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Human β-defensin 2: a connection between infections and allergic skin diseases

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Abstract

Beta defensins (β-defensins) are peptides primarily produced by epithelial cells in mammals to safeguard the skin, other organs, and mucosa from microbial colonization. These peptides are generated by epithelial cells, keratinocytes, and macrophages, mainly in response to interactions with microorganisms (bacteria, viruses, and fungi) or the influence of various pro-inflammatory cytokines. Human β-defensin (HBD) 2 plays an indirect role in allergic reactions by promoting mast cell activation and degranulation. In dermatological and allergic conditions, the role of HBD2 has been well documented. Although HBD2 is predominantly produced in keratinocytes, along with HBD3 it has also been detected in serum. Elevated serum levels of HBD2 have been observed in patients with skin diseases such as atopic dermatitis and psoriasis. In addition, HBD2 is significant in chronic spontaneous urticaria (CSU), in which urticarial skin lesions can be triggered by infections. Notably, CSU is often accompanied by angioedema, which may be related to HBD2 because patients with CSU and associated angioedema have higher serum HBD2 levels compared to those without angioedema. Current evidence suggests that HBD2 could serve as a marker of inflammation and may have potential therapeutic applications. However, due to limited data on HBD2 levels and its expression in the skin of patients with allergic skin diseases, further research is needed to elucidate the underlying causes and mechanisms of elevated HBD2 levels in these conditions.

Keywords: human β-defensin 2, allergic skin diseases, atopic dermatitis, urticaria, angioedema

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Introduction

Beta defensins (β-defensins) are peptides primarily produced in the epithelial cells of mammals, serving to protect the skin, other organs, and mucosa from microbial colonization. In humans, β-defensins also support the immune system by promoting immune cell chemotaxis and producing antimicrobial peptides in white blood cells. In addition, human β-defensin 2 (HBD2) plays an indirect role in allergic reactions by inducing mast cell activation and degranulation (1–4).

Structurally, HBD2 is a low-molecular-weight cationic peptide, rich in cysteine and composed of 41 amino acids (5–8). It is produced by epithelial cells, keratinocytes, and macrophages, mainly in response to exposure to microorganisms (bacteria, viruses, and fungi) or various pro-inflammatory cytokines (Fig. 1). HBD2 is crucial for immune system activation and modulating signaling pathways and inflammatory responses, where it protects against microorganisms by primarily targeting bacteria and fungi. Beyond its antimicrobial functions, HBD2 is involved in the chemotaxis of immune cells and activation of toll-like receptors (TLR) on cell surfaces, and it has a strong binding affinity to the C1 complement component. In vitro, it promotes inflammation by recruiting CD4+ T lymphocytes and macrophages through chemokine receptors (CCR) 2 and 6 (9, 10).

Furthermore, HBD2 induces mast cell degranulation by interacting with the mast cell Mas-related G protein-coupled receptor member X2 (MRGPRX2), which in vivo increases vascular permeability. This interaction with MRGPRX2, a receptor abundant in cutaneous mast cells, sensory neurons, and keratinocytes, triggers immunoglobulin (Ig) E–independent type I hypersensitivity-like reactions (pseudoallergic reactions) (11, 12).

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This review provides a comprehensive summary of the current understanding of the role of HBD2 in the context of infections, dermatological conditions, and allergic skin diseases, as well as the interconnections between these areas.

Methods

A literature search was conducted using the PubMed database, focusing on studies and articles relevant to the research topic. The search employed specific keywords, including *human β-defensin 2*, *allergic skin diseases*, *atopic dermatitis*, *urticaria*, and *angioedema*.

Results

Data on human β-defensin 2 in various dermatological and allergic conditions

The role of HBD2 has been demonstrated in various dermatological and allergic conditions affecting the skin (Table 1) (13–21). Although it is primarily produced in keratinocytes, HBD2, along with HBD3, has also been detected in serum. Elevated serum levels of HBD2 have been reported in patients with skin diseases such as atopic dermatitis (AD) and psoriasis (22, 23). In skin diseases, HBD2 functions as a pro-inflammatory pruritogen. Its interaction with TLR4 stimulates the activation of MRGPRX2, leading to itch that occurs independently of histamine (24, 25).

Several studies have explored the role of HBDs in AD (Fig. 2). According to the literature, a potential cause of AD involves abnormalities in skin cell components and antimicrobial peptides, such as HBD1, HBD2, and HBD3, in addition to genetic and environ-

mental factors and imbalances in the immune response (16). For instance, Hata et al. reported low levels of antimicrobial peptides, including HBD2, HBD3, and cathelicidin LL-37, in the lesional skin of AD patients (17). Similarly, Ong et al. found significantly lower levels of β-defensins in the inflamed skin lesions of patients with AD (19).

Other research has demonstrated a significant correlation between HBD2 levels, impaired skin barrier function, and the severity of AD (18). However, a study by de Jongh et al. indicated increased HBD2 expression in AD, consistent with earlier findings, showing that HBD2 is expressed at levels more than 20 times higher in psoriasis than in AD (21). Similarly, elevated HBD2 mRNA

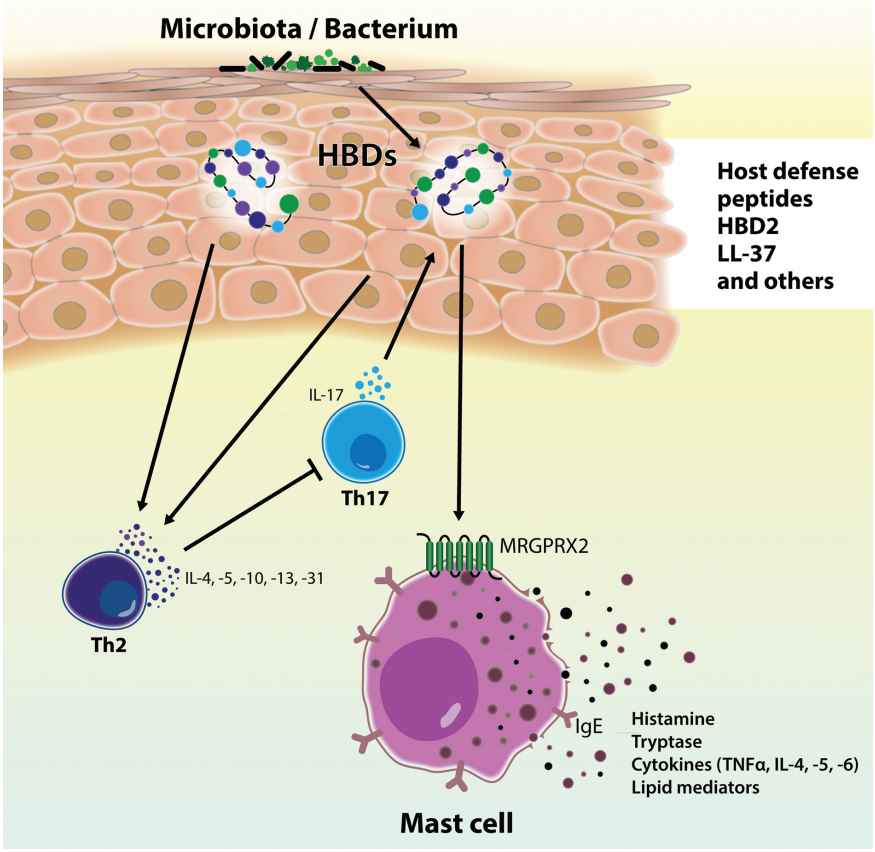

Figure 1 | Skin factors associated with human beta defensin (HBD) 2. LL-37 = cathelicidin LL-37, IL = interleukin, Th = T helper cell, MRGPRX = Mas-related G protein-coupled receptor member X2, TNFα = tumor necrosis factor alpha, Ig = immunoglobulin.

Table 1 | Reports on human beta defensin 2 (HBD2) in allergic skin diseases and similar conditions.

Study	Type	Participants and factors analyzed	Results
Tra Cao et al. (2021) (13)	Experimental study	Serum samples from 124 CSU patients and 56 healthy persons screened for HBD2 levels	Higher serum HBD2 levels in the CSU group than in healthy persons, higher in those with angioedema than without
Jansen et al. (2009) (14)	Experimental study	Thirty-eight patients with psoriasis, 12 AD patients, 40 patients with rheumatoid arthritis, and 70 healthy persons analyzed for HBD2 mRNA expression	Increased HBD2 mRNA expression in AD compared to normal skin, where it was undetectable
Yu et al. (2022) (15)	Review	Summary of currently developed potential AD biomarkers	NOS2/iNOS, HBD2, and MMP8/9 are potential candidate biomarkers for AD diagnosis
Park et al. (2020) (16)	Review	Review of skin cell components and antimicrobial peptides in AD	Abnormalities in skin cell components and antimicrobial peptides (HBD1, HBD2, HBD3) are a possible cause of AD, along with other factors (genetic, environmental factors; imbalance in immune response)
Hata et al. (2008) (17)	Review	Review of antimicrobial peptides and skin infections in AD	Low levels of antimicrobial peptides cathelicidin, HBD2, and HBD3 in lesional skin of atopics
Clausen et al. (2013) (18)	Experimental study	β-defensins assessed in 25 AD patients and 11 controls (HBD2 and other factors)	A significant correlation between HBD2, disturbed skin barrier function, and AD severity
Ong et al. (2002) (19)	Experimental study	HBD assessed in eight patients with moderate-to-severe AD, 11 patients with psoriasis, and six healthy persons	Significantly lower HBD levels in inflamed AD skin lesions
Li et al. (2017) (20)	Experimental study	18 AD-like GVHD patients, 12 LP-like GVHD patients, and 14 healthy persons assessed for HBD2 mRNA	Increased HBD2 mRNA expression in skin lesions of AD-like GVHD and LP-like GVHD patients
De Jongh et al. (2005) (21)	Experimental study	Analysis of expression of HBD2 in 20 patients with psoriasis, 16 AD patients, and 11 healthy persons	Increased HBD2 expression in AD, similar to previous findings, but expressed at levels more than 20 times higher in psoriasis than in AD

AD = atopic dermatitis, CSU = chronic spontaneous urticaria, GVHD = graft-versus-host disease, LP = lichen planus, HBD2 = human beta defensin 2, NOS2/iNOS = nitric oxide synthase 2 / inducible nitric oxide synthase, MMP8/9 = matrix metalloproteinases 8/9.

expression has been observed in skin lesions of patients with AD-like graft-versus-host disease (GVHD) and lichen planus–like GVHD (20). Another study found increased HBD2 mRNA expression in AD skin compared to normal skin, where it was undetectable (14). In addition, previous research has suggested that HBD2, along with nitric oxide synthase 2 / inducible nitric oxide synthase (NOS2/iNOS) and matrix metalloproteinases (MMP) 8/9, could serve as potential biomarkers for diagnosing AD (15).

Beyond its role in AD and psoriasis, HBD2 is also significant in chronic spontaneous urticaria (CSU), in which urticarial skin lesions can be triggered by infections. This process involves the activation of mast cells, basophils, macrophages, and T cells, which can elevate HBD2 production in the dermis (Fig. 3) (13, 26). CSU is often accompanied by angioedema, which may be associated with HBD2 because patients with CSU and angioedema have been shown to have higher serum HBD2 levels than those without angioedema (Fig. 4) (13).

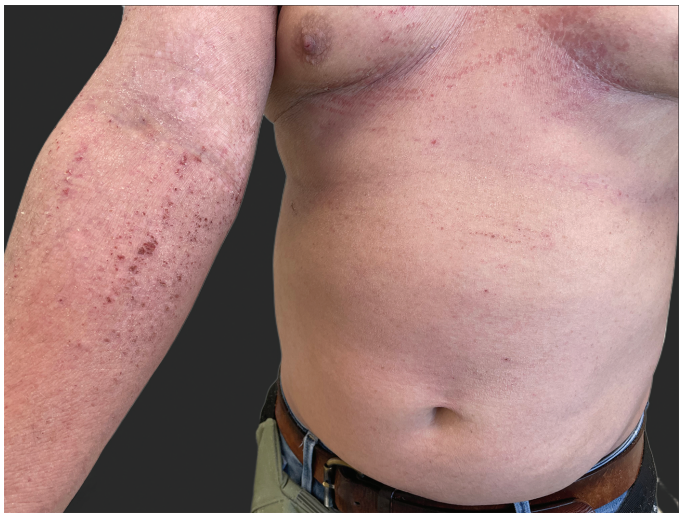

Figure 2 | Clinical picture of atopic dermatitis.

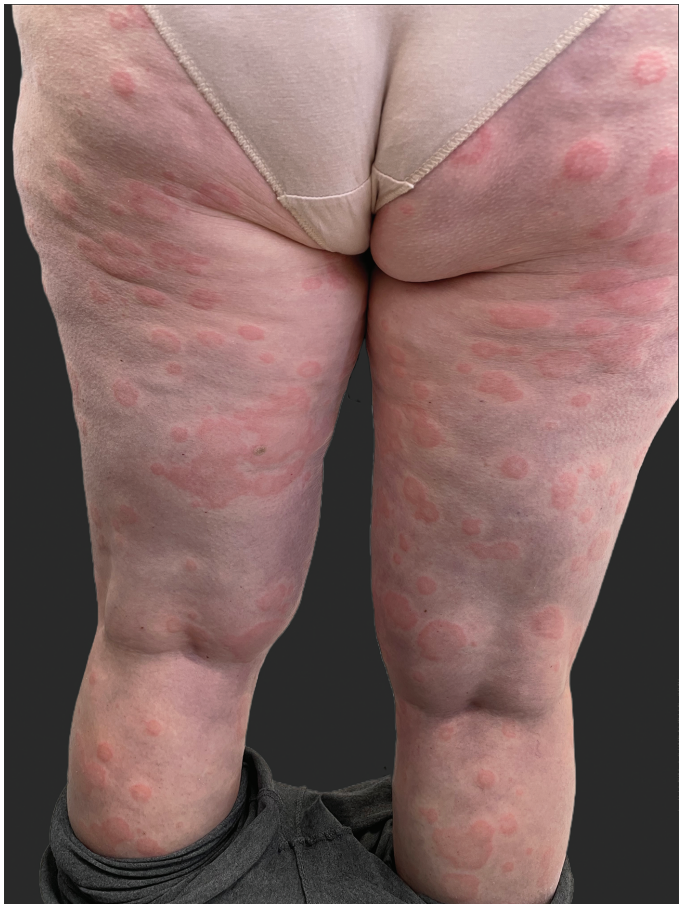

Figure 3 | Clinical picture of chronic urticaria.

Research findings indicate that histamine can synergistically increase HBD2 production in human keratinocytes when combined with tumor necrosis factor alpha (TNFα) or interferon gamma (IFNγ). Because HBD2 can stimulate mast cells to release histamine and attract TNF-α-activated neutrophils via chemotaxis, it is possible that a paracrine loop between HBD2 and histamine levels in the skin of CSU patients enhances interactions between keratinocytes, mast cells, and other inflammatory cells (27, 28). However, it is also noted that such a positive feedback loop between histamine and HBD2 levels is not present in patients with other inflammatory skin diseases (27).

In addition to skin diseases associated with HBD2, such as AD, CSU, psoriasis, and lichen sclerosis, elevated levels of HBD2 have been observed in various other conditions, with potential therapeutic implications. These include periodontal diseases, *Helicobacter pylori* infections, and inflammatory bowel diseases. HBD2 is also suspected to play a therapeutic role in viral infections, allergic conditions such as allergic asthma, oral lichen planus, wound healing, cell damage caused by smoking, and the risk of premature birth (29).

HBD2 is produced in the oral cavity by epithelial cells of the gingival mucosa, as confirmed by the expression of mRNA for HBD2 in these cells and its presence in saliva (30, 31). The production and secretion of HBD2 by oral epithelial cells are primarily triggered by pro-inflammatory cytokines or bacterial endotoxins, leading to a substantial increase in HBD2 synthesis upon contact with these stimuli (32). In addition, studies have shown that HBD2 levels are significantly higher in the saliva of patients with periodontal diseases compared to healthy individuals, suggesting that HBD2 could serve as a potential biomarker for detecting and preventing periodontal diseases (33, 34).

Current knowledge and perspectives on the association between human β-defensin 2 and chronic spontaneous urticaria and angioedema

A recent study found that patients with CSU have significantly higher serum levels of HBD2 compared to healthy individuals (13). In addition, CSU patients exhibited elevated serum HBD2 levels

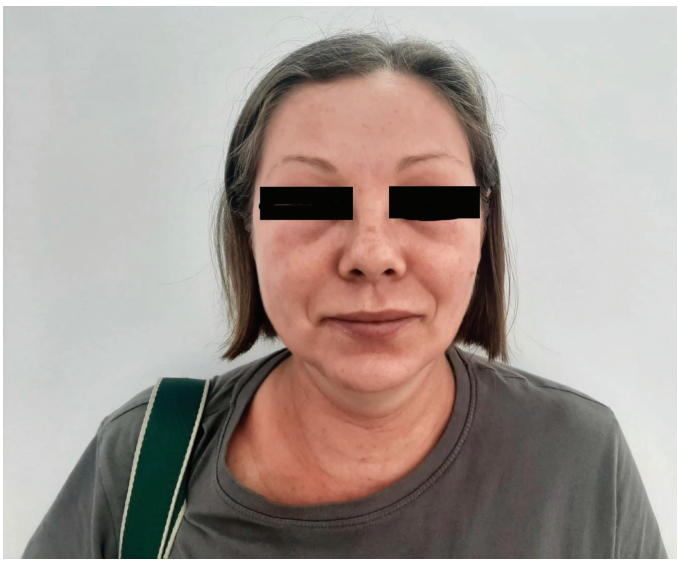

Figure 4 | Clinical picture of angioedema.

that correlated with the percentage of peripheral basophils, serum levels of translationally controlled tumor protein (TCTP), and vitamin D. This was in contrast to both healthy individuals and patients with other allergic conditions, including asthma and CSU (13, 35). Notably, TCTP is a critical factor in histamine release. In the skin of CSU patients, an oxidative environment enriched with cytokines is created by the activation of various inflammatory cells and autoimmune processes, such as the presence of IgG against Fc epsilon receptor alpha (FcεRα). This environment can lead to conformational changes in TCTP, converting it into its active dimeric form (36). Furthermore, CSU patients have shown increased levels of dimerized TCTP, which can trigger mast cell degranulation and basophil activation independently of IgE sensitization (36). Typically, TCTP induces basophil histamine release in an IgE-dependent manner.

CSU pathogenesis involves mast cell activation through both Fc epsilon receptor I (FcεRI) regulators and IgE-independent pathways, such as MRGPRX2, tetraspanins, and the CD300 family of proteins (37). Mast cell activation can be triggered by various factors, including thyroid proteins, nuclear antigens such as double-stranded DNA, and interleukin (IL) 24 via FcεRI cross-linking (38). Two distinct autoimmune subtypes of CSU, type I and type IIb autoimmunity, have been identified, both involving the activity of the FcεRI receptor.

However, CSU patients also show significantly increased serum levels of substance P, which activates mast cells via MRG-PRX2, indicating a potential IgE-FcεRI–independent mechanism in CSU pathogenesis (39). Because infections can serve as triggers for CSU, HBD molecules may play a role due to their anti-infective properties and function as mast cell secretagogues, contributing to neurogenic inflammation and itch through a non-FcεRI cross-linking mechanism (40–43).

In CSU patients with angioedema, measurements of HBD2 (using the Dunnett T3 test) revealed higher levels compared to those without angioedema and healthy individuals. However, no significant difference in HBD2 levels was found between CSU patients without angioedema and the healthy group. A negative correlation was observed between serum levels of HBD2 and the percentage of peripheral basophils in CSU patients, although no significant correlation was found between HBD2 levels and disease severity, as measured by the weekly Urticaria Activity Score (UAS7).

Multiple logistic regression analysis indicated that higher HBD2 levels (> 72 pg/ml) and more severe disease (UAS ≥ 28) are significantly associated with the presence of angioedema. No associations were found between angioedema and age, sex, or vitamin deficiency. Because basophil levels are biomarkers of CSU severity, with peripheral basopenia indicating skin basophil activation, it is notable that CSU patients exhibited a correlation between elevated HBD2 levels and lower basophil counts, as well as increased TCTP levels. This suggests that elevated HBD2 levels may serve as a potential biomarker for basophil and mast cell activation (44, 45).

When angioedema occurs alongside CSU, it is crucial to consider this condition because it may provide insights into the role of HBD2. Most cases of angioedema in CSU patients are histaminergic, mast cell–mediated, and often associated with itching (46). Clinically, CSU patients with angioedema tend to exhibit more severe disease activity and a longer duration of disease than those without angioedema (47, 48). Given that the UAS7 score, a common measure of CSU severity, only accounts for hives and pruritus but not angioedema, it is important to also evaluate the presence and extent of angioedema when assessing overall disease status and quality of life in CSU patients.

One study found that, although higher CSU severity (higher UAS7 scores) and elevated HBD2 levels were associated with angioedema, there was no significant correlation between HBD2 levels and CSU severity (UAS7) alone (13). This suggests that HBD2 may play a role in the pathogenesis of concomitant angioedema in CSU patients, even though it is not strongly linked to itching or the formation of hives. However, given the different types of urticaria and angioedema, it is possible that these findings may vary depending on the specific type of urticaria, angioedema, or other underlying conditions (49).

Finally, it is important to note that HBD2 has multiple roles and is involved in complex communication networks within the skin (50, 51). Therefore, in conditions such as allergic skin diseases, further studies are needed to evaluate the significance of HBD2 in specific patient subgroups.

Conclusions

Given the limited data on HBD2 levels and its expression in the skin of patients with allergic skin diseases, further research is necessary to understand the causes or etiology of elevated HBD2 levels in these individuals. This need is particularly pronounced in CSU patients, especially those with angioedema, for whom comparative studies on HBD2 levels and gene expression between CSU patients and healthy controls could provide valuable insights. In addition, exploring potential links between pathogenic pathways and HBD2 levels would be beneficial. Overall, considering the diverse properties of HBD2, current evidence suggests that it may serve as a marker of inflammation and could have potential therapeutic effects, including antimicrobial activity, inflammation suppression, and reduction of oxidative stress.

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