

The Role of the Histamine H4 Receptor in Atopic Dermatitis

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Abstract The pathology of atopic dermatitis is orchestrated on the cellular level by several different cell types in the characteristic skin lesions. In such lesions, histamine as a mediator of many biological functions is also present in high concentrations. Most of the cells involved in the inflammatory responses express the histamine H1 and H2 receptors, but drugs targeting these receptors are not clinically effective. The discovery of the fourth histamine receptor, which is differentially expressed on immune and nonimmune cells, has shed new light on the actions of histamine in the complexity of atopic dermatitis. In this review, we describe a possible genetic impact on the expression level of the histamine H4 receptor and summarize the current data regarding the activity of the histamine H4 receptor on the key effector cells in atopic dermatitis. We do so in the context of whether the histamine H4 receptor offers a novel target for effective treatments of inflammatory skin diseases.

Keywords Histamine · Histamine H4 receptor · Atopic dermatitis

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a characteristic phenotype of intensely pruritic, erythematous papules associated with excoriation and oozing exudation [1]. It has been shown that AD has a complex etiology by activating multiple immunologic and inflammatory pathways [2]. AD inflammation displays two phases that are orchestrated by a differential infiltrate of mononuclear cells in the dermis and by a switch of the local tissue expression of proinflammatory cytokines and chemokines. The initial phase is associated with an increase in T-helper type 2 (Th2) cells in acute lesions, followed by a later chronic phase characterized by the infiltration of inflammatory dendritic epidermal cells (IDECs), macrophages, and eosinophils. The interleukin (IL)-12 production by these various immune cells results in the switch from the acute Th2 phase dominated by secretion of IL-4, IL-13, and IL-5 to a Th1-type cytokine milieu associated with increasing presence of interferon (IFN)- γ -producing Th1 cells [1]. Intense pruritus is a major symptom of AD that affects patients' quality of life. In AD, elevated histamine levels in both lesional and uninvolved skin have been detected, and an important role for this mediator in the pathogenesis of itching has been suggested [3].

The clinical observation that pruritus in patients with AD is often not relieved by antihistamines targeting the histamine H1 receptor (H1R) or histamine H2 receptor (H2R) [4] led to the assumption that histamine is binding to other histamine receptors expressed on the immune cells taking part in AD. In this regard, the histamine H4 receptor (H4R) as the immune system histamine receptor [5] could be an attractive target for the treatment of inflammatory skin diseases [6•]. The H4R, the latest histamine receptor to

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be identified, was independently cloned and characterized by several groups [7, 8], and like the other histamine receptors, it is a G-protein-coupled receptor containing a transmembrane region consisting of seven α -helical bundles. Since its discovery, several selective H4R agonists and antagonists have been developed. The availability of these compounds was necessary to provide insights into a broad spectrum of immunomodulatory processes mediated by the H4R that are of potential therapeutic relevance. In contrast to other histamine receptors, the H4R possesses an extremely high affinity to histamine, with a K_d value of around 5 nM. This supports the role of the H4R in AD, where particularly in the chronic phase, lower levels of histamine are released from infiltrating immune cells [9]. It has been shown that histamine is released after de novo synthesis in various cells involved in the inflammatory response, such as monocytes, eosinophils, and T cells [10]. Furthermore, coexpression of the H1R, H2R, and H4R on diverse immune cells has been detected. Therefore, histamine can have varying and possibly counteracting effects on distinct cell types, depending on the concentration in the tissue and the histamine receptor that is activated [11]. Regarding the H4R, it appears the receptor is expressed at low levels, and its regulation can change in response to cytokines that characterize a specific microenvironment in the course of AD. For example, T cells stimulated *in vitro* express higher H4R levels in a Th2 cytokine milieu, which reflects the acute phase of AD [12•]. On the other hand, the Th1 cytokine IFN- γ , which is highly expressed in the chronic phase of AD, has been proven to upregulate the H4R on IDECs [13]. In addition, variability in H4R expression in inflammatory skin diseases has been observed. For example, the H4R is upregulated in chronic allergic dermatitis on myeloid dendritic cells (DCs) [14] and on keratinocytes (KCs) cultured from AD patients (Gschwandtner et al., unpublished results). Moreover, patients with AD express increased levels of H4R on T cells of the peripheral blood [12•]. The present review focuses on these puzzling observations by discussing the influence of genetic factors on H4R expression. In the second part of the article, the differential expression and function of the H4R on immune cells influencing the course of AD are critically analyzed via a description of the latest literature relevant to this topic.

Impact of Variations Within the Histamine H4 Receptor Gene on the Receptor Expression and Function

AD is a multifactorial, complex disease that is influenced by multiple genes and environmental factors [1]. Family and twin studies support a genetic contribution to the

pathogenesis of AD [15]. A study by Yu et al. [16•] described three single nucleotide polymorphisms (SNPs) within the H4R gene that were found to be significantly associated with AD, indicating a role of the H4R in the development of this disease. In this study, 301 patients with AD and 313 healthy controls without allergic disorders, all of Chinese origin, were included. Biological investigations of the detected gene variants revealed increased mRNA expression and prolonged protein stability of one of these mutations [16•]. These effects could be mechanisms explaining the differential expression of the H4R regulated by inflammatory stimuli or the donor-dependent expression of the receptor. Given that the underlying genetic structure between the Chinese and Caucasian populations is often different, it would be an interesting approach for future investigations to optimize the SNP selection and to conduct replication studies in the Caucasian population. In a more recently published article, the same research group analyzed variations in the copy numbers of the H4R gene and revealed an association of amplification of the H4R gene with increased risk of systemic lupus erythematosus [17]. Because copy number variations, as another genome-encoded factor, are expected to alter gene dosage and affect gene expression, it is tempting to speculate that copy number variations of the H4R gene also influence the course of inflammatory skin diseases. Another possible mechanism to regulate receptor expression on the genomic level is the occurrence of different splice variants of the H4R gene transcript [18]. Two nonfunctional, truncated H4R splice variants were identified and shown to decrease surface expression of the full-length H4R if the receptor was coexpressed with one of these variants. The differential expression of these splice variants in distinct cell types leads to reduced availability for H4R ligands followed by a possibly altered signal transduction and therefore might explain functional effects via the H4R [18].

Characteristics of the Histamine H4 Receptor on Cells Involved in Atopic Dermatitis

In AD, both asymptomatic skin and different stages of eczema are associated with the infiltration of leukocytes [2]. The first studies showed biologic effects of the H4R on human eosinophils [19, 20] and mast cells [21], describing migration behavior and calcium mobilization. Adding new data, we describe in the following sections the expression and function of the H4R on cell types relevant in AD, focusing on T cells and antigen-presenting cells (APCs) and briefly mentioning natural killer (NK) cells and KCs. This is also summarized in Table 1 and illustrated in Fig. 1.

Table 1 Expression and function of the human H4R in key effector cells of atopic dermatitis

Cell types	H4R expression	Function via H4R	Study
T cells			
Th cells			
•Th1 cells	On mRNA and protein level	Suppression of antigen-induced IFN- γ and IL-5	Sugata et al. [29]
•Th2 cells	Upregulated on Th2 cells	Upregulation of IL-31 mRNA, induction of AP-1	Gutzmer et al. [12•]
•Th17 cells	On mRNA and protein level	Upregulation of IL-17 mRNA and protein, induction of AP-1	Mommert et al. [32]
Tregs	Not described	Recruitment of Tregs, upregulation of IL-10	Morgan et al. [35]
Invariant natural killer T cells	On mRNA and protein level	Not described	Unpublished results
Natural killer cells	On mRNA and protein level	Chemotaxis via H4R	Damaj et al. [42]
Antigen-presenting cells			
Monocytes	On protein level Upregulated by IFN- γ	Chemotaxis via H4R Induction of calcium influx, downregulation of CCL2 Suppression of lipopolysaccharide-induced IL-27	Damaj et al. [42] Dijkstra et al. [14] Gutzmer et al. [43]
Monocyte-derived dendritic cells	On mRNA and protein level	Suppression of poly-IC-induced IL-12, chemotaxis via H4R, induction of AP-1	Gutzmer et al. [45]
Inflammatory dendritic epidermal cells	On protein level, upregulated by IFN- γ	Suppression of poly-IC-induced IL-12, downregulation of CCL2	Dijkstra et al. [13]
6-Sulfo LacNac-expressing dendritic cells	On mRNA and protein level	Suppression of lipopolysaccharide-induced TNF- α and IL-12	Gschwandtner et al. [47]
Plasmacytoid dendritic cells	On mRNA and protein level	Suppression of CpG DNA-induced TNF- α , IFN- α , and CXCL8 (IL-8); chemotaxis via H4R	Unpublished results
Langerhans cells	On mRNA and protein level	Downregulation of CCL2, chemotaxis via H4R	Gschwandtner et al. [48•]
Keratinocytes	On mRNA and protein level; upregulated in differentiated keratinocytes; upregulated in atopic dermatitis	Not described	Yamaura et al. [50•] and unpublished results

AP-1 activating protein 1, *H4R* histamine H4 receptor, *IFN* interferon, *IL* interleukin; *Th* T-helper, *TNF* tumor necrosis factor, *Treg* regulatory T cell

T Cells

The main types of CD4⁺ T cells—Th1, Th2, and Th17 cells—have been found in the skin during various inflammatory diseases. Studies in T-cell immunodeficiency disorders [22] and in animal models of AD [23] support the key role of T cells as immune effector cells in AD. AD inflammation is associated with increased numbers of Th2 cells in acute lesions and a predominantly IL-4 cytokine milieu [1]. We showed in a recently published work that the IL-4-dominated micromilieu upregulates the H4R on the mRNA and protein level on CD4⁺ T cells [12•]. In our study, patients with AD showed a trend toward higher H4R expression on peripheral CD4⁺ T cells as compared with healthy controls, which may reflect an increased number of Th2 cells and Th2 cytokines in the circulation

of patients with AD [4]. Moreover, we demonstrated higher H4R expression on in vitro polarized Th2 cells as compared with Th1 cells. Underlining these data, an induction of the transcription factor activating protein 1 (AP-1) via H4R was only observed in Th2 cells. In addition, H4R stimulation upregulated the mRNA levels of IL-31 in peripheral blood mononuclear cells (PBMCs) and Th2 cells, an effect that was more pronounced in PBMCs isolated from patients with AD [12•]. IL-31 represents a newly discovered cytokine—mainly produced by activated T cells—that has been shown to be associated with pruritus and severity of AD [24]. Thus, this study provides a new link between the effects of histamine via the H4R and induction of pruritus. Furthermore, enhanced release of IL-31 via H4R might exacerbate inflammatory reactions via the induction of proinflammatory cytokines

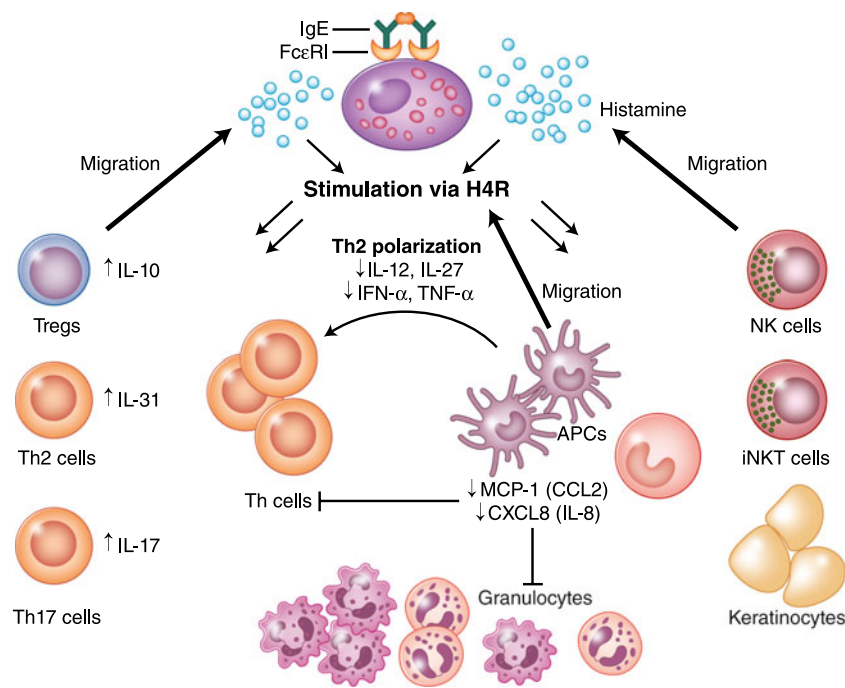


Fig. 1 The effects of histamine via the histamine H4 receptor (H4R) on human immune cells relevant in atopic dermatitis. Histamine acting on antigen-presenting cells (APCs) may drive T-helper type 2 (Th2) polarization by inhibiting the production of proinflammatory cytokines, in particular interleukin (IL)-12 and IL-27. In addition, the stimulation of the H4R on APCs suppresses the release of the monocyte chemoattractant protein 1 (MCP-1) (CCL2) and CXCL8 (IL-8), thereby reducing the migration of CD3⁺ lymphocytes and

granulocytes, respectively. Histamine itself induces chemotaxis via the H4R in regulatory T cells (Tregs), APCs, and natural killer (NK) cells (**bold arrows**). Furthermore, the H4R mediates direct effects on Th17 cells via release of IL-17, and on Th2 cells via release of IL-31, a cytokine that contributes to itch. Keratinocytes and invariant natural killer T (iNKT) cells express the H4R, but the functional effects on these cells are not described at present. *IFN* interferon, *TNF* tumor necrosis factor

in activated human monocytes and macrophages, which has been observed as a new function of IL-31 by our own research group [25].

In line with our data, an effective antipruritic and anti-inflammatory function of two potent and specific H4R antagonists in a Th2-cell-mediated murine skin model that mimics several features of AD was demonstrated in a recent work [26•]. In this study, the levels of diverse proinflammatory cytokines and chemokines, including IL-4, IL-5, and IL-17, were inhibited by treatment with H4R antagonists; this reduction of proinflammatory mediators might be responsible for the attenuation of edema formation, which also has been observed. Of note, these effects were partially accounted for by a reduction in the migration of antigen-presenting DCs via H4R agonists [26•].

In addition, the H4R plays a decisive role in the scratching behavior of mice in another Th2-dominated dermal inflammation model. In this approach, treatment with the H4R antagonist JNJ777120 attenuated the pruritic response but failed to reduce the allergic inflammatory response associated with allergic dermatitis [27•].

Further evidence that histamine causes a shift toward a Th2 response has been shown in a study by Horr et al. [28], in which histamine exerted its effects through the H4R by

suppressing the mitogen-induced signal transducer and activator of transcription 1 phosphorylation, which blocks IFN- γ -mediated events and drives Th2 polarization. Because these experiments were performed with PBMCs, the effect could not be clearly attributed to Th cells [28].

Histamine also regulates cellular immune responses. Data from Sugata et al. [29] suggest that H4R agonists inhibit antigen-specific human T-cell responses by reducing IFN- γ and IL-5 production.

More recently, Th17 cells, as a newly delineated subset of CD4⁺ T cells, have been shown to play a potential role in AD. It was demonstrated that the number of Th17 cells is increased in the peripheral blood of AD patients and is associated with the severity of AD [30]. Studies performing immunohistochemistry revealed that IL-17-producing cells are more abundant in acute compared with chronic lesions of AD [30, 31]. On human memory T cells, which were polarized into Th17 cells by the cytokines IL-1 β ⁺ and IL-23, as well as on IL-17-positive cells in lesions of inflamed skin, we detected the expression of the H4R. After H4R stimulation, we observed upregulation of IL-17 mRNA, enhanced secretion of IL-17 protein on the single-cell level, and the induction of the transcription factor AP-1 [32]. Because IL-17 is a pleiotropic cytokine, the enhanced release

upon histamine stimulation may influence the immunologic responses taking part in inflammatory skin diseases.

High numbers of CD4⁺CD25⁺ regulatory T cells (Tregs) in combination with increased induction of their key transcription factor, forkhead box P3, were found in the blood of AD patients [33]. The presence of Tregs in the skin of patients with AD was also demonstrated in a study by Schnopp et al. [34].

Morgan et al. [35] reported on the potential of H4R to induce migration of CD4⁺ T cells, which are enriched for T cells with a regulatory phenotype expressing forkhead box P3 and increased IL-10 production. This was demonstrated in a murine model of allergic asthma and in vitro on human CD4⁺ T cells [35]. Moreover, a recently published review discusses a possible proinflammatory role of the H4R in murine asthma models [36], and further synergistic interactions of the H1R and H4R in an acute murine asthma model have been observed [37]. The beneficial effect of the H4R agonist described by Morgan et al. [35] might be attributed to the local administration of the compound and to the resulting concentration gradient within the lung, which would facilitate the migration of the immune suppressive Tregs.

A protective role for invariant natural killer T (iNKT) cells in the skin has been suggested with regard to their ability to recognize bacterial glycolipids, to promptly produce several cytokines (eg, IL-4 and IFN- γ), and to serve as antimicrobial immune sentinels. iNKT cells are characterized by a conserved invariant V α 24J α 18 T-cell receptor chain paired with a V β 11 chain [38]. Most recently, iNKT cells were detected among infiltrating T lymphocytes in the lesional skin of atopic eczema and other inflammatory skin diseases in which they are exposed to histamine [39•].

Very few data are currently available concerning H4R expression and function on this rare subset of T lymphocytes. Studies with histidine decarboxylase-deficient mice (lacking histamine) and H4R knockout mice showed impaired IL-4 and IFN- γ levels that resulted from lower iNKT cell counts and functional deficiencies in these cells [40•]. We expanded iNKT cells in vitro via stimulation of PBMCs with the glycolipid α -galactosylceramide, and then isolated CD3⁺ and V α 24J α 18⁺ cells by fluorescence-activated cell sorting and showed for the first time the expression of the H4R on the mRNA and protein level on human iNKT cells (unpublished results). Functional studies with H4R ligands are planned with these cells with the intent of extending the knowledge of the role of iNKT cells in inflammatory skin diseases.

Natural Killer Cells

NK cells in humans are phenotyped as CD3⁺CD56⁺ lymphocytes. High cytotoxic capacity and the production

of a variety of soluble mediators are the main functions of this cell type. In lesions of atopic eczema, NK cells were observed in close proximity to DCs, which points to a role of NK cells in modulating the function of DCs in AD [41]. The expression of the H1R and H4R on human activated NK cells was identified on the protein level [42]. In this study, histamine presented a robust chemotactic factor for these cells to attract them to the sites of inflammation. Furthermore, it was shown that this effect was inhibited by the H3R and the H4R antagonist thioperamide. Because NK cells lack the expression of the H3R, this effect was specifically attributed to the H4R. Interestingly, histamine failed to induce the mobilization of calcium in these cells, suggesting uncoupling of chemotaxis and calcium mobilization [42].

Antigen-Presenting Cells

APCs such as monocytes and DCs play a pivotal role in the initiation of allergic inflammation via their special properties of antigen uptake and presentation and by secreting cytokines and chemokines to generate a cytokine network.

The first studies on human monocyte-derived DCs (MoDCs) and monocytes showed that the H4R is expressed on mRNA and the protein level and controls cytokine and chemokine production. On human monocytes, histamine mediates chemotaxis [42], induces calcium mobilization and downregulates the spontaneous secretion of monocyte chemoattractant protein 1 (CCL2) via the H4R; this effect was reversed by an H4R antagonist [14]. In addition, recent findings from our group support the more anti-inflammatory capacity of the H4R on APCs by demonstrating the downregulation of the lipopolysaccharide-induced production of the cytokine IL-27, a novel member of the IL-12 family of cytokines. This effect seems to be influenced by a reduced nuclear factor- κ B signaling capacity and is mediated by the H2R and H4R [43]. We recently detected expression of IL-27 in chronic human eczematous skin lesions and showed that human KCs stimulated in vitro with IL-27 released enhanced amounts of the Th1-cell-attracting chemokine CXCL10 [44]. In line with this observation, it was shown that the incubation of KCs with supernatants from monocytes containing reduced IL-27 levels upon histamine treatment resulted in decreased secretion of CXCL10 [43].

The stimulation of the H2R and H4R induces the activation of the transcription factor AP-1 and suppresses poly-IC-induced IL-12p70 production on human MoDCs. As IL-12 is a key cytokine in inducing differentiation of Th1 response, suppressive effects via H4R on the IL-12 level might contribute to shifts from a Th1- to a more Th2-

dominated profile. Furthermore, a chemoattractive effect of histamine via H2R and H4R has been demonstrated [45].

The H4R also could be detected on murine bone marrow–derived DCs, and enhanced migration of these cells via H4R in *in vitro* chemotaxis assays and skin migration assays was demonstrated [46].

The latest studies have focused on certain subtypes of DCs that participate in the inflammatory response in the skin (eg, IDECs, inflammatory DCs characterized by the 6-Sulfo LacNac group on their surface [slanDCs], plasmacytoid DCs [pDCs], and Langerhans cells [LCs]) as the prototypic APCs in the skin.

IDECs can populate the epidermis and the dermis but were mainly found in the inflamed epidermis of patients with AD. The H4R is expressed on IDECs on the protein level, and downregulation of IL-12 and CCL2 via H4R was described [13].

Investigation of slanDCs shows expression of the H1R, H2R, and H4R. Human slanDCs represent a major population of DCs present in the human blood and are characterized as highly proinflammatory by their capacity to induce T-cell responses and proinflammatory cytokines and their recruitment to inflamed skin. Histamine reduces the proinflammatory capacity via a strong decrease in the lipopolysaccharide-induced production of tumor necrosis factor- α and IL-12, particularly via activation of the H4R [47].

Increased numbers of pDCs have been found in the peripheral blood of AD patients, but in contrast to other inflammatory skin diseases, only low numbers are present in skin lesions in AD [2]. The existence of the H4R on the surface of pDCs was also demonstrated by our group, and the H4R was functional because its stimulation suppressed the production of tumor necrosis factor- α , IFN- α , and CXCL8 (IL-8), which were induced in response to stimulation with unmethylated CpG DNA (unpublished results).

LCs are the first DCs to come into contact with microbial antigens. After antigen uptake and processing, they migrate from the epidermis to the local lymph nodes to initiate a T-cell response. The H4R is expressed on *in vitro*–generated, monocyte-derived LCs on mRNA and on the protein level, and on primary LCs from human and murine skin samples on the protein level. As previously shown for monocytes and IDECs, downregulation of CCL2 was also mediated via H4R, and histamine-induced *ex vivo* migration of LCs from the human epidermis was detected [48•].

It has been shown conclusively that the H4R is expressed on different human DC subtypes and influences immune responses via downregulation of proinflammatory cytokines (IL-12, IL-27, tumor necrosis factor- α , IFN- α) and chemokines (CCL2, CXCL8 [IL-8], CXCL10 [indirect

effect]). Furthermore, histamine acts as a chemoattractant factor via H4R by modulating DC migration. Thus, regarding the effects on human APCs, H4R agonists might provide more beneficial effects compared with antagonists by reducing the proinflammatory responses taking place in AD.

Keratinocytes

KCs are proinflammatory effector cells located at the outermost layer of the body that react to hazardous agents via the coordinated production of antimicrobial peptides, proinflammatory cytokines, and chemokines. Growing evidence supports the role of KCs as enhancer cells of the inflammatory response in AD [49].

Immunohistochemical studies on human epidermal tissue revealed expression of the H4R in which the receptor was found to be upregulated in differentiated KCs in the upper layer compared with basal KCs [50•]. Confirming this, we were also able to detect the expression of the H4R on human primary KCs. In addition, we generated KC cultures from AD patients and compared the H4R expression with healthy KCs. We detected an upregulation of the H4R expression on the KCs derived from AD patients compared with healthy controls (unpublished results). Further work is needed to determine the expression mechanism and function of the H4R on KCs.

Conclusions

Taken together, *in vitro* studies on human immune cells and *in vivo* data obtained from murine models support the immunomodulatory role of the H4R on various cell types relevant in AD.

Histamine might promote inflammation in AD via the H4R acting on Th cells with enhanced release of proinflammatory cytokines, and on APCs as a potent chemoattractant. In contrast, H4R controls inflammation by suppressing the production of cytokines as well as chemokines in APCs and thereby can influence Th-cell polarization linking innate and adaptive immune pathways. In the context of these conflicting activities of the H4R, additional research is needed to clarify whether H4R agonists or antagonists can yield promising drugs in the treatment of AD.

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- Of importance
- Of major importance

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