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Innate immunity and the role of the antimicrobial peptide cathelicidin in inflammatory skin disease

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Abstract

Cathelicidin antimicrobial peptide is an important mediator of the innate immune response. In addition to its potent antimicrobial activity, cathelicidin has been shown to have chemoattractant and angiogenic properties. Recent research has demonstrated that, in addition to its aforementioned functions, cathelicidin plays an important role in the complex pathogenesis of several chronic inflammatory skin diseases. This review will present a concise overview of the role of cathelicidin in infection and in the development of atopic dermatitis, psoriasis, and rosacea. This understanding will direct future research efforts to identify therapeutic approaches that use cathelicidin as a novel drug itself, or aim to modify its expression and regulation.

Introduction

The skin is the body's first line of defense, forming a protective physical barrier to the external environment and a constant bombardment of pathogenic microbes in the form of bacteria, viruses, and fungi. The skin's epithelial surface contains cellular and preformed biochemical components that constitute the innate arm of the immune system, providing an additional level of fortification to counter a continuous risk of infection.

Keratinocytes, dendritic cells, and mast cells are now recognized as important mediators in the innate immune response of the skin. Antimicrobial peptides (AMPs) encompass a diverse group of soluble peptides in the skin that are a vital element of the innate immune system's defense against microbes. Of particular importance is the cathelicidin family of AMPs. They were among the first described in humans and a large body of work exists detailing their regulation and role in preventing infection. Recent evidence suggests that altered regulation of cathelicidin antimicrobial peptides is involved in the complex pathogenesis of human inflammatory skin disease. In this review, we will focus our discussion on the role of cathelicidin in skin infection, in the development of atopic dermatitis, psoriasis, and rosacea, and as a potential therapeutic target.

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Cathelicidin antimicrobial peptide

Antimicrobial peptides are an important component of the innate immune system, providing a non-specific, rapid response to foreign pathogens. Defensins and cathelicidins are two of the major classes of human antimicrobial peptides well characterized in literature. The human cationic antimicrobial protein 18 (hCAP18) is the only known member of the human cathelicidin family of antimicrobial peptides. It is the 18 kilodalton peptide product of the gene CAMP, located on chromosome 3p21.3 [1]. Cathelicidin is produced and stored intracellularly as a prepropeptide, requiring proteolytic processing for activity [2]. When enzymatically cleaved by serine proteinases, it releases a cationic, amphipathic C-terminal fragment termed LL-37 that has been shown to have rapid antimicrobial activity against a wide range of gram-positive and gram-negative pathogenic microbes, as well as viruses and fungi [3-5]. The N-terminal cathelin domain is also active upon processing and has been shown to function as an antimicrobial as well as an inhibitor of proteinase activity [6]. LL-37 derives its function as an antimicrobial through its N-terminal alpha helical structure, which inserts into and disrupts bacterial membranes [7]. Originally recognized as a neutrophil specific peptide, it is now known that cathelicidin is expressed by many cell types in the skin including epidermal keratinocytes, mast cells, sebocytes, and eccrine glands [8-10]. It is also produced by circulating monocytes, NK, T, and B cells and by squamous epithelium throughout the body [11]. The active form of vitamin D, 1,25(OH)₂D₃ has been shown to directly induce cathelicidin production in keratinocytes and myeloid cells via a vitamin D response element in the promoter of the CAMP gene [12]. Inflammation, infection, and injury have been shown to result in upregulation of cathelicidin expression through a vitamin D dependent mechanism [13,14]. In addition to cathelicidin's antibiotic effect, it has been shown to play a role in communication between the innate and adaptive immune responses, acting as chemotactic factor for CD4 T cells, neutrophils, monocytes, and mast cells [15,16]. Moreover, studies have demonstrated a role for LL-37 in angiogenesis, injury, and wound healing [17,18].

Cathelicidins and infection

A wealth of evidence exists to suggest cathelicidin's crucial role as an antibiotic in the protection of epithelial surfaces, particularly the skin. The clinical significance of cathelicidin's antimicrobial activity can be seen in patients with Kostmann's syndrome, a rare genetic condition resulting in severe neutropenia. These patients suffer from chronic and recurrent infections. Patients treated with granulocyte colony stimulating factor (G-CSF) had recovery of their neutrophil count, but did not demonstrate clinical improvement. Upon further analysis, the neutrophils lacked production of cathelicidin [19]. Cathelicidin has been shown to provide cutaneous defense against many bacterial pathogens including Group A Streptococcus (GAS), *Staphylococcus aureus*, and methicillin-resistant *S. aureus* [5,20]. Cathelicidin has also proven to be effective against viral infections including herpes simplex virus, vaccinia virus, and fungal infections [3,21,22]. Not surprisingly, some bacterial pathogens have developed mechanisms that confer some level of resistance to antimicrobial peptides like cathelicidin. *S.aureus* can alter its lipid membrane constituents to include more positively charged species, thus repelling the cationic cathelicidin. GAS has been shown to produce peptides that can bind cathelicidin and block its antimicrobial activity and downstream effects [23]. Despite the existence of such mechanisms, complete bacterial resistance to cathelicidin has not yet been described. Cathelicidin antimicrobial peptide exhibits potent broad-spectrum antimicrobial activity coupled with little evidence of pathogen resistance, making it an ideal candidate for future research into novel antimicrobial therapies for use in infection and wound healing.

Atopic Dermatitis

Inflammatory skin diseases are extremely common worldwide and sufferers are known to have a severely diminished quality of life. Atopic dermatitis (AD) or eczema is a relatively common, chronic inflammatory disease of the skin, often associated with asthma and allergic rhinitis. It affects up to twenty percent of children worldwide and its incidence appears to be increasing [24]. AD usually begins in childhood before the age of five, and is clinically characterized by chronic pruritic, dry, lichenified skin, with acute exacerbations and recurrent skin infections. Distribution and severity of symptoms vary with the age of the patient. The pathogenesis of AD is complex, but thought to be due to a combination of epidermal barrier disruption and immune dysregulation, as well as genetic and environmental factors [25,26]. As mentioned above, cathelicidin production is increased in normal skin in response to injury and inflammation. In AD skin, cathelicidin production fails to increase upon injury, leading to increased susceptibility to infection by bacteria and viruses [3,27]. This phenomenon is thought to be due to the altered cytokine milieu of AD skin. The skin of patients with AD demonstrates an over expression of the Th2 cytokines IL-4 and IL-13, which prevent increased production of cathelicidin by inhibiting the stimulatory effect of TNF α and INF γ through STAT6 signaling pathways during injury and pathogen challenge [28]. In addition, increased levels of IL-10 in AD have been shown to indirectly hinder cathelicidin production in keratinocytes by inhibiting monocyte production of pro-inflammatory cytokines, further contributing to an impaired response to potential infection [29]. As a result, AD patients have a higher rate of bacterial colonization and infection than normal patients, as well as an increased risk of developing disseminated viral infections [30]. Vitamin D3, which has been shown to directly influence the expression of cathelicidin in the skin, has also been demonstrated to be moderately deficient in atopic dermatitis skin. Narrowband UV-B irradiation, a frequently used therapy in the treatment of AD, has been shown to increase vitamin D production in the skin of AD patients, and subsequently, the level of cathelicidin also increases, leading to an improved clinical picture [31]. Administration of oral vitamin D has also been shown to increase levels of cathelicidin in AD skin [32], but there exists little data to support the notion that UV-B therapy or oral vitamin D and the resultant increase in cathelicidin reduces the rate of infectious complications.

Psoriasis

In contrast to atopic dermatitis, where patients have an increased risk of microbial infection secondary to decreased cathelicidin production, psoriatic skin demonstrates increased production and activity of cathelicidin [27]. Psoriasis is a chronic inflammatory dermatosis with a wide range of clinical manifestations and a multifactorial pathogenesis. It affects up to five percent of the population worldwide. In its most common form, patients frequently demonstrate distinct erythematous plaques with silvery scales, often located on the knees, elbows, trunk, and scalp. Psoriasis has long been considered an autoimmune process, however the exact auto-antigens remain unknown. Recently, cathelicidin has been linked as a trigger of inflammation in psoriasis. Cathelicidin was shown to bind and complex with self-DNA released from apoptotic cells, activating plasmacytoid dendritic cells in the skin through TLR-9 and inducing the production of interferon- α [33]. Consequently, increased levels of INF- α lead to the activation of myeloid dendritic cells and T cells, playing a role in inflammation and lesion development. With the discovery of cathelicidin's role in the development of psoriasis, targeting the expression and regulation of cathelicidin may provide an important approach in the treatment of the disease. Interestingly, like atopic dermatitis, vitamin D analogues and UV-B therapy have a role in the treatment of psoriasis. UVB treatment led to a significant decrease in inflammation in psoriasis, reversal of vitamin D deficiency, and also increased levels of cathelicidin [31]. UVB therapy's paradoxical

affect on cathelicidin levels and inflammation in psoriasis may have more to do with vitamin D's ability to influence inflammation and the local cytokine milieu [34].

Rosacea

The development of rosacea is also associated with abnormal regulation of cathelicidin. Rosacea is a chronic inflammatory skin disease that classically involves the face and is characterized by flushing, persistent erythema, telangiectasias, papules and pustules [35]. It is a very common disorder, particularly in individuals with skin phototypes I and II. Cathelicidins were investigated in the pathogenesis of rosacea because they have vasoactive and pro-inflammatory properties, potential mechanisms in the development of the distinguishing clinical features. Studies have since demonstrated that cathelicidin levels were indeed elevated in rosacea skin in comparison to normal skin [36]. Increased expression of Toll-like receptor 2 (TLR2) on keratinocytes was also demonstrated in rosacea, which in turn leads to increased production and activity of the serine proteases that are responsible for converting cathelicidin to its active form, LL-37 [37].

Tetracycline antibiotics, which have successfully been used in the treatment of rosacea, likely derive some of their effect through the ability to inhibit the activity of these proteases [38]. Vitamin D may also play a role in the development of rosacea. Certain polymorphisms in the vitamin D receptor gene have been associated with severe rosacea phenotypes [39]. Therapeutic strategies targeting cathelicidin expression through the vitamin D pathway or targeting the activity of serine proteases involved in cathelicidin's activation may benefit the clinical picture of inflammation in rosacea.

Conclusion

Given cathelicidin's antimicrobial activity against an array of pathogenic microbes, particularly gram-positive staphylococcal and streptococcal species involved in skin infection, and the apparent lack of microbial resistance, cathelicidin has the potential to be a powerful new class of antimicrobial drugs. To date, cathelicidin has yet to be used therapeutically in the treatment or prevention of infection. It is possible that an active form of cathelicidin or a synthetic analogue of cathelicidin could be delivered directly to wounds to aid healing, speed up local neovascularization and epithelial cell migration, and to prevent infection. Cathelicidin-like peptides could also be a powerful tool to combat staphylococcal biofilms and in the prevention of nosocomial infections. In addition to infection, the abnormal regulation of cathelicidin is central in the pathogenesis of the inflammatory skin diseases atopic dermatitis, psoriasis and rosacea.

Therapeutic strategies that target cathelicidin's induction or inhibition through the vitamin D signaling pathway, as well as targeting important cytokines and proteases involved in the regulation of cathelicidin stand to be important avenues for future investigations.

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