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The molecular pathology of rosacea

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Abstract

Rosacea is a common and chronic inflammatory skin disease that affects over 10 million Americans. Although the phenotypes of rosacea are clinically heterogeneous, they are all related by the presence of chronic facial skin inflammation. Until recently, the pathophysiology of this disease has been poorly understood and limited to descriptions of factors that exacerbate or improve this disorder. Recent molecular studies suggest that an altered innate immune response is involved in the pathogenesis of the vascular and inflammatory disease seen in patients with rosacea. These findings may help explain the benefits of current treatments and suggest new therapeutic strategies helpful for alleviating this disease. This article discusses the possible molecular mechanisms for the pathogenesis of rosacea from current clinical observations and laboratory research.

Introduction

Most individuals affected by rosacea are of northern European origin and up to 1/3 have a family history of the disorder [1]. The disease affects mostly facial skin and is characterized by flushing, nontransient erythema, papules, pustules, inflammatory nodules and telangiectasia. Secondary features that often occur include burning and stinging of the face, occasional dermatitis or scaling of the face, and edema. In many sufferers, rosacea can be worsened or triggered by factors that initiate flushing, such as exercise, emotion, menopause and alcohol [2]. In 2002, the National Rosacea Society Expert Committee created a standard classification system for rosacea [3] and grading system in 2004 [4]. The purpose of the committee is to develop a standard system that can serve as an instrument to investigate the manifestation of rosacea for both clinician and researchers.

Since the phenotypes of rosacea are clinically heterogeneous, rosacea studies were diversely conducted based on the findings in clinical manifestations, histology, and factors exacerbating the skin disorder. From the diverse findings, the pathology of rosacea was thought be ‘unknown’ and was expected to be from multiple factors. We recently reported findings of a consistently aberrant innate immune response in rosacea. The multiple factors that lead to a trigger of the innate immune system would explain the diverse findings on rosacea etiology and help to understand why the current therapies are effective. This article attempts to organize the possible pathology of rosacea by connecting proposed mechanisms through the window of

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The authors declare no conflict of interest in the descriptions and findings from this manuscript.

the innate immune system. We categorized pathological mechanisms of rosacea in a) innate immunity, b) vascular changes, c) reactive oxygen species, d) ultra violet radiation, and e) microbes. These molecular events can now be linked to each other with our current knowledge of innate immunity.

Innate immunity

We have proposed the hypothesis that a dysregulation of the innate immune system in patients with rosacea could unify current clinical observations. In innate immunity, the pattern recognition system, which includes the TLR (toll-like receptor) and NLR (nucleotide-binding domain and leucine-rich repeat-containing) families, respond to environmental stimuli such as UV, microbes, physical and chemical trauma. Triggering the innate immune system normally leads to a controlled increase in cytokines and antimicrobial molecules in the skin [5,6]. One of these antimicrobial molecules is a peptide known as cathelicidin [7]. Some forms of cathelicidin peptides were known to have a unique capacity to be both vasoactive and proinflammatory. Therefore, given the potential for a single molecule to affect both of the events that describe rosacea, we began an analysis of cathelicidin in rosacea. Individuals with rosacea expressed abnormally high levels of cathelicidin [8]. Importantly, the cathelicidin peptide forms found in rosacea were not only more abundant but were different from those in normal individuals. These forms of cathelicidin peptides promote and regulate leukocyte chemotaxis [9], angiogenesis [10], and expression of extracellular matrix components [11]. The presence of the vasoactive and inflammatory cathelicidin peptides in rosacea was subsequently explained by abnormal production of local protease kallikrein 5 (KLK5), which controls the production of cathelicidin peptides in epidermis [8,12]. To confirm the importance of these observations and test the hypothesis that abnormal cathelicidin could induce the signs of rosacea, we injected these peptides or the enzymes that produce cathelicidin into the skin of mice. This rapidly resulted in skin inflammation resembling pathological changes in rosacea, therefore confirming our hypothesis [8]. Combined, these findings indicated that an exacerbated innate immune response induces abnormal cathelicidin, and that this then leads to the clinical findings.

Normally, the innate immune system of the skin is programmed to detect microbes, tissue damage such as UV-induced apoptosis, or damage of the extracellular matrix [13,14]. As described above, sun exposure, dermal matrix changes and microbes have been shown to be triggers of rosacea. Our preliminary data showed that TLR2 expression is altered in rosacea skin, which enhances skin susceptiblity to innate immune stimuli and leads to increased cathelicidin and kallikrein production [15]. Interestingly, TLR2 involvement in other disorders is also suggested by the clinical findings in glucocorticoid inducing rosacea-like dermatitis, so-called perioral dermatitis [16-19]. Although the precise molecular mechanisms of the steroid-induced dermatitis is not determined, Shibata et al recently reported that glucocorticoid increases TLR2 expression in epidermal keratinocytes, and that *P. acnes* enhanced glucocorticoid-dependent TLR2 induction [20]. Thus, our new findings and accumulated knowledge on rosacea suggest the innate immune response in rosacea has gone awry. For a variety of reasons these patients are more susceptible to stimuli that do not cause inflammatory reactions in normal patients. Innate immunity is triggered by the events previously associated with worsening of the disease.

Vascular changes

Much of the previous work on the pathophysiology of rosacea has focused on attempts to make sense of associations between triggers of the disease and its clinical manifestations. Most patients report flushing episodes, thus leading to a common hypothesis that vascular hyperreactivity and increased blood play a role in the susceptibility to this disease. A few

studies have demonstrated a measurable increase in blood flow in skin lesions of patients with rosacea [21,22]. Some factors that trigger flushing such as emotional stress, spicy food, hot beverages, high environmental temperatures and menopause worsen rosacea [23], thus supporting this hypothesis. Resolution of erythema and flushing by topical α1-adrenergic receptor agonist application also supports the hypothesis that vascular hyperreactivity is major factor of rosacea pathology [24].

Elevated expression of vascular endothelial growth factor (VEGF), CD31, and lymphatic endothelium maker D2-40 are observed in the skin of patients with rosacea [25]. VEGF proliferate vascular endothelial cells as well as increase permeability of vessels. CD31 is platelet/endothelial cell adhesion molecule (PECAM1 in gene symbol), and anti-CD31 antibody recognizes the endothelial cells. Anti-D2-40 monoclonal antibody identifies a 40 kDa O-linked sialoglycoprotein and has also been demonstrated to label lymphatic endothelium whereas it is unreactive with vascular endothelium. Elevated expression of VEGF, CD31 and D2-40 in rosacea suggests rosacea skins have more stimulants for vascular and lymaphtic endothelial cells and increase endothelia cells. As discussed later, UV irradiation induces VEGF in human keratinocytes and skin [26], which could be involved in the molecular mechanism of rosacea exacerbation after sun and UV exposure. From the aspect of innate immunity, cathelicidin would be one of triggers of hyper vascularity in rosacea. Injection of cathelicidin peptides LL-37 in mouse skin induced vasodilatation [8], and application of LL-37 resulted in neovascularization in a rabbit model of hind-limb ischemia [10]. The angiogenesis by LL-37 is mediated by formyl peptide receptor-like 1 (FPRL1), a G-protein coupled receptor expressed on endothelial cells [10]. LL-37 transactivates epidermal growth factor receptor (EGFR) and downstream signaling in epithelial cells [27,28], and EGFR signaling induces VEGF in epidermal keratinocytes [29]. Thus, cathelicidin induces endothelial cell changes through several signaling pathways, and could be a common explanation for some vascular effects.

Reactive oxygen species (ROS)

ROS involvement in rosacea pathology has been discussed as explanation for the action of medicines for rosacea treatment. Inhibition of ROS generation in neutrophils by tetracyclins [30], azelaic acid [31], metronidazole [32], and retinoids [33], which are used for rosacea treatment, provokes the hypothesis of ROS involvement in rosacea pathology. Erythromycin and azithromycin, the other effective medicine for rosacea treatment, have been shown to have antioxidant effects [34,35]. ROS levels were examined in skin biopsy samples from rosacea and healthy individuals, and confirmed higher ROS activity in rosacea lesional skin than healthy controls [36,37]. The decrease of ROS in rosacea skin was also observed after azithromycin treatment [36], suggesting rosacea treatments affect ROS activity and supporting the hypothesis of ROS involvement in rosacea pathology. Although the precise localization of ROS activities is not determined in rosacea skin, the source of ROS would be infiltrated leukocytes and epidermal keratinocytes.

ROS activates cellular signaling. UV radiation generates ROS and activates cellular signaling in keratinocytes [37,38]. ROS mediates cytokine induction by TNFα in human keratinocytes [39] and chemokine production by TLR2 stimuli in monocytes [40,41]. ROS simulate fibroblast and alters matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMP) expression. UVA radiation increases MMP-1, and ROS increase MMP-2 mRNA and suppressed TIMP-1 in human dermal fibroblast [42]. In a three-dimensional culture, normal human dermal fibroblasts increase MMP-1 and MMP-2 mRNA expression by ROS, whereas both proalpha1(I) and proalpha1(III) collagen mRNA production were suppressed by ROS. Thus, increased ROS activity in skin would enhance inflammatory reactions and degenerate collagens and matrix in dermis.

Ultra violet radiation

UV and sun exposure are known to cause a flushing response and appears to worsen the clinical symptoms of rosacea [23]. Mechanistically, in mice, UV-B induces cutaneous angiogenesis that is histologically similar to the telangiectasia seen in rosacea histopathology [43]. In skin, epidermal keratinocytes are a major source of angiogenic factor VEGF (vascular endothelial growth factor) and FGF2 (fibroblast growth factor 2, also know as basic FGF) [29,44]. UV-B increases VEGF and FGF2 secretion from human keratinocytes and expression in mouse epidermis [26,43,45]. As discussed previously, UV irradiation also produces ROS, which cause vascular and dermal matrix damage via upregulation of matrix metalloproteinases [46-48]. The abnormal and damaged dermal matrix may permit leakage and accumulation of inflammatory mediators and prolonged retention of inflammatory cells, factors which could lead to inflammation in the disease. Thus UV irradiation could induce erythema in the skin by increasing expression of angiogenic factors and by degenerating extracellular matrix.

Recent publication suggests involvement of innate immune molecules in UV-mediated cytokine and matrix metalloproteinases expression in keratinocytes. Myeloid Differentiation Factor 88 (MyD88), an essential adaptor molecule for Toll-like receptors (TLR) family signaling, increases expression in UV-irradiated human cultures keratinocytes as well as photo-aged human skin [49]. Overexpression of dominant negative form of MyD88 prevented UV-induced expressions of IL-6 and MMP-1 in human keratinocytes, whereas overexpression of dominant positive form of MyD88 increases IL-6 and MMP-1 expression. Combining with ROS involvement in chemokines production by TLR2 stimuli [40,41], TLRs/MyD88 signaling would be the part of the link between UV irradiation to skin inflammation. The future studies of photo-aging in animals lacking TLRs signaling molecules will be of great interest.

Proteases

Although proteases involvements have not been discussed well in rosacea pathology, protease actions would be responsible for a part of rosacea histology. We identified serine protease kallikrein 5 (KLK5, also know as stratum corneum tryptic enzyme SCTE) as the processing enzyme of cathelicidin and found high KLK5 expression in rosacea skin [8,12]. KLK5 expresses in upper epidermis (granular to cornfield cell layer) in normal skin, and rosacea skin expresses KLK5 in the entire epidermis. KLK5 digest corneodesmosome proteins desmocollin 1 and desmoglein 1 in epidermis, and suppose to affect desquamation of epidermal keratinocytes [50,51]. KLK5 also efficiently digest the extracellular matrix components, collagens type I, II, III, and IV, fibronectin, and laminin [52]. Considering the high KLK5 expression in basal cells of rosacea epidermis, KLK5 could play a part of skin inflammatory reactions in rosacea by affecting dermal matrix and vascular remodeling.

The other supports for hypothesis of proteases involvement in rosacea pathology is evidence that tetracyclines inhibit several matrix metalloproteinases and serine proteases [53-55]. MMPs digest dermal matrixes such as collagens, fibronectin, elastin etc, and balances of MMPs and their inhibitor TIMPs dictate dermal components and vascular remodeling [56]. Although MMPs expressions in rosacea skin were not reported so far, MMPs are inducible by UV irradiation and ROS stimulation in keratinocytes and fibroblasts [42,49], and MMP-8 (collagenase 2) and MMP-9 (gelatinase B) activities are higher in the fluid of ocular rosacea than normal subjects [54,55]. Thus, the effective rosacea treatments might be partially dependent on their anti-protease properties.

Microbes

Two microbes have been discussed in rosacea pathology: *Demodex folliculorum* and *Helicobacter pylori*. *D. folliculorum*, a mite that lives within sebaceous follicles, has been

implicated as a trigger of rosacea since histological studies revealed inflammation of the pilosebaceous follicle units. Studies have shown increased density of the mites in patients with rosacea compared with control patients [57-59]. Lacey et al isolated *Bacillus oleronius* from *D. folliculorum* and identified the antigens reacting to sera from rosacea individuals but not from control individuals [60]. The extracts of the *B. oleronius* stimulate proliferation of mononuclear cells from patients with rosacea suggesting that rosacea individuals are exposed to the *B. oleronius* molecules and that *B. oleronius* from *D. folliculorum* induces inflammatory in rosacea. Interestingly, they identified heat shock proteins (HSP) and a lipoprotein in the antigenic molecules of *B. oleronius*. HSP and lipoproteins from microbes are also known to be stimulant for TLRs [61,62]. This report supports the hypothesis of mite and pilosebaceaous unit involvement in rosacea. Further studies are required to examine if these *B. oleronius* molecules evokes innate immune reaction or if rosacea is caused by adaptive immune reaction against *B. oleronius* and *D. folliculorum.*

Correlation of *H. pylori* infection and rosacea is controversial and inconsistent among clinical observation [63-67]. Several reports showed seropositivity to *H. pylori* in rosacea individuals [68]. Eradication therapy for gastric *H. pylori* infection showed preferable outcome for rosacea symptoms though it is not clear if the improve of rosacea is due to *H. pylori* eradication [69-71]. *H. pylori* produces ROS [72-74] and rosacea individuals showed higher ROS including NO (nitric oxide) in plasma than controls [68,75]. *H. pylori* induce cytokine release through TLR2 and TLR4 in gastric epithelial cells [76,77]. Thus ROS and cytokines released by TLRs stimuli in organs other than skin may be mediators that worsen rosacea by *H. pylori* infection. However, concrete molecular evidence is still required to support the involvement of *H. pylori* in rosacea pathology.

Summary

The newly discovered role of Cathelicidin in promotion of inflammation in rosacea creates new and exciting questions about the origins of this disease. The factors that promote cathelicidin production include innate immune molecules that to connect clinical and molecular observations (Figure). Microbes and environmental changes, such as sun and UV exposure, would be sensed by innate immune systems through pattern recognition molecules. The innate immune systems would enhance and be enhanced by cytokine, ROS, antimicrobial peptide, and proteases, which lead histological changes observed in rosacea. The multiple factors may heap up to cause rosacea clinical manifestations, while individual susceptibility to the factors is highly counted to cause rosacea. These new associations give us clues to further our understanding of the mechanisms responsible for the disease. Importantly, these advances also provide informed strategies for the optimal treatment of the clinical findings. While much work needs to be done, we hope this article facilitates future progress in basic research for the diagnosis and treatment of rosacea.

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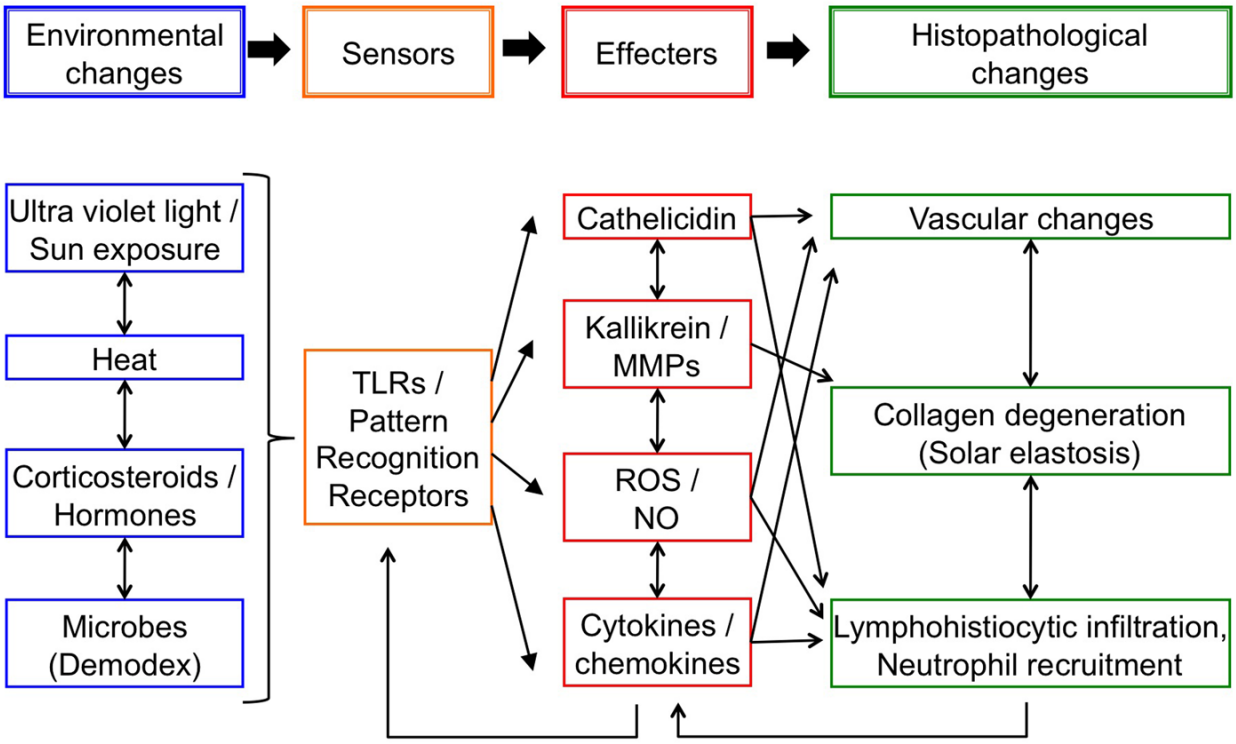

Figure. The possible molecular mechanisms for the pathogenesis of rosacea

Environmental changes, altered hormone balances and microbe challenges are sensed by TLRs (Toll-like receptors) and other pattern recognition receptors. TLRs signaling induce effecter molecules: cathelicidin, kallikrein, MMPs (matrix metalloproteinases), ROS (reactive oxygen species), NO (nitric oxides), cytokines, and chemokines. These effectors modify the dermal structure by vascular changes and collagen degeneration accompanied with inflammatory cells recruitments. Infiltrated neutrophils and lymphocytes will be the further source of effecter molecules, which activate TLRs directly and indirectly.