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Review article

The role of altered cutaneous immune responses in the induction and persistence of rosacea

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ABSTRACT

Rosacea is a chronic inflammatory skin condition that predominantly affects the skin of the face and the eyes. Several factors are associated with the onset and persistence of the condition, including an altered immune response in the skin and elevated levels of *Demodex* mites. Alterations in the immune response include elevated levels of LL-37 in rosacea skin, increased expression of TLR-2 and increased amounts of vitamin D_3 in epidermal tissue. The combined effect of these changes may make the skin more sensitive to external and internal stimuli. External stimuli that may trigger or sustain rosacea inflammation include exposure to ultraviolet light, while internal factors may include the presence of elevated numbers of *Demodex* mites. These mites may directly stimulate an immune response or release bacteria within the pilosebaceous unit that act as a trigger for inflammation. This review will highlight the changes that occur in the immune response of the skin and describe how *Demodex* mites and associated bacteria may activate this response and lead to the characteristics of rosacea.

Contents

1. Introduction

Rosacea is a chronic cutaneous disorder that primarily affects the central region of the face and is characterized by chronic inflammation and fibrosis [1]. The standard classification system for rosacea describes four distinct clinical subtypes [2]. Erythematotelangiectatic rosacea (ETR) is characterised by flushing and persistent central facial erythema with or without telangiectasia (Fig. 1). Papulopustular rosacea (PPR) is associated

Abbreviations: AMPs, antimicrobial peptides; ETR, erythematotelangiectatic rosacea; hTCEpi, telomerase-immortalized human corneal epithelial cell line; MC, mast cells; KLK5, kallikrein 5; PPR, papulopustular rosacea; PRR, pattern recognition receptors; TLR, toll-like receptor; PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns.

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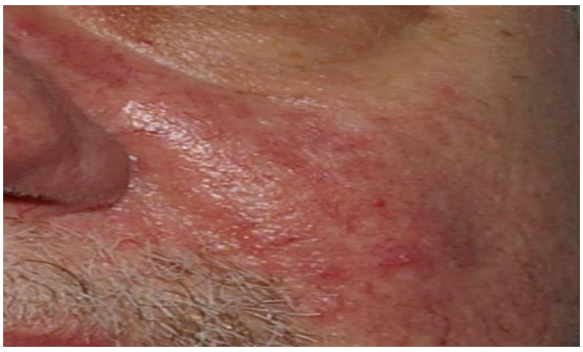

Fig. 1. Erythemic rosacea showing flushing and redness in the centre of the face.

with persistent central facial erythema with transient, central facial papules or pustules or both (Fig. 2). Phymatous rosacea is characterized by skin thickening, irregular surface nodularities and enlargement (Fig. 3). Locations affected include the nose, chin, forehead, cheeks, and ears. Ocular rosacea, displays symptoms such as foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital oedema (Fig. 4). While four subtypes of rosacea are recognised patients can display a number of subtypes simultaneously e.g. ocular rosacea in erythematotelangiectatic rosacea patients.

The incidence of rosacea in the population may range from less than 1% to 22%, with a higher prevalence amongst fair-skinned individuals of northern European or Celtic ancestry [3]. Females are more likely to suffer the symptoms of rosacea, the onset of which usually occurs between the ages of 30–50 [4]. Males, however are at greater risk of developing the phymatous form of the condition, particularly around the nasal area (rhinophyma) [3].

Although its aetiology remains unclear, the pathophysiology of rosacea appears to be dictated by the complex interaction of a dysfunctional cutaneous-innate immune system and a dysregulated neurovascular system [1,5]. This review will explore some of the key components that contribute to the development of rosacea focusing particularly on the role of the cutaneous-innate immune response, and how certain environmental and microbial stimuli influence this immune response to produce the phenotypic characteristics of rosacea.

1.1. The cutaneous immune response

Within the various epidermal layers of the skin multiple cell-types act synergistically to maintain homeostasis and defend the host against disease [6]. Epidermal keratinocytes are skin cells that

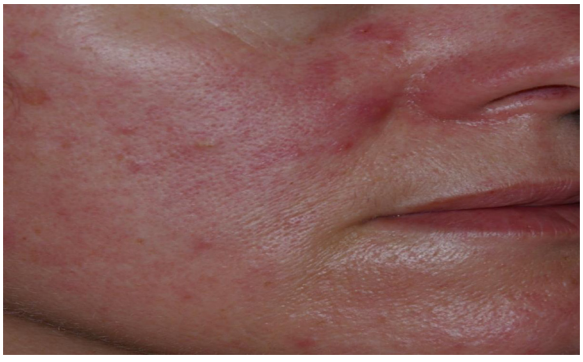

Fig. 2. Papulopustular rosacea showing persistent erythema, teleangiectases, papules and pustules.

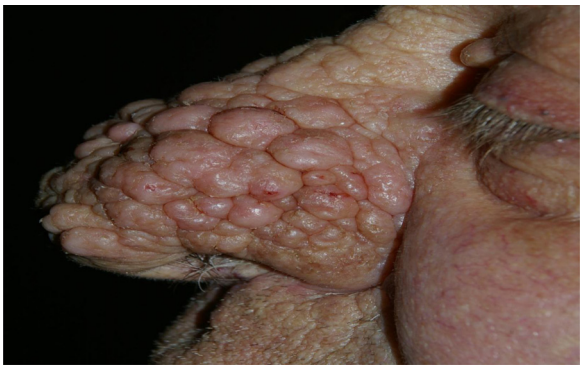

Fig. 3. Phytamous rosacea with proliferation and inflammation of skin surrounding nasal passage.

primarily dictate the structure of the epidermis but also play a role as innate immune cells by detecting pathogens and tissue damage. This process is mediated by pattern recognition receptors (PRRs) which recognise pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) respectively [6]. In normal skin, triggering an innate immune response through PRRs such as Toll-like receptors (TLRs) normally induces the carefully controlled expression and release of cytokines, chemokines and antimicrobial peptides (AMPs)—effector molecules that mediate a proinflammatory response by recruiting and activating leucocytes [7]. However, individuals with rosacea do not experience the same tightly regulated inflammatory response. Instead, the pathophysiology of rosacea appears to be defined by consistently abnormal innate immune activity which is exemplified by the chronic inflammation associated with the disease [8].

1.2. Cathelicidin/LL37; a major contributor to inflammation in rosacea

Human cathelicidins are multi-functioning proteins that are stored in the granules of neutrophils and in lamellar bodies of keratinocytes [9]. The nascent cathelicidin antimicrobial peptide (*CAMP*) gene product, hCAP18 is secreted as an inactive pro-protein, and in normal skin expression is kept low but dramatically upregulated upon skin-wounding and infection [9]. Enzymatic processing of hCAP18 generates the biologically active peptide LL-37, which can be cleaved further, to positively or negatively modify its antimicrobial activity [10].

LL-37 proteins play a dual role in the innate immune system by functioning as antimicrobials and as mediators of leucocyte recruitment [11,12]. Additional roles for LL-37 involve wound-healing responses including the induction of angiogenesis through binding formyl peptide receptor-like-1 on endothelial cells and stimulating the expression of extracellular matrix components

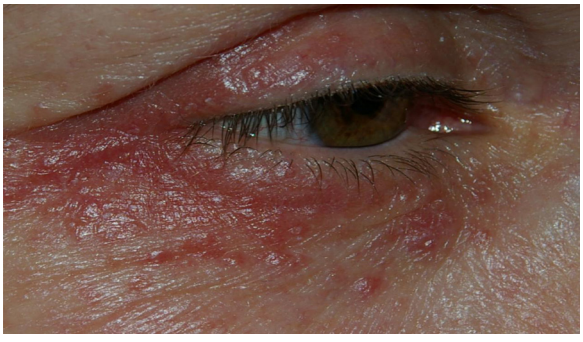

Fig. 4. Ocular rosacea demonstrating eye lid margin inflammation.

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