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REVIEW ARTICLE

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Nothing to sneeze at: Histamine and histamine receptors in oral carcinogenesis

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Abstract

Oral squamous cell carcinoma (OSCC), the most common oral malignancy, shows an increasing rate of incidence worldwide. In spite of the recent advances in cancer research, OSCC therapy continues to have unfavourable outcomes, and thus, patient's prognosis remains relatively poor. Current research has been devoted to identifying novel therapeutic targets also in the tumour microenvironment (TME). Histamine and its G-protein-coupled receptors (H1R-H4R) play vital roles in multiple cancer-associated processes in TME, where histamine is mainly produced by mast cells. However, oral epithelial cells were recently shown to produce low concentrations of histamine in autocrine and paracrine modes. These findings, together with the discovery of the high-affinity histamine H4 receptor, have led to a massive increase in our understanding of histamine functions. In this review, we aim to summarize the most recent findings regarding histamine and its receptors and their involvement in oral carcinogenesis—from oral potentially malignant disorders (OPMDs) to invasive OSCC. Importantly, histamine receptors are differentially expressed in OPMDs and OSCC. Furthermore, H1R and H4R are associated with clinicopathological characteristics of OSCC patients, suggesting a role in prognosis. Due to the enormous success of histamine-based medications, histamine receptors may also represent promising and viable drug targets in oral cancer.

KEYWORDS

epithelial dysplasia, histamine, histamine receptors, mast cells, oral lichen planus, oral squamous cell carcinoma

1 | INTRODUCTION

Cancer continues to be a leading cause of death and the most crucial hurdle to extend life expectancy in the current century (Bray et al., 2018). In spite of the substantial advancement in cancer research over the last decades, anti-cancer approaches remain largely ineffective and long-term survival continues to be disappointing in many solid tumours (Apolone, Joppi, Bertele', & Garattini, 2005). Oral squamous cell carcinoma (OSCC) is the most common oral malignancy, which accounts for about 90% of all malignant neoplasms of the oral cavity (Johnson, Jayasekara, & Amarasinghe, 2011). It has been documented that OSCC may develop from pre-existing chronic oral inflammatory conditions, and other potentially premalignant disorders, such as lichen planus, lichenoid reaction, leukoplakia and erythroplakia (Speight, Khurram, & Kujan, 2018). Unfortunately, OSCC has an

unfavourable prognosis with the 5-year overall survival is stagnant at around 50% (Sim, Hwang, & Ahn, 2019). In addition, OSCC therapy can provoke detrimental effects in patients, including impairment of vital functions, severe toxicity and poor responses (Lo Nigro, Denaro, Merlotti, & Merlano, 2017; Rivera, 2015). In order to overcome such challenges, recent research has been devoted to identifying and targeting novel "druggable" components of the tumour microenvironment (TME) (Roma-Rodrigues, Mendes, Baptista, & Fernandes, 2019). Indeed, a better understanding of cancer biology as well as the interactions between various components of TME is imperative to discover novel anti-cancer drugs with an improved efficacy and reduced side effects.

Histamine is one of the most studied substances in medicine, and it has long been suggested as a crucial player in tumorigenesis (Medina et al., 2013). Histamine regulates a wide variety of physiological and pathological processes including neurotransmission, allergic reactions and inflammatory responses to foreign pathogens (Panula et al., 2015). In addition, histamine influences numerous carcinogenesis-associated events such as cell division, proliferation and apoptosis (Chen & Hu, 2018; Cricco et al., 2006; Jakhar, Paul, Bhardwaj, & Kang, 2016). Furthermore, most cancer cells and in vitro tumour models contain considerable amounts of endogenous histamine, which signify its role as a crucial player in cancer (Massari, Nicoud, & Medina, 2020). The involvement of histamine and histamine receptors in different types of cancer has been extensively summarized in several comprehensive reviews (Kennedy, Hodges, Meng, Alpini, & Francis, 2012; Massari et al., 2020; Nicoud, Formoso, & Medina, 2019). However, in this mini-review, we aim to focus on the current knowledge regarding histamine and histamine receptors and their potential role in oral carcinogenesis.

2 | HISTAMINE SYNTHESIS AND DEGRADATION

Histamine [2-(4-imidazolyl)-ethylamine] is a short-acting biogenic amine that is synthesized from the essential amino acid histidine via the catalytic enzyme L-histidine decarboxylase (HDC). Histamine is ubiquitously distributed throughout the body with higher concentrations in the skin and gastrointestinal tract (Panula et al., 2015). It is released into the extracellular milieu and produces its actions through autocrine and paracrine mechanisms (Thangam et al., 2018). The typical cellular sources of histamine in the body are the pluripotent mast cell (MC), gastric enterochromaffin-like cells, the histaminergic neurons and basophils (Tiligada & Ennis, 2020). These cells synthesize and store copious amounts of histamine and represent the major or "professional" histamine-producing cells (Huang, Li, Liang, & Finkelman, 2018; Konttinen et al., 2013). In addition, other cell types were reported to synthesize and release about 1000-fold less quantities of histamine and hence named "non-professional" histamine-producing cells, including T-lymphocytes, dendritic cells and oral epithelial cells (Salem, Rozov, et al., 2017). Professional histamine-producing cells, such as MCs, secrete histamine by active exocytosis in a burst-like manner following activation by stimulants. In contrast, non-professional histamine-producing cells release histamine passively along its concentration gradient through organic cation transporters (OCTs) such as OCT3 (Ogasawara et al., 2006) (Table 1).

To terminate its effects, histamine concentration in the intra- and extracellular spaces should be regulated by an efficiently controlled enzymatic degradation system. Histamine degradation is carried out either by diamine oxidase (DAO) or by histamine N-methyltransferase (HNMT), which both exhibit distinct functions and localization patterns (Darvas et al., 2003). The latter cytosolic enzyme, HNMT, degrades the intracellular histamine via ring methylation, while DAO degrades extracellular histamine via oxidative deamination (Smolinska, Jutel, Crameri, & O'Mahony, 2014).

3 | HISTAMINE RECEPTORS

Histamine exerts its effects via four distinct G-protein-coupled receptors: histamine H1R through histamine H4 receptor (H1R-H4R), which contain three domains—extracellular, transmembranous and

TABLE 1 Main differences between professional and non-professional histamine-producing cells[a]

Feature	Professional cells	Non-professional cells
Main cell types	Mast cells, basophils and histaminergic neurons	Tumour cells, dendritic cells, lymphocytes and epithelial cells
Histamine-synthesizing enzyme	Short-length HDC (53 KD)	Full-length HDC (74 KD)
Histamine synthesis rate	Fast and efficient	Slow (~1,000 times slower)
Histamine storage	Yes (in secretory granules)	No
Amount of released histamine	High (micromolar)	Low (nanomolar or less)
Mode of histamine release	Active (require stimulus)	Passive (concentration gradient)
Main functional receptors	Low-affinity (H1R, H2R)	High-affinity (H3R, H4R)
Time range of the effect	Short-term	Long-term
Spatial range	Pathological "hotspots"	Pathophysiological

Abbreviations: DAO, diamine oxidase; HDC, L-histidine decarboxylase; HNMT, histamine *N*-methyltransferase; KD, kilodalton.

[a]Modified from Konttinen et al., 2013.

intracellular. The first discovered receptor subtype of histamine, H1R, is mainly localized on the vascular endothelial and smooth muscle cells. Histamine stimulates H1R through $G\alpha_{q/11}$, which in turn activates phospholipase C and elevates intracellular Ca^{++} levels. Consequently, this results in the contraction of smooth muscles, increases vascular permeability and induces the production of prostacyclin and platelet-activating factor (Panula et al., 2015; Thangam et al., 2018).

The first generation of H1R-based anti-histamines has led to the production of very successful medications. However, scientists noticed that certain histamine-driven effects were not managed by H1 antagonists and thus the second receptor subtype, H2R, was characterized. The H2R is $G\alpha_s$-coupled receptor, which upon activation can induce mucus production and secretion of gastric acid (Thangam et al., 2018). As it is mainly expressed on the parietal cells, antagonizing H2R (via H2-blockers) has revolutionized the management of gastric and duodenal ulcerations by inhibiting the production of hydrochloric acid (Konttinen et al., 2013). In addition, H2R was found in some immune cells, such as neutrophils and eosinophils. In this context, targeting H2R seems to support Th2-mediated effects and to counteract Th1-type inflammatory response (Akdis & Simons, 2006). Based on pharmacological evidence, the detection of the third histamine receptor, H3R, in 1983 indicated a profound influence of histamine on various neurotransmitter balances (Panula et al., 2015). The H3R is coupled to the $G\alpha_{i/o}$ and it is almost exclusively expressed in neurons, and thus, blocking ligands are researched as therapeutic targets in CNS disorders (Massari et al., 2020).

At the turn of the millennium, the newest histamine receptor, H4R, was characterized independently by different research groups (Panula et al., 2015). The H4R is a $G\alpha_{i/o}$-coupled receptor and it shares a 37% homology with H3R, but unlike H3R, it is predominantly expressed in cells of the immune system such as MCs, T-lymphocytes and natural killer cells (Nicoud et al., 2019; Thurmond, 2015; van Rijn et al., 2008). Indeed, the identification of potent ligands for H4R (agonists, neutral antagonists and inverse agonists) has revealed its immunomodulatory role in inflammatory responses and in cancer (Medina et al., 2013; Thurmond et al., 2008). Interestingly, activation of H4R resulted in immune cell chemotaxis in MCs, eosinophils, dendritic cells and regulatory T cells. For instance, activation of H4R by a selective agonist (4-methylhistaminet) induced the expression and release of various pro-inflammatory cytokines and chemokines such as transforming growth factor beta-1, tumour necrosis factor alpha and beta, and macrophage colony-stimulating factor, in addition to many interleukins (e.g. IL-8, IL-6, IL-16, IL-3, IL-10) in human MCs. Furthermore, targeting H4R with another selective agonist (clobenpropit) resulted in a concentration-dependent release of IL-16 from cytotoxic T cells. Importantly, H4R exhibits a differential expression in various primary neoplasms compared with normal tissues, such as oesophageal, gastric, colorectal and breast cancers, which indicates a possible involvement in carcinogenesis (Jemima, Prema, & Thangam, 2014; Nicoud et al., 2019; Panula et al., 2015). The main features of histamine receptor subtypes are summarized in Table 2.

4 | CONCENTRATION-DEPENDENT ACTION OF HISTAMINE

Although histamine has been exploited in medicine since 1930s, ligands targeting H1R-H3R remain, by and large, ineffective in treating many immune-associated diseases and cancer. In fact, such limitation has been attributed to the substantial variations in the extracellular levels of histamine in different body tissues (Konttinen et al., 2013; Panula et al., 2015). Extracellular histamine can be too low to induce signalling cascade through the low-affinity receptors, H1R and H2R (pKi = 4.3; 4.2, respectively), but already high enough to activate the high-affinity receptors, H3R and H4R (pKi = 8.0; 8.3, respectively) (Konttinen et al., 2013; Lim et al., 2005; Thurmond et al., 2008). This indicates that low concentrations of histamine can mediate numerous unidentified effects in immune cells through the H4R (Konttinen et al., 2013). Therefore, the local level of histamine and the differential expression of its receptors are considered important factors in determining the biological response (Panula et al., 2015; Salem, Rozov, et al., 2017).

This is particularly important in terms of the recent identification of non-professional histamine-producing cells and their role in mediating crucial pathophysiological processes (Konttinen et al., 2013). In this context, low levels of histamine, produced by non-professional histamine-producing cell, may sustain long-term oxidative stress injury and thus induce progressive disorders including tumorigenesis and angiogenesis (Khatami, 2016). Emerging evidence suggests that ligands targeting H4R, in part because of its high affinity, may provide new drug targets to the therapy of chronic oral inflammatory lesions and cancer (Salem et al., 2019). For instance, activation of H4R by nanomolar agonist interfered with apoptosis and reduced cleavage of the early-apoptotic marker, poly (ADP-ribose) polymerase, in cultured salivary gland cells (Stegajev et al., 2014).

5 | INVOLVEMENT OF HISTAMINE IN ORAL POTENTIALLY MALIGNANT DISORDERS

Numerous lesions are associated with an increased risk of developing oral squamous cell carcinoma (OSCC), and hence, they were termed *oral potentially malignant disorders* (OPMDs) (Speight et al., 2018). Such lesions include, for instance, leukoplakia, erythroplakia, submucous fibrosis, oral lichen planus (OLP), lichenoid reactions and proliferative verrucous leukoplakia (Salem et al., 2018, Speight et al., 2018). There are many factors associated with the higher risk of malignant transformation, such as lesional site; tobacco and alcohol abuse, and detection of epithelial dysplasia (Speight et al., 2007, 2018). In spite of the ongoing efforts, there is no clear clinical success of any specific intervention in the treatment of OPMDS (Speight et al., 2018). The involvement of histamine and histamine receptors in OPMDs is summarized in Figure 1.

The pluripotent MC plays a crucial role in the development and perpetuation of many OPMDs by releasing potent pro-inflammatory

TABLE 2 Main characteristics of histamine receptor subtypes

	H1R	H2R	H3R	H4R
Identification	1937	1972	1983	2000
Gene cloning	1993	1991	1999	2000
Amino acids	487	359	445	390
G-protein coupling	$G\alpha_{q/11}$	$G\alpha_{s}$	$G\alpha_{i/o}$	$G\alpha_{i/o}$
HA affinity (pK_i)	4.2	4.3	7.8	8.3
HA activation	Requires high HA levels	Requires high HA levels	Respond to ~1,000 times less HA	Respond to ~1,000 times less HA
Tissue distribution	Wide; mainly in lung, blood vessels	Wide; mainly in stomach, heart	Neurons; central nervous system	Bone marrow; immune cells
Main effects	Bronchoconstriction; vasodilatation	Gastric acid secretion	Sleep-wake regulation	Immune responses
Main disorders	Allergic lesions	Gastric and duodenal ulcers	Epilepsy, cognitive disorders, insomnia	Inflammatory lesions and cancer
Relevance to oral cancer	Yes; correlated with poorer DFS rates in OSCC patients	Yes; enhanced anti-cancer therapy in OSCC models	No evidence	Yes; associated with the histopathologic grade of OTSCC

Abbreviations: DFS, disease-free survival; HA, histamine; OSCC, oral squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma.

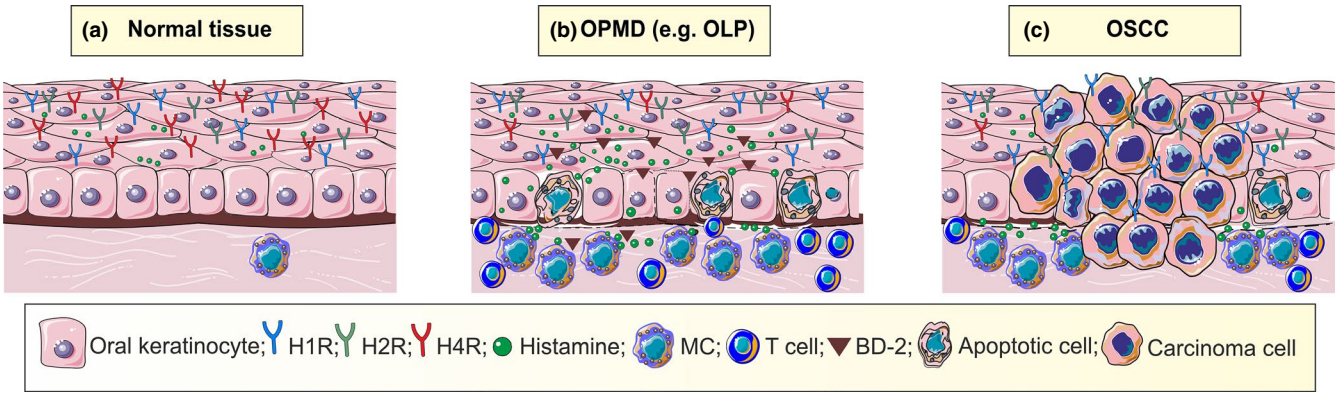

FIGURE 1 Role of histamine and histamine receptors in oral carcinogenesis. (a) Normal oral keratinocytes express H1R, H2R and H4R. In addition, these cells can synthesize and release low levels of histamine. (b) In oral potentially malignant disorders (OPMD), such as oral lichen planus (OLP), mast cell (MC) count is noticeably increased in the lamina propria. Moreover, histamine metabolism is deranged in OLP, which leads to increased surplus histamine levels, upregulation of H1R and downregulation of the high-affinity H4R. Consequently, loss of H4R can affect the maintenance of oral epithelium and perpetuate the inflammatory response. On the other hand, histamine induces beta-defensin 2 (BD-2) synthesis and release from keratinocytes, which seems to be regulated in part by H4R. (c) In oral squamous cell carcinoma (OSCC), the number of tumour-associated MC is also increased, which may trigger an "angiogenic switch" and induce further tissue degradation. Histamine regulates the expression of certain OSCC-associated oncogenes in oral keratinocytes. Furthermore, in OSCC, both H1R and H2R are upregulated while H4R is strongly diminished

mediators such as histamine, cytokines and chemokines (Michailidou, Markopoulos, & Antoniades, 2008; Salem et al., 2019). In this regard, the number of degranulated MCs was doubled in leukoplakia, oral submucous fibrosis and OLP, in an immediate vicinity of the lesional epithelium, compared with normal oral mucosa (Ankle, Kale, & Nayak, 2007; Salem et al., 2015). Similarly, an increased MC count was also observed in the lamina propria of oral epithelial dysplasia (Salem, Almahmoudi, et al., 2017).

Oral epithelial cells can synthesize and release low levels of histamine (Salem, Rozov, et al., 2017). Interestingly, histamine metabolism and transport are deranged in OLP lesions. Of note, histamine-synthesizing and transporting molecules (i.e. HDC and OCT3, respectively) were strongly increased while HNMT was decreased in OLP (Salem, Rozov, et al., 2017). Consequently, this could result in an accumulation of surplus histamine in the lesional epithelium and sustain long-term oxidative stress. In addition, surplus histamine can over time deteriorate the epithelial basement membrane by downregulating integrins and other important cellular adhesion molecules (Salem, Rozov, et al., 2017). Eventually, such persistent low-grade changes may perpetuate the inflammatory response and facilitate the potential tumorigenesis in OLP (Salem et al., 2019; Salem, Rozov, et al., 2017).

Histamine seems to regulate the epithelial-driven antimicrobial response in OLP (Salem et al., 2019). MC-derived histamine is able to stimulate the synthesis and release of the antimicrobial peptide, beta-defensin 2 (BD2), from oral epithelial cells (Kanda & Watanabe, 2007). In turn, BD2 induces Ca^{++} mobilization and subsequent degranulation of MCs via Mas-related gene X2, which leads to further production of histamine and BD2 (Subramanian et al., 2013). Importantly, activation of H4R showed regulatory effects on lipopolysaccharide-induced BD2 expression in cultured oral epithelial cells (Salem et al., 2019).

The immunoreactivity of H4R in oral epithelial cells was negatively correlated with MC count in OLP and epithelial dysplastic lesions (Salem, Almahmoudi, et al., 2017). In these lesions, H4R staining was markedly decreased and shifted towards upper epithelial cell layers, possibly as a result of the burst-released histamine from MCs. In agreement with this, higher micromolar concentrations of histamine strongly downregulated the H4R transcript in vitro oral epithelial cells (Salem et al., 2015). On contrary, the H1R was strongly induced in OLP lesions, and the pattern was consistently distributed throughout the oral epithelial layers (Salem et al., 2019). Overall, and based on the current research findings, H4R seems to play an important role in the maintenance of normal oral epithelium, which is disturbed in some premalignant lesions due to an increased histamine production followed by H4R downregulation and H1R upregulation (Figure 1).

6 | INVOLVEMENT OF HISTAMINE IN ORAL CANCER

Persistent potent responses in TME, mediated by variety of cells and substances, including MCs and histamine, are involved in promoting cancer development and invasion (Marichal, Tsai, & Galli, 2013; Multhoff et al., 2012). Such profound procancerous effects of tumour-associated MCs include angiogenesis, tissue degradation, mediating cell interaction and remodelling of TME (Marichal et al., 2013).

Histamine and histamine receptors exhibit deranged expression in numerous types of cancer (Massari et al., 2020). In OSCC, Grimm et al. showed that H1R was expressed in OSCC cell lines BICR56 and BICR3. Moreover, H1R status was correlated with a significantly poor disease-free survival in OSCC patients signifying the role of H1R signalling in OSCC (Grimm et al., 2013). In another study, H2R expression was induced in OSCC tissue compared with the adjacent normal tissue in hamster model of oral cancer (Parihar, Dube, & Gupta, 2013). It was also interesting that coupling of histamine to chlorin p6 enhanced the efficacy of photodynamic therapy and resulted in complete regression of large OSCC tumours (Parihar et al., 2013). Furthermore, administration of low concentrations of histamine reduced the boron neutron capture therapy-associated mucositis in hamster OSCC without jeopardizing the therapeutic effects (Monti Hughes et al., 2015).

Oral epithelial cells revealed a uniform pattern of H4R staining, which was strongly diminished in mobile tongue SCC (Salem, Almahmoudi, et al., 2017; Salem et al., 2015). Interestingly, such staining pattern was negatively associated with the histopathological grade of OSCC specimens. Thus, samples with a higher OSCC grade had a higher MC count and a substantially lower H4R immunoreactivity (Salem, Almahmoudi, et al., 2017). These findings were also supported by in vitro cell culture findings. HDC and H4R were downregulated in the aggressive HSC-3 and SCC-25 mobile tongue SCC cells compared with the normal oral epithelial cells (Salem, Almahmoudi, et al., 2017).

The OSCC-associated MCs were observed mainly at the lamina propria surrounding the tumour invasive front (Almahmoudi et al., 2018; Salem, Almahmoudi, et al., 2017). Increased MC count was also seen in hotspot microvascular density (MVD) areas (Michailidou et al., 2008; Salem, Almahmoudi, et al., 2017). Michailidou et al. concluded that during the progression from normal epithelium to invasive OSCC, both MC and MVD counts are significantly increased and thus they might promote oral carcinogenesis (Michailidou et al., 2008). In fact, MCs induce neovascularization by releasing a wide variety of proangiogenic factors, such as vascular endothelial growth factor, tryptase, IL-8 and histamine (Gaje et al., 2016). Supernatants obtained from degranulated in vitro MCs regulated the expression of several oral oncogenes, such as epidermal growth factor (EGF), EGF receptor and anti-apoptotic genes. Furthermore, histamine downregulated B-cell lymphoma 2 (Bcl-2) expression in cultured oral epithelial cells (Salem, Almahmoudi, et al., 2017). Based on the aforementioned evidence, the weakened expression of H4R together with the induced levels of H1R/H2R and tumour-associated MCs seem to play crucial roles in promoting oral carcinogenesis (Figure 1). The infiltration of MCs into developing OSCC can also trigger an "angiogenic switch" that enhances neovascularization in the developing tumour.

7 | CONCLUDING REMARKS

According to the GLOBOCAN 2018 estimates, cancer incidence and mortality are swiftly increasing worldwide (Bray et al., 2018). Hence, there is an urgent need to identify and validate new cancer-relevant targets. Undoubtedly, there is an immense amount of data that signifies the role of histamine receptors in cancer initiation, progression and invasion (Massari et al., 2020). In particular, the discovery of the high-affinity H4R and its immunomodulatory effects has paved the way for novel perspectives in cancer research (Nicoud et al., 2019). Nevertheless, further mechanistic studies in preclinical models are needed to better elucidate the complex pathways triggered by histamine signalling in TME. Recently, much of interest has been revived in histamine as a promising therapeutic approach in cancer patients. For instance, an immunotherapy with histamine dihydrochloride combined with low-dose IL-2 significantly decreased the relapse rate in phase III clinical trial of acute myeloid leukaemia patients (Kiffin et al., 2018). Due to the enormous pharmacological success of ligands targeting histamine receptors, this review encourages further research to better

understand the role of histamine signalling and whether it represents a viable drug target in oral cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Abdelhakim Salem: Conceptualization; Data curation; Visualization; Writing-original draft; Writing-review & editing. **Tuula Salo:** Data curation; Project administration; Resources; Writing-review & editing.

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