Rosacea Pathogenesis

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KEYWORDS

• Kallikrein • Cathelicidin • Matrix metalloproteinase • Mast cells • *Demodex*

KEY POINTS

- The pathogenesis of rosacea is not fully understood but involves genetic factors, immune dysregulation, neurovascular dysregulation, and various environmental factors.
- LL-37 (Cathelicidin antimicrobial peptide) and kallikrein 5 are key contributors to immune dysregulation in the skin of patients with rosacea.
- Mast cells are up-regulated and play a role in promoting inflammation.
- Increased activity of transient receptor potential (TRP) cation channels leads to increased levels of vasoregulatory neuropeptides, which mediate flushing in rosacea.
- Skin commensals, such as *Staphylococcus epidermidis* and *Demodex* species as well as bacteria not typically present on the skin, contribute to the pathogenesis of rosacea.

INTRODUCTION

Rosacea is a chronic inflammatory skin disorder with varying prevalence across populations. Affected individuals are typically Fitzpatrick skin type I or II and from northern European or Celtic ancestry. In a Swedish population study, rosacea prevalence was 10%.[1] Rosacea is characterized by the presence of persistent facial erythema with or without edema, telangiectasias, and a tendency for facial flushing and may include inflammatory lesions, eye findings, and skin surface changes over time. Based on clinical characteristics, rosacea is classified into four subtypes, including erythematotelangiectatic rosacea, papulopustular rosacea, ocular rosacea, and phymatous rosacea, although there may be subtype overlap.[2] Histologic findings vary based on the subtype of rosacea, but in inflammatory cases, there are prominent lymphohistiocytic infiltrates around pilosebaceous units and blood vessels.[2] The pathogenesis of rosacea is not fully understood, but genetics, immune factors, neurovascular dysregulation, microorganisms, and environmental factors are thought to play a role (**Fig. 1**).[3]

GENETIC FACTORS

In a cohort study of twins, a higher correlation of clinical rosacea scores was noted between monozygous twins than between heterozygous twins.[4] In a genome-wide association study, two single-nucleotide polymorphisms were identified in European individuals with rosacea, suggesting that certain genes may predispose to the development of rosacea.[5]

IMMUNE DYSREGULATION

Immune dysregulation is an important component of the pathogenesis of rosacea. Activation of the innate immune system leads to increased production of cytokines and antimicrobial peptides.[3] In patients with rosacea, there are higher baseline levels of cathelicidin and kallikrein 5 (KLK5) in lesional skin.[6] There are a variety of cathelicidins, which have been identified in other mammals, but the only human cathelicidin is human cationic antibacterial protein of 18 kDa (hCAP18).[7] A cathelicidin is an antimicrobial protein, which is stored in the granules of neutrophils and

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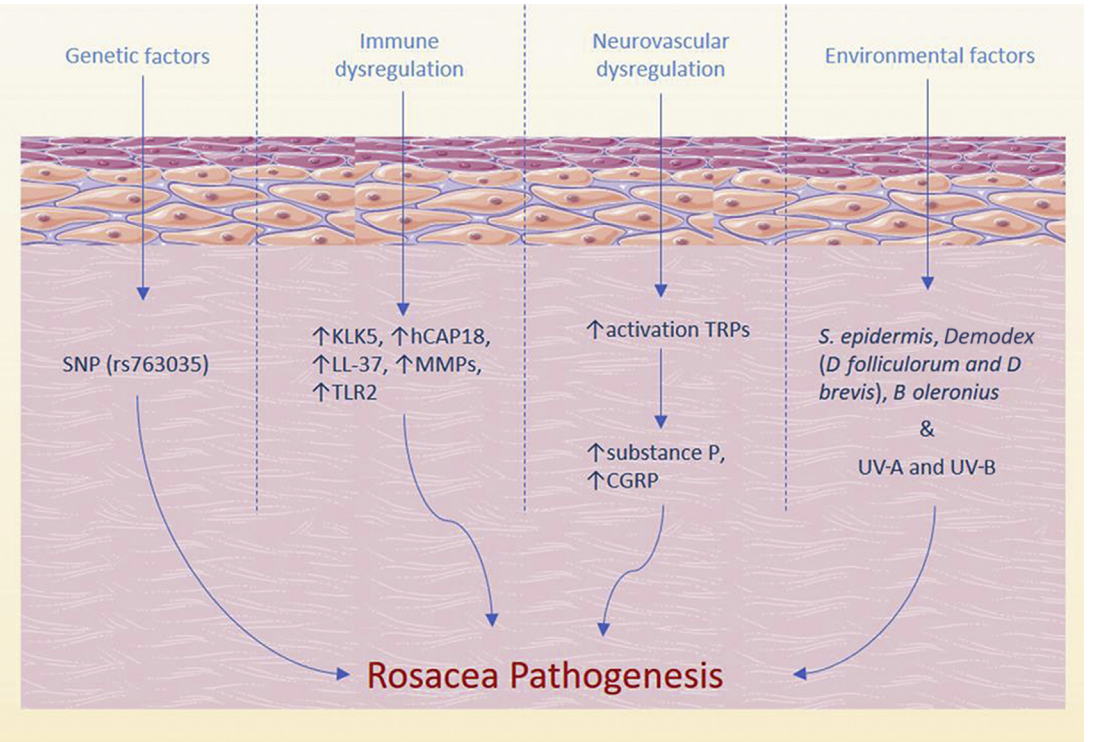

Fig. 1. Schematic of factors contributing to rosacea pathogenesis. An understanding of rosacea pathogenesis is in its infancy; however, hypothesized mediators include genetic factors, immune dysregulation, neurovascular dysregulation, and various environmental factors. hCAP18, human cathelicidin antimicrobial protein; CGRP, calcitonin gene-related peptide; LL-37, cathelicidin antimicrobial peptide, 18kDa; SNP, single-nucleotide polymorphism. (*From* Servier medical art. Available at: http://smart.servier.com/ under a Creative Commons Attribution 3.0 Unported License. Accessed September 8, 2017.)

lamellar bodies of keratinocytes. The inactive protein, hCAP18, is secreted and cleaved into its active peptide form, LL-37, by KLK5 and proteinase 3.[3,8,9] LL-37 has activity against bacteria, fungi, and parasites and is constitutively expressed in neutrophils, mast cells, macrophages, and monocyte granules. In mast cells, LL-37 promotes degranulation and release of inflammatory mediators.[9] In the skin of individuals with rosacea, LL-37 is expressed at higher levels and processed into shorter fragments. The shorter fragments of LL-37 have antimicrobial properties and immune-activating properties; they promote angiogenesis, induce leukocyte chemotaxis, and are involved in the production of proinflammatory cytokines.[10,11] When injected into mice, LL-37 fragments cause erythema, vascular dilatation, flushing, and telangiectasias, symptoms characteristic of rosacea.[6]

Patients with rosacea have higher levels of toll-like receptor 2 (TLR2) and matrix metalloproteinases (MMPs). TLR2, a membrane-bound protein, activates the innate arm of the immune system in response to bacterial, fungal, and viral pathogens. The increased expression of TLR2 on keratinocytes in rosacea-affected skin is the result of multiple factors, including endoplasmic reticulum stress and the presence of *Demodex*, and leads to higher levels of expression of KLK5 and LL-37. MMPs activate KLK5 via cleavage of the proenzyme. There are increased levels of MMP-2 and MMP-9 in the skin of patients with rosacea, which may lead to increased KLK5 and LL-37 levels.[3,12]

Mast cells likely play a role in rosacea pathogenesis. LL-37, which is secreted by mast cells, influences mast cell activity through induction of chemotaxis, degranulation, and the release of proinflammatory cytokines, including interleukin 6 and MMP-9. In a mouse model study, injection of LL-37 into mast cell knockout mice failed to produce any inflammation. When the mice were reconstituted with mast cells, injection of LL-37 led to inflammation, suggesting that mast cells promote the inflammatory state of rosacea.[3,13,14]

NEUROVASCULAR DYSREGULATION

Transient receptor potential (TRP) cation channels, which are widely expressed on neuronal and non-neuronal cells, such as keratinocytes and endothelial cells, have increased our understanding of