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Invited review article

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.

Contents

1. 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, non-transient 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

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disorder. From the diverse findings, the pathology of rosacea was thought to 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 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.

2. 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 anti-microbial molecules in the skin [5,6]. One of these anti-microbial 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 susceptibility 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 that 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.

3. 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 proliferates vascular endothelial cells as well as increases 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.

4. 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