exclusively in OcR.	Sobrin et al., 2000
MMP-8	CC, RA	OcR	22 OcR, 22 HCs	\	MMP-8 concentration and activation degree in tear fluid are increased in OcR reflecting inflammatory.	Määttä et al., 2006
MMP-9, IL-1a	CC	OcR	13 OcR, 13 HCs	\	High MMP-9 activity was found in OcR.	Afonso et al., 1999
MMP-1, -9	RS	GR	11 GR, 11 NGR	\	Increased expression of MMPs was found in GR.	Park et al., 2019
MMPs, cytokines	CC	GR	20 GR, 20 non-GR	\	The increased MMPs in the dermis role in granuloma formation related to UVR.	Jang et al., 2011
TGF-β						
TGF-β	RA	Rhinophyma	\	Cell	Persistent overexpression or dysregulated activation of TGF-β is associated with fibroblast in rhinophyma.	Payne et al., 2006
TGF-β-1/3	CC	Rhinophyma	8 rhinophyma, 9 HCs	\	Fibro-genic cytokine TGF-β 1, 2, 3 were up-regulated in rhinophyma.	Payne et al., 2002
TGF-β-2	CC	Rhinophyma	5 rhinophyma, 5 HCs	\	High of the fibro-genic protein TGF-β 2 and its receptor in rhinophyma may related to fibrosis.	Pu et al., 2000
TLR	**9**					
TLR2, GC	RA	Rosacea	\	Cell	GC enhanced TLR-2 gene expression, further stimulated by P. acnes, TNF, and IL-1.	Shibata et al., 2009
TLR, *Demodex*	RA	\	\	Cell	*Demodex* secreted bioactive molecules that affected TLR2 receptor expression by sebocytes inducing inflammation	Lacey et al., 2018
TLR, iNOS	CC	Rosacea	19 PPR, 7 non-PPR, 2 non-identified rosacea	\	High levels of TLR2, TLR4 and iNOS were found in rosacea group.	Moura et al., 2018
TLR-1/2- and TLR4-activation	RA	PPR	5 PPR, 5 PPA, 5 HCs at least	Cell	TLR1/2/4 promoted inflammation early. Lipid metabolism, the primary feature of sebocytes promoted inflammation late. (Genome wide analysis)	Törőcsik et al., 2018
TLR-1/2, 3, 5, and 2/6 ligands	RA	Rosacea	Rosacea (not detailly)	Cell	TLR signaling promotes LEKTI in keratinocytes, leading to aberrant serine protease activities in inflammatory.	Sugimoto et al., 2018
TLR-2	CC, RA	Rosacea	11 rosacea, 8 HCs	Cell +mice	Abnormal TLR2 function enhanced inflammatory responses to environmental stimuli.	Yamasaki et al., 2011
TLR-2, cytokines.	RA	Rosacea	19 rosacea, 10 HCs	\	TLR signaling pathway was highlighted. (Bioinformatics)	Sun et al., 2021
TLR-3, GC-synthetic enzyme	RA	GC-induced	\	Cell	Innate immunity modulates GC-synthetic enzymes expression via the TLR3 axis in epidermal keratinocytes.	Shimada et al., 2020
TLR-4	CC	OcR	12 OcR, 12 HCs	\	Innate immune system mediated by TLR4 in rosacea.	Wladis et al., 2013
Other						
MAPKp 1, GC	RA	GC-induced	\	Cell	Glucocorticoids enhanced MAPKp 1 expression.	Shibata et al., 2009
HLA-DR, ICAM-1	CC	Rosacea	13 rosacea, 13 dry eye syndrome, 24 HCs	\	High level of HLA-DR and ICAM-1 by epithelial cells was found in OcR.	Pisella et al., 2000
Immune-related DEGs	CC, RA	PPR	6 PPR, 9 HCs	\	IL, TNF, JAK3, PARP, have been shown. (Bioinformatics)	Shih et al., 2020
MYD 88	CC	Rosacea	15 rosacea, 14 HCs	\	MYD88 is enriched in eyelid specimens of rosacea	Wladis et al., 2021

NFκB	CC	Rosacea	1.12 rosacea, 12 HCs (Immunohistochemical); 2. 15 rosacea, 14 HCs (WB)	\	Activated form of NFκB is enriched in rosacea,	Wladis et al., 2019
STAT 1/IRF 1 signature	CC, RA	Rosacea	21 ETR, 30 PPR, 13 PhR, 24 HCs	\	STAT 1 might the critical networks connecting the epithelial-immune crosstalk in rosacea. (RNA-seq)	Deng et al., 2021
Cytokines	CC	OcR	13 OcR, 13 HCs	\	The concentrations of 5 cytokines were enriched in OcR.	Wladis et al., 2012
Cytokines	CC	Rosacea	20 rosacea; 22 HCs	\	Tear and serum levels of cytokines and growth factors measured with a large variation in rosacea.	Topcu et al., 2013
IL-17	CC	Rosacea	60 rosacea, 60 HCs	\	Serum IL-17 levels were significantly higher in rosacea.	Hayran et al., 2021
IL-1β	DS, RA	PPR	5 PPR	\	MAPK and TNF signaling pathways highlighted IL-1β role in PPR.	Harden et al., 2021
p38 and Erk kinases	CC, RA	OcR	1. 18 rosacea, 13 HCs (cutaneous biopsies), 2. 12 rosacea, 12 HCs (paraffin-embedded archival)	\	Increased levels of phosphorylated (active) p38 and Erk kinases shown in OcR.	Wladis et al., 2017

(PDC, Plasmacytoid dentritic cells; ADA, Adenosine deaminase; SCTE, Stratum corneum tryptic enzyme; mTORC1, Mechanistic target of rapamycin complex 1; hBD, human beta-defensin; JAK, Janus kinase; STAT, Signal transducer of activators of transcription; PAR-2, Protease-activated receptor 2; MMP, Matrix metalloproteinase; TGF-β, Transforming growth factor-β; TLR, Toll-like receptor; GC, Glucocorticoid; iNOS, Inducible nitric oxide synthase; MAPKp 1, Mitogen-activated protein kinase phosphatase-1; HLA-DR, Human lymphocyte antigen-DR; ICAM-1, Intercellular adhesion molecule-1; MYD88, Myeolid differentiation factor 88; NF-κB, Nuclear factor kappa-B; IRF 1, Interferon regulatory factor 1; DS, Description study; CC, Case control; RA, Research article; CS, ; cohort study; CSS, Cross-sectional study; PPR, Papulopustular rosacea; OcR, Ocular rosacea; ETR, Erythematotelangiectatic rosacea; GR, Granulomatous rosacea; HCs, Human controls; PhR, Phymatous rosacea; LE, Lupus erythematosus; SLE, Systemic lupus erythematosus; TP, Telangiectatic photoaging; NGR, Non-granulomatous rosacea; TSLP, Thymic stromal lymphopoietin; IL-17, Interleukin 17; IFN-γ, Interferon-γ; CRP, C-reactive protein; ADAM-DEC1, ADAM-like Decysin-1; NLRP3, Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3; MCs, Mast cells; DGEs, Differentially expressed genes; UVB, Ultraviolet rays B; TIMP-1, Tissue inhibitor of metalloproteinase 1; UVR, Ultraviolet radiation; LEKTI, Lympho-epithelial Kazal-type-related inhibitor; TNF, Tumor necrosis factor.)

Table 4 Neurogenic mechanism of the rosacea pathogenesis

Subtitle	Design	Differentiation	Human sample	Cell/mice	Mechanism	Ref.
Neuropeptides						
Bradykinin release	DS	Rosacea	19 rosacea	\	Bradykinin increased in rosacea at the climax of flushing.	Guarrera et al., 1982
CGRP-α	CC	ETR	26 ETR, 20 TP, 11 HCs	\	Neuropeptides CGRP-α, substance P was significantly increased in ETR	Helfrich et al., 2015
PACAP, a regulator of vasodilation and edema	DS	ETR	35 ETR	\	PACAP38 increased facial skin blood flow, dilated the superficial temporal artery.	Wienholtz et al., 2021
Substance P	CC	ETR	26 ETR, 20 TP, 11 HCs	\	Neuropeptides CGRP-α, substance P was significantly increased in ETR	Helfrich et al., 2015
Substance P	RA	Rosacea	\	Cell +mice	Non-anticoagulant sulfated anionic polysaccharides, SAGEs inhibite P-selectin rosacea.	Zhang et al., 2011
Substance P	CC	Rosacea	5 rosacea, 3 HCs	\	SP-immunoreactive nerves were increased considerably around the blood vessels in the papillary dermis.	Kürkçüoğlu et al., 1991
TRPV						
TRPV	CC	Rosacea	1. 7 ETR, 7 PPR, 7 PhR, 7 LE, 8 HCs (immunohistochemistry); 2. 11 ETR, 11 PPR, 6 PhR, 12 HCs (qPCR)	\	Dermal immunolabeling and gene expression of TRPV is significantly increased in rosacea.	Sulk et al., 2012
TRPV1	CC	GR	11 GR, 11 NGR	\	TRPV1 expression in GR lesions was statistically higher.	Park et al., 2019
TRPV3	RA	Inflammatory skin conditions, itch, and pain.	\	\	TRP channel activation is related to inflammatory skin conditions, itch, and pain.	Singh et al., 2018
TRPV4, LL 37	RA	Rosacea	\	Cell +mice	LL37-induced upregulation of TRPV4 may depend on MRGX2 activity related to inflammation in rosacea.	Mascarenhas et al., 2017
VEGF						
VEGF	CC	Rosacea	20 rosacea (lesion vs. non-lesion)	\	Marked immunostaining of lesional skin with VEGF, CD31 and D2-40 in rosacea.	Gomaa et al., 2007
VEGF- A	CC	Reddened skin as a transient or persistent facial erythema	5 reddened skin and 5 HCs	\	The expression of VEGF-A was increased in the basal layer of the epidermis as well as in the stratum corneum of reddened skin.	Kajiya et al., 2017
VEGF genes	CC	Rosacea	100 rosacea, 100 HCs	\	405C/G+ polymorphism of the VEGF gene increases the risk of rosacea.	Hayran et al., 2019
VEGF, inflammatory	DS	Rosacea	20 rosacea	\	VEGF receptor-ligand binding may contribute to the vascular changes and cellular infiltration that occurs in rosacea.	Smith et al., 2007
Others						
Nerve fibres, axon	CC	Rosacea	31 rosacea, 29 HCs	\	Activation of nociceptive nerve fibres contributes to skin sensitivity in rosacea. Axon reflexes augment flushing in patients with the most severe symptoms.	Drummond et al., 2012
Sensory nerves, Mast cells	CC	Rosacea	1. 9 ETR, 9 PPR, 9 PhR, 10 HCs, 9 LE (morphometric); 2. 11 ETR, 11 PPR, 6 PhR, 12 HCs (gene)	\	Sensory nerves were closely associated with blood vessels and mast cells, and were increased in ETR	Schwab et al., 2011
Sympathetic, axon	CC	Rosacea	20 rosacea, 20 HCs	\	Heat stress induced more rapid sweating and cutaneous vasodilation onset in rosacea leading to SSNA and that hyperresponsiveness to trigger a sympathetic component.	Metzler et al., 2015
Embarrass	CC	Rosacea	31 rosacea, 86 HCs	\	Rosacea sufferers are more aware of and embarrassed by blushing.	Drummond et al., 2012
Heat stimuli and stress	CC	Neurogenic rosacea, ETR	17 neurogenic rosacea, 16 ETR	\	Heat stimuli and stress were major aggravating factors.	Kim et al., 2021

(CGRP-α, Calcitonin gene-related peptide-α; PACAP, Pituitary adenylate cyclase-activating polypeptide; TRPV, Transient receptor potential vanilloid; VEGF, Vascular endothelial growth factor; DS, Description study; CC, Case control; RA, Research article; ETR, Erythematotelangiectatic rosacea; GR, Granulomatous rosacea; TP, Telangiectatic photoaging; HCs, Human controls; PPR, Papulopustular rosacea; PhR, Phymatous rosacea; LE, Lupus erythematosus; NGR, Non-granulomatous rosacea; SAGEs, Semi-synthetic glycosaminoglycan ethers; MRGX2, Mas-related gene X2)

Supplemental table 5 Abnormal barrier function mechanism of the rosacea pathogenesis

Main title	Design	Differentiation	Human sample	Cell /mice	Mechanism	Ref.
Eye						
Collagen content	CC	ETR	5 ETR, 5 HCs	\	Decreased collagen content is related to vessel growth and dilation in rosacea.	Thompson et al., 2021
Corneal disorder	CC	OcR	34 OcR, 34 HCs	\	Corneal biomechanical measurements (CH and CRF) were significantly lower in OcR.	Yildirim et al., 2015
Corneal thickness, tear	CC	Rosacea	51 rosacea, 51 HCs	\	Central corneal thinner and tear related function is related to rosacea.	Onaran et al., 2012
Corneum permeability barrier, etc. (epidermal homeostasis)	CC	PPR	29 PPR, 34 HCs	\	A more alkaline centrofacial region and reduced epidermal hydration in rosacea.	Ní Raghallaighet al., 2014
Meibomian gland	CC	Rosacea	41 rosacea, 44 HCs	\	Meibomian gland dysfunction was found in OcR.	Machalińska et al., 2016
Meibomian gland disorder	CC	OcR	18 OcR, 19 HCs	\	OcR causes dry eye and significant meibomian gland loss- meibography.	Palamar et al., 2015
Meibomian glands	CC	OcR	50 OcR, 54 HCs	\	Meibomian glands is involved in OcR.	Yaylali et al., 2002
Tear hyperosmolarity and tear film dysfunction.	CC	OcR	25 rosacea, 20 HCs	\	OcR is associated with tear hyperosmolarity and tear film dysfunction.	Karaman et al., 2016
Tear lactoferrin level	CC	Acne rosacea	8 acne rosacea, 10 seborrheic blepharitis, 10 HCs	\	Low concentrations of tear lactoferrin may related in rosacea.	Kiratli et al., 2000
Tear, inflammatory	CC	Rosacea	20 rosacea; 22 HCs	\	Decreased tear IL-10 may lead to exacerbate ocular surface inflammation, and deteriorate tear function tests.	Topcu et al., 2013
Skin						
Claudin reduction	CC, RA	Rosacea	12 ETR, 12 PPR, 8 PhR, 12 HCs	Cell	Claudin, CLDN reduction may associate with an impaired skin barrier.	Deng et al., 2019
Hypersensitivity	CC	Rosacea	8 ETR, 8 PPR, 8 HCs	\	Enhanced sensitivity to noxious heat stimuli in rosacea.	Guzman et al., 2007
Hypersensitivity	DS	Rosacea	361 rosacea	\	Irritant or doubtful patch test reactions provoked by substances is related to the heightened sensitivity of skin.	Jappe et al., 2005
Hypersensitivity	DS	Rosacea	143 rosacea	\	A high contact sensibilization rate (37.8%) was detected in rosacea.	Diczig et al., 2018
Hypersensitivity	DS	Rosacea	69 rosacea	\	MCs may contribute to inflammation, angiogenesis and tissue fibrosis.	Aroni et al., 2008
Hypersensitivity	CC	PPR	92 PPR, 92 HCs	\	Increased density of Demodex and delayed hypersensitivity were found in PPR.	Georgala et al., 2001
Hypersensitivity	DS	Rosacea	78 rosacea	\	The reactions to the irritant SLS may mirror the extreme skin sensitivity in rosacea.	Jappe et al., 2008
ICAM-1	DS, family study	Rosacea, CMC	Mother and nonidentical twin sons	\	The associations recorded with ICAM-1 and hyper-Ig E syndrome in rosacea.	Ee et al., 2005
ICAM-1	CC	OcR	12 OcR, 12 HCs	\	Vascular abnormalities mediated by intercellular adhesion molecule and CD105.	Wladis et al., 2013
ICAM-1, M1/MUC5AC, HLA-DR	CC	OcR	13 OcR, 13 dry eye syndrome, 24 HCs	\	HLA-DR, ICAM-1, M1/MUC5AC were related to inflammatory and goblet cells in OcR.	Pisella et al., 2000
Keratinization	CC	PPR	6 PPR, 9 HCs	\	Alterations of immune and geratinization gene expression in PPR. (Whole Transcriptome Analysis)	Shih et al., 2020
Mucin deposit	DS	Rosacea	20 rosacea	\	Mucin is a common finding in the granulomas in rosacea.	Fernandezet al., 2010
Mucin deposit, etc.	DS	Rhinophyma	17 rhinophyma	\	Dermal thickness, absence of folliculosebaceous structures, sclerotic collagen bundles with large amounts of mucin.	Aloi et al., 2000
Sebaceous fatty acid composition	CC	PPR	25 PPR, 24 HCs	\	An abnormal sebaceous fatty acid composition in PPR, with reduced long chain saturated fatty acids.	Ní Raghallaigh et al., 2012
Sebaceous glands	CC	Rosacea	22 ETR, 6 PPR	\	Sebocytes can express antimicrobial peptides (cathelicidin and β-defensin-2) leading to as inflammatory.	Lee et al., 2020
Sebum secretion, *demodex*	DS	Rosacea	17 ETR, 15 PPR, 8 FR	\	The changing sebaceous microenvironment in rosacea leads to increased *demodex*.	Falay et al., 2018
Skin barrier	CC	Rosacea	25 rosacea (lesion, non-lesion)	\	Bacterial dysbiosis is related to skin barrier.	Diaz et al., 2003et al., 2003
TEWL atopic diathesis	CC	Rosacea	75 rosacea, 75 PD, 125 HCs	\	TEWL was significantly increased in rosacea.	Dirschka et al., 2004
TEWL, SCH	CC	Rosacea &AD	28 ETR, 31 AD, 32 HCs	\	A lower IT patient had higher TEWL values and lower SCH. Positive allergic reactions had significantly lower IT.	Darlenski et al., 2013
Tight junction organizations, barrier alarmins	CC	PPR	8 PPR, 8 HCs	\	The cornified envelope and intercellular lipid lamellae formation, desmosome and tight junction organizations, barrier alarmins, and antimicrobial peptides.	Medgyesi et al., 2020
Water content of the stratum cornuem and skin surface lipid level	CC	PPR, acne vulgaris	463 PPR, 412 acne vulgaris, 400 HCs	\	The epidermal barrier function was damaged in PPR.	Zhou et al., 2016

Water content, TEWL	CC	Rosacea	586 rosacea, 115 HCs	\	Lower water content and higher transepidermal water loss (TEWL).	Xie et al., 2017
Zonulin	CC	Acne rosacea	30 rosacea, 31 HCs	\	Zonulin is a protein that reversibly increases intestinal permeability in rosacea.	Yüksel et al., 2020

(ICAM-1, Intercellular adhesion molecule-1; HLA-DR, Human lymphocyte antigen-DR; TEWL, Transepidermal water loss; SCH, Stratum corneum hydration; DS, Description study; CC, Case control; RA, Research article; PPR, Papulopustular rosacea; OcR, Ocular rosacea; ETR, Erythematotelangiectatic rosacea; CMC, Chronic mucocutaneous candidiasis; AD, atopic dermatitis; HCs, Human controls; PhR, Phymatous rosacea; FR, fimatous rosacea; PD, perioral dermatitis; CH, corneal hysteresis; CRF, Corticotropin-releasing factor; CLDN, Claudins; IL-10, Interleukin 10; MCs, Mast cells; IT, irritant threshold.)

Supplemental table 6 Other mechanism of the rosacea pathogenesis

Main title	Design	Differentiation	Human sample	Cell/mice	Mechanism	Ref.
Oxidative stress						
Antioxidant status and oxidative stress	CC	Rosacea	87 rosacea, 81 HCs	\	Low serum bilirubin and uric acid antioxidant levels in rosacea related to ROS.	Turkmen et al., 2020
Oxidative stress	CC	Rosacea	30 rosacea, 15 HCs	\	Increased GSTT1, GSTP1, and GSTM1 lead to extreme free radical generation from triggered neutrophils or ultraviolet vulnerability.	Takci et al., 2020
Oxidative stress	CC	Rosacea	39 rosacea, 140 HCs	\	Decreased PON1 activity and increased oxidative stress were found in rosacea.	Takci et al., 2015
Oxidative stress (thiol/disulfide homeostasis)	CC	Rosacea	50 rosacea, 42 HCs	\	Mean disulfide/native thiol ratio/ disulfide/total thiol ratio were higher in rosacea as a marker for oxidative stress.	Sener et al., 2019
Oxidative stress (thiol/disulfide homeostasis)	CC	Rosacea	22 ETR, 48 PPR, 30 HCs	\	TAS, TOS and AOPP levels were significantly higher in rosacea.	Erdogan et al., 2018
Oxidative stress (thiol/disulfide homeostasis)	CC	Rosacea	13 ETR, 36 PPR, 11 PhR, 11 HCs	\	Higher ferritin peroxide levels, and lower antioxidative potential is related to systemic oxidative stress in rosacea.	Tisma et al., 2009
Oxidative stress (thiol/disulfide homeostasis)	CC	Rosacea	19 rosacea, 17 HCs	\	Decreased capacity in antioxidant defense system, increased malondialdehyde levels were found in rosacea.	Oztas et al., 2003
Oxidative stress and insulin resistance	CC	Rosacea	42 rosacea, 50 HCs	\	Rosacea has a metabolic milieu with increased oxidative stress and insulin resistance.	Demir et al., 2021
ROS	CC	Rosacea	29 rosacea, 20 HCs	\	Rosacea is an oxidative stress condition, with increased ROS activity and decreased AOP, regardless of HP infection.	Baz et al., 2004
Systemic oxidative stress	CC	Rosacea	17 ETR, 15 PPR, 8 FR, 40 HCs	\	Systemic oxidative stress and inflammation parameters were found high in systemic circulation as more prone to systemic diseases.	Falay et al., 2018
UV						
UVB-induced	CC, RA	Rosacea	5 rosacea, 5 HCs	Cell	UVB exposure promote both double-stranded RNA and LL-37 was responsible for the endothelial response to keratinocytes.	Kulkarni et al., 2020
Sun exposure and *Demodex*	DS	Rosacea	100 rosacea	\	Increased density of Demodex was found in increased in rosacea promoted by chronic sun exposure.	Lazaridou et al., 2010
UVB-induced	RA	Rosacea (UVB-triggered)	\	Cell	LL-37 modulates the proinflammatory and proangiogenic effects of UV radiation.	Salzer et al., 2014
UVB-induced	CC, RA	Rosacea	30 rosacea, 11 HCs	Cell	Rosacea skin with abundant LL-37 may robustly produce and release IL-33 when exposed to UV radiation.	Suhng et al., 2018
UVR-induced	CC	GR	20 GR, 20 NGR	\	The increased MMPs in the dermis role in granuloma formation related to UVR.	Jang et al., 2011
Vitamin D						
VDR, LL-37	DS, RA	Rosacea	17 PPR,12 ETR	\	Serum vitamin D was lower in rosacea, while serum cathelicidin was higher than that of the controls. VDR was revealed in the cathelicidin gene promoter.	Park et al., 2018
VDR, LL-37	DS, RA	Rosacea	17 PPR,12 ETR	\	Serum vitamin D was lower in rosacea, while serum cathelicidin was higher than that of the controls. VDR was revealed in the cathelicidin gene promoter.	Park et al., 2018
Vitamin D	CC	Rosacea	44 rosacea, 32 HCs	\	Patients with rosacea have relatively high serum vitamin D levels.	Ekiz et al., 2014
GCs						
GCs	RA	Steroid-induced	\	Cell +mice	GCs induce expression of CCL20 in keratinocytes related to inflammation.	Wang et al., 2021
GCs, TLR	RA	Steroid-induced	\	Cell	Steroid-induced TLR2 together with P. acnes existing contribute to rosacea.	Shibata et al., 2009
Glycosylation						
O-and N- glycans, glycosylation	CC	OcR	1. 23 OcR, 28 HCs (tear); 2. 17 OcR, 25 HCs (saliva)	\	The numbers of sulfated glycans were dramatically increased in tear and saliva of rosacea.	Vieira et al., 2012
O-Glycans in saliva and tear	CC	OcR	1. 23 OcR, 28 HCs (tear); 2. 17 rosacea, 25 HCs (saliva)	\	Sulfated oligosaccharides released from mucins in tears were highly up-regulated in OcR.	Ozcan et al., 2013
Oligosaccharides in tear	CC	OcR	16 OcR, 21 HCs	\	The high abundance of oligosaccharides in the tear fluid in rosacea.	An et al., 2005
Hormone						
Androgen receptor	DS	Rosacea	23 rosacea	\	Increased androgen receptors were found in rosacea.	Erkek et al., 2004
GCs synthesis	DS	Steroid-induced ETR	12 ETR	\	Abnormal glucocorticoid synthesis in the lesion skin of ETR.	Hong et al., 2019
Insulin resistance	CC	Rosacea	42 rosacea, 50 HCs	\	Rosacea has a metabolic milieu with increased oxidative stress and insulin resistance.	Demir et al., 2021

Others						
C pneumoniae	DS	Rosacea	10 rosacea	\	Strongly implicate C pneumoniae in the pathogenesis of acne rosacea.	Fernandez et al., 2007
Erdr1	CC, RA	Rosacea	15 rosacea, 15 HCs	Mice	rErdr1 is related to inflammation and angiogenesis in rosacea.	Kim et al., 2015
GIIAPLA (2)	CC	OcR	21 OcR, 21 HCs	\	The GIIAPLA (2) concentration in tears which could kill gram-positive bacteria.	Kari et al., 2005
Heat	DS	Rosacea	24 rosacea	\	The active agent causing flushing in coffee at 60 degrees C is heat, not caffeine in rosacea.	Wilkin et al., 1981
NLRP 3 inflammasome, LL-37	RA	Rosacea-like skin inflammatory phenotypes	\	Cell +mice	NLRP 3 inflammasome is related to LL-37-induced skin inflammation in rosacea.	Yoon et al., 2021
UA level	CC	Rosacea	61 rosacea, 64 HCs	\	Serum UA and CRP values were significantly higher in rosacea related to comorbidities.	Karaosmanoglu et al., 2020

(ROS, Reactive oxygen species; UVB, Ultraviolet rays B; VDR, Vitamin D receptor; TLR, Toll-like receptor; GC, Glucocorticoid; GIIAPLA (2), Group IIA phospholipase A(2); NLRP 3, Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3; UA, Uric acid; DS, Description study; CC, Case control; RA, Research article; OcR, Ocular rosacea; ETR, Erythematotelangiectatic rosacea; GR, Granulomatous rosacea; PPR, Papulopustular rosacea; HCs, Human controls; PhR, Phymatous rosacea; NGR, Non-granulomatous rosacea; GSTT1, Glutathione S-transferase theta 1; GSTM1, Glutathione-S-transferase μ-1; GSTP1, Glutathione S-transferase P1; PON1, Paraoxonase-1; FR, fimatous rosacea; AOPP, Advanced oxidation protein products; TAS, Total antioxidant status; TOS, Total oxidant status; AOP; Antioxidant potential; HP, Helicobacter pylori; IL-33, Interleukin 33; UV, Ultraviolet; MMPs, Matrix metalloproteinases; UVR, Ultraviolet radiation; CRP, C-reactive protein.)

Supplemental table 7 Primary data for the whole trend analysis on rosacea.

Year	Number of published	Sequential growth rate
1992	1	\
1999	38	\
2000	44	16%
2001	44	0%
2002	33	-25%
2003	57	73%
2004	85	49%
2005	81	-5%
2006	65	-20%
2007	72	11%
2008	78	8%
2009	100	28%
2010	72	-28%
2011	93	29%
2012	113	22%
2013	103	-9%
2014	134	30%
2015	145	8%
2016	153	6%
2017	201	31%
2018	215	7%
2019	207	-4%
2020	262	27%
2021	249	-5%
2022	1	

Supplemental table 8 Primary data for trend analysis.

Year	Immune	Microorganisms	Barrier function	Gene	Neurogenic	ROS	UV	Other
1948	1	0	0	0	0	0	0	0
1969	1	0	0	0	0	0	0	0
1975	1	0	0	0	0	0	0	0
1980	1	0	0	0	0	0	0	0
1981	0	0	0	0	0	0	0	1
1982	1	0	0	0	1	0	0	0
1984	1	0	0	0	0	0	0	0
1990	1	0	0	0	0	0	0	0
1991	0	0	0	0	1	0	0	0
1992	0	1	0	0	0	0	0	0
1998	1	1	0	0	0	0	0	0
1999	1	1	0	0	0	0	0	0
2000	3	1	3	1	0	0	0	0
2001	0	1	1	0	0	0	0	0
2002	1	3	1	0	0	0	0	0
2003	0	3	1	0	0	1	0	0
2004	0	1	1	1	0	1	0	1
2005	1	2	2	1	0	0	0	2
2006	2	0	0	1	0	0	0	0
2007	2	2	1	0	0	0	0	1
2008	1	1	2	0	0	0	0	0
2009	1	0	0	0	0	1	0	1
2010	0	2	1	0	0	0	1	0

2011	3	0	0	0	0	0	1	0
2012	2	6	2	0	0	0	0	1
2013	2	2	3	0	0	0	0	1
2014	4	4	1	0	0	0	1	1
2015	2	4	2	3	0	1	0	1
2016	1	4	3	1	0	0	0	0
2017	2	5	1	1	0	0	0	0
2018	8	10	2	1	0	2	1	1
2019	5	5	1	2	0	1	0	1
2020	5	7	4	2	0	2	1	1
2021	9	7	1	2	0	1	0	3

(ROS: Reactive oxygen species; UV: Ultraviolet.)

Supplemental table 9 Primary data for pie chart.

Type	Number	Subtype	Number
Immune	68	Autoimmunity	5
		Cell	21
		LL-37	12
		MMPs	7
		Other	11
		TGF-β	3
		TLR	9
Microorganisms	83	Demodex infection	49
		H. pylori infection	13
		Dysbacteriosis	21
Barrier function	33	Eye	10
		Skin	23
Gene	16	gene	16
Neurogenic	19	Neuropeptides	6
		TRPV	4
		VEGF	4
		Others	5
Other	32	Oxidative stress	10
		UV	5
		Vitamin D	3
		Glycosylation	3
		Hormone	3
		GCs	2
		Others	6

(MMPs: Matrix metalloproteinases; TGF-β: Transforming growth factor-β; TLR: Toll-like receptor; TRPV: Transient receptor potential vanilloid; VEGF: Vascular endothelial growth factor; UV: Ultraviolet; GCs: Glucocorticoids.)

Abbreviations used:

ADA	Adenosine deaminase
ADAMDEC1	Disintegrin Metalloprotease ADAM-like Decysin-1
AzA	Azelaic acid
BMI	Body mass index
BTNL2	Butyrophilin-like 2
CC	Case control
CCT	Central corneal thickness
CGRP-α	Calcitonin gene-related peptide-α
CLDN	Claudins
CMC	Chronic mucocutaneous candidiasis
CRF	Corticotropin-releasing factor
CRISPR/Cas9	Clustered regularly interspaced short palindromic repeats -CRISPR-associated protein 9
CSU	Chronic Spontaneous Urticaria
DGEs	Differentially expressed genes
DS	Description study
Erdr1	Erythroid differentiation regulator 1
ESCI	Emerging Sources Citation Index
ETR	Erythematotelangiectatic rosacea
FR	Fimatous rosacea
GC	Glucocorticoid
GERD	Gastroesophageal reflux disease
GIIAPLA (2)	Group IIA phospholipase A (2)
GOF	Gain-of-function
GR	Granulomatous rosacea
GSTM1	Glutathione-S-transferase μ-1
GSTs	Glutathione S-transferases
GSTT1	Glutathione S-transferase theta 1
hBD-2	Human-beta-defensin-2
HCs	Human controls
HLA-DR	Human lymphocyte antigen-DR
HNP 1-3	Human-neutrophil-peptides 1-3
IBS	Irritable bowel syndrome
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon-γ
IL-1	Interleukin 1
iNOS	Inducible nitric oxide synthase
IP3	Inositol 1,4,5-trisphosphate
JAK	Janus kinase
KLK5	Kallikrein 5
LE	Lupus erythematosus
LEKTI	Lympho-epithelial Kazal-type-related inhibitor
LGV	Lymphogranuloma venereum

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LLR	Loglikelihood ratio
M1/MUC5AC	Peptidic core of the conjunctival mucin
MAPKp 1	Mitogen-activated protein kinase phosphatase-1
MDD	Major depressive disorder
MGD	Meibomian gland disease
MMPs	Matrix metalloproteinases
MRGX2	Mas-related gene X2
mTORC1	Mechanistic target of rapamycin complex 1
MYD88	Myeolid differentiation factor 88
NF-κB	Nuclear Factor κ-B
NGR	Non-granulomatous rosacea
NLRP3	Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3
NOD	Nucleotide-binding and oligomerization domain
NRS	Numerical rating scale
OcR	Ocular rosacea
PACAP	Pituitary adenylate cyclase-activating polypeptide
PAR-2	Protease-activated receptor 2
PD	Perioral dermatitis
PDC	Plasmacytoid dentritic cells
PDL	Pulsed-dye-laser
PhR	Phymatous rosacea
PPARγ	Peroxisome proliferator-activated receptor γ
PPR	Papulopustular rosacea
PS	Prospective study
PSQI	Pittsburgh Sleep Quality Index
RA	Research article
RCTs	Randomized controlled trials
ROS	Reactive oxygen species
RXR	Retinoic X receptor
SAGEs	Semi-synthetic glycosaminoglycan ethers
SCH	Stratum corneum hydration
SCIE	Science Citation Index Expanded
SCTE	Stratum corneum tryptic enzyme
SIBO	Small intestinal bacterial overgrowth
SLE	Systemic lupus erythematosus
SLS	Sodium lauryl sulphate
SSCI	Social Science Citation Index
STAT	Signal transducer of activators of transcription
TACR3	Tachykinin receptor 3
TEWL	Transepidermal water loss
TIMP-1	Tissue inhibitor of metalloproteinase 1
TLR	Toll-like receptor

TNF	Tumor necrosis factor
TP	Telangiectatic photoaging
TRPA1	Transient receptor potential ankyrin 1
TRPV	Transient receptor potential vanilloid
TSLP	Thymic stromal lymphopoietin
UA	Uric acid
UV	Ultraviolet
UVB	Ultraviolet rays B
UVR	Ultraviolet radiation
VDR	Vitamin D receptor
VEGF	Vascular endothelial growth factor
WoS	Web of Science
MCs	Mast cells
PON1	Paraoxonase-1
TOS	Total oxidant status
TAS	Total antioxidant status
AOPP	Advanced oxidation protein products
AOP	Antioxidant potential
HP	Helicobacter pylori
CRP	C-reactive protein
NEAT1	Nuclear-enriched abundant transcript 1
PDE5i	Phosphodiesterase-5 inhibitors
GNP	Gold nanoparticles
HCQ	Hydroxychloroquine
CB1	Cinnamtannin B1
ssON	Single-stranded oligonucleotide
SOD3	Superoxide dismutase 3
DRG	Topical Dermasence Refining Gel
TXA	Tranexamic acid
ART	Artemisinin
ERK	Extracellular signal-regulated kinase
SOCS3-ASK1-p38	Suppressor of cytokine signaling 3-apoptosis signal-regulating kinase 1-p38
WT	Wild type
TGF-β	Transforming growth factor-β
CS	Cohort study
ADAM-DEC1	ADAM-like Decysin-1
CSU	Chronic Spontaneous Urticaria
FR	Fimatous rosacea
AD	Atopic dermatitis
PD	Perioral dermatitis
CH	Corneal hysteresis
IT	Irritant threshold
NO	Nitric oxide

LPND	Yttrium-aluminum-garnet laser
P/N	Positive/Negetive
F/M	Female/Male
IRR	Incidence rate ratio