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Histamine H_4 receptor: insights into a potential therapeutic target in breast cancer

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1. ABSTRACT

Breast cancer is the second most common cancer worldwide, and the leading cause of cancer death in women. Several studies underlined the critical role of histamine in breast cancer development and progression. This review addresses the latest evidence regarding the involvement of histamine and histamine receptors in breast cancer, focusing particularly in the histamine H_4 receptor (H_4R). Histamine concentration in breast cancer tissues was found to be higher than that in normal tissues of healthy controls by means of an increase in the activity of histidine decarboxylase (HDC), the enzyme involved in histamine production. The expression of H_4R in different experimental models and human biopsies, the associated biological responses, as well as the *in vivo* treatment of experimental tumors with H_4R ligands is reviewed. Evidence demonstrates that the H_4R exhibits a key role in histamine-mediated biological processes such as cell proliferation, senescence and apoptosis in breast cancer. The polymorphisms of the H_4R and HDC genes and their association with breast cancer risk and malignancy reinforce the critical (patho) physiological role of H_4R in breast cancer. In addition, H_4R agonists display anti-tumor effects *in vivo* in a triple negative breast cancer model. The findings support the exploitation of the H_4R as a molecular target for breast cancer drug development.

2. INTRODUCTION

Breast cancer is the second most common cancer worldwide after lung cancer, and the leading cause of cancer death in women. Even with advances in early detection, about 30% of patients with early-stage breast cancer have recurrent disease, which is metastatic in most cases, showing a 5-year survival rate of 20% (1-3). Breast cancer is a heterogeneous disease in terms of presentation, morphology, molecular profile, and clinical response to therapy (4-6). In particular, triple-negative breast cancer (TNBC) characterized by the lack of expression of the estrogen receptor (ER), progesterone receptor and human epidermal growth factor 2 receptor (HER2) proteins, accounts for approximately 15% of breast cancers. Consequently, TNBC is a poor prognostic factor for disease-free and overall survival and thus, it represents an important area of research for novel specific targeted therapy (7-9).

Histamine is a pleiotropic biogenic amine with a broad range of activities in both physiological and pathological conditions. Histamine is involved in growth regulation, differentiation and functioning of mammary gland during development, pregnancy and lactation (6,10). In addition, both the enzyme involved in histamine production (histidine decarboxylase, HDC) and all the histamine receptor subtypes (Table 1 and 2) and are present in breast cancer cells (6, 10-13). Histamine regulates diverse biological responses related to breast cancer growth, including cell proliferation, migration, differentiation and apoptosis; and is also able to modulate tumor invasion, immunity and metastatic potential (6,13,14). Histamine concentration in breast cancer tissues was found to be higher than that in normal tissues of healthy controls by means of an increase in the activity of HDC (15,16) while polymorphisms of

Table 1. Functional effects of H_1R, H_2R and H_3R ligands on breast cancer experimental models

Specie	Model	Receptor subtype	Ligand	Function	References
Rat	NMU-induced experimental mammary carcinoma	H_1R	Astemizole	↑ tumor volume; ↓ latency period	19, 24
			3F-MPHA	↑ cAMP, Activation of PLC; ↓ tumor cell proliferation	19, 25
		H_2R	Ranitidine, Cimetidine	↓ tumor cell proliferation	19, 25
			Dimaprit	Activation of PLC; ↑ tumor cell proliferation	19, 25
Human	HBL-100 cell line	H_1R, H_2R, H_3R	Histamine	Does not modify proliferation	18, 32
		H_1R	3F-MPHA	Does not modify cAMP, ↑ PI	27
		H_2R	Dimaprit	Does not modify cAMP, ↑ PI	27
	MCF-7 cell line	H_1R	3F-MPHA	↓ proliferation	33
		H_2R	Anthamine; Dimaprit	↓ proliferation	33
		H_3R	Rα-MeH; Imetit	↓ proliferation	33
		H_2R	Histamine (effect blocked with famotidine)	↑ cAMP	33
	MDA-MB-231 cell line	H_1R	3F-MPHA	↓ proliferation	18,32
		H_2R	Anthamine; Dimaprit	↓ proliferation	18, 32
		H_3R	Rα-MeH; Imetit	↑ proliferation, ↑ migration	18, 32
		H_1R, H_2R	Histamine	Does not modify cAMP	33
Human	MDA-MB-231 xenograft	H_3R	JNJ10181457	↓ Tumor volume	34
	tumor induced in *nude* mice				
Human	Biopsies derived from human benign lesions	H_1R	3F-MPHA	Activation of PLC	28
		H_2R	Dimaprit	↑ cAMP	28
	Biopsies derived from human malignant lesions	H_1R	3F-MPHA	Activation of PLC	28
		H_2R	Dimaprit	Activation of PLC, ↑ cAMP	28
Human	Clinical trial	H_2R	Cimetidine	Does not modify tumor cell growth	29
		H_2R	Famotidine	Induces tumor-infiltrating lymphocytes	30

3F-MPHA: 2-(3-(trifluoromethyl) phenyl) histamine (H_1R agonist); astemizole (H_1R antagonist); anthamine and dimaprit (H_2R agonists); ranitidine, famotidina and cimetidine (H_2R antagonists); Rα-MeH: Rα-methylhistamine and Imetit (H_3R agonists); JNJ10181457 (H_3R antagonist); PLC: Phospholipase C; PI: Phosphoinosithide; cAMP: Cyclic adenosine monophosphate

HDC gene seemed to be associated with breast cancer risk (17).

The identification of the human histamine H_4 receptor (H_4R) more than 10 years ago by several groups has helped refine our understanding of histamine roles including its participation in tumor progression (14).

This review addresses the latest evidence regarding the involvement of histamine and histamine receptors in breast cancer, focusing particularly in the histamine H_4 receptor (H_4R).

3. HISTAMINE METABOLISM IN BREAST CANCER

Histamine plays a critical role in the (patho) physiological aspects of the mammary gland (11,13,14). Higher histamine concentration was found in human ductal breast tumors compared with normal tissues,

which leaded to increased histamine levels in plasma derived from ductal breast cancer patients compared to healthy group. The significant elevation of histamine concentration in cancerous tissues of women with the ductal breast cancers was associated with an increased HDC activity and a decreased activity of the catabolic enzyme, diamine oxidase (DAO). In addition, histamine plasma concentration depends on the number of involved lymph nodes and the grade of histological malignancy (15,16).

Histamine endogenous levels were also evaluated in cell lines derived from human mammary gland. The triple negative breast cancer MDA-MB-231 cells exhibited higher histamine content than the estrogen-responsive human breast cancer cell line, MCF-7, being this higher than that of the non-tumorigenic breast epithelial HBL-100 cells, suggesting a direct correlation of endogenous histamine levels with malignancy of breast cells (18). Histamine catabolizing enzymes DAO and histamine N-methyltransferase (HMT) were further investigated in MDA-MB-231 and MCF-7 cell lines. DAO was not detected in both cell lines either at the protein or mRNA levels in both cell lines. On the other hand, HMT enzyme protein expression and activity were detected in MDA-MB-231 and MCF-7 cells and histamine exogenous treatment decreased its activity, suggesting a crucial role of this enzyme in histamine catabolism in breast cancer cells (14).

In agreement with the described findings, in the N-nitro-N-methylurea (NMU)-induced rat mammary adenocarcinoma, histamine content and HDC activity and expression were higher than in the normal mammary gland or other rat tissues and importantly, HDC lost its normal response to estrogen, a fact that seemed to point to an earlier, common event of the tumorigenic pathway (19).

It is well known that histamine is an important mediator of immunologic reactions. Previous data demonstrated that histamine can modulate antigen-specific T helper (Th) cells by changing the cytokine production from a Th1 to a Th2 pattern, principally inhibiting the synthesis of interleukin 12 and promoting the production of interleukin 10 by antigen-presenting cells (20). Furthermore, it was shown that effective antitumor responses in breast cancer have been linked to Th1 cells and/or their primary effector cytokine, interferon gamma (21). In this line, experiments in syngeneic breast cancer induced in histamine-free (HDC knock-out) and wild-type mice, demonstrated that endogenous histamine stimulates the growth of breast adenocarcinoma tumor implants by suppressing anti-tumor immunity accompanied by a predominantly Th2-polarized cytokine pattern (22).

In addition, recent findings indicated that polymorphisms of HDC gene but not of HMT gene were significantly associated with breast cancer in Chinese Han population, highlighting the importance of HDC in this disease (17).

4. HISTAMINE RECEPTORS AND BREAST CANCER

4.1. Histamine H_1, H_2 and H_3 receptors associated signaling pathways and biological responses

Previous data demonstrated that histamine exerts a regulatory function on cell growth by acting directly on specific H_1R and H_2R expressed on cell membrane in NMU-induced experimental mammary carcinomas. In this experimental model, astemizole (H_1R antagonist, 2 mg/kg.day) not only did increase the number of tumors per rat but also significantly decreased their latency period. In addition, *in vivo* treatment with H_2R antagonists (ranitidine or cimetidine) produced a significant decrease in tumoral incidence and in the number of tumors developed per rat, as well as an increase in the latency period (19, 23-25) (Table 1). *In vitro* studies employing the NMU-induced mammary tumors indicate that tumor cells produce high levels of endogenous histamine that are actively released to the extracellular medium and have the ability to subsequently interact with the membrane receptors triggering biological responses. The activation of the H_2R with histamine concentrations up to 50 nM or H_2R agonists increases cell proliferation via the phospholipase C (PLC)-dependent pathway. On the other hand, higher histamine levels inhibit cell growth via a cAMP-dependent mechanism through the activation of the H_1R (19, 25) (Table 1).

The presence of H_1R and H_2R in human normal and malignant breast cancer tissues was also demonstrated. H_2R produced an increase in cAMP levels while H_1R was coupled to PLC activation in benign lesions. On the other hand, H_1R was invariably linked to PLC pathway but H_2R stimulated both transductional pathways in carcinomas (26). Although many reports indicate the expression of these two histamine receptor subtypes in normal and malignant tissues as well as in different cell lines derived from human mammary gland (6,26,27,28), preclinical studies with H_1R antagonists (23) and the clinical trials carried out with H_2R antagonists in cancer patients demonstrated inconclusive results for breast cancer (29,30). No relationship between preoperative cimetidine administration and tumor cell proliferation was seen (29). On the other hand, preoperative short course famotidine induced tumor-infiltrating lymphocytes in breast cancer and patients with significant tumor infiltrating lymphocytes demonstrable in their operative specimens have an improved disease-free survival (30). In addition, it was recently showed that the use of H_2R blockers overall, cimetidine and famotidine was not associated with an increased risk of either invasive ductal or invasive lobular breast cancer, while current

Table 2. Expression of H_4R in human breast cancer

Specimen	H_4R function and/or characteristic	References
MDA-MB-231 cell line	H_4R agonists: ↓ proliferation; ↑ apoptosis; ↑ senescence	32, 33
MCF-7 cell line	H_4R agonists: ↓ proliferation; ↑ apoptosis; ↑ senescence	33
MDA-MB-231 xenograft tumor induced in *nude* mice	H_4R agonists: ↓ tumor volume; ↓ angiogenesis. Histamine: ↑ survival	34
Biopsies derived from human benign and malignant lesions	Slight increase in the level of expression of H_4R in malignant compared to benign lesions	32
Breast cancer in Chinese Han populations	Polymorphisms of H_4R gene were significantly associated with the risk and malignant degree of breast cancer	40

users of ranitidine had a 2.2-fold increased risk of ductal carcinoma (31). Therefore, the treatment with H_1R and H_2R antagonists does not seem to be useful from the therapeutical point of view.

Recently, it was demonstrated that the H_3R is expressed in cell lines derived from human mammary gland (18). Histamine modulated the proliferation of the TNBC cell line MDA-MB-231, in a dose-dependent manner producing a significant decrease at 10 μM concentration whereas at lower concentrations it increased proliferation moderately through the H_3R and no effect on proliferation was observed in non-tumorigenic HBL-100 cells (18,32) (Table 1). The negative effect on proliferation in MDA-MB-231 cells was associated with the induction of cell cycle arrest, differentiation and a significant increase in the number of apoptotic cells. Also, it was related to an increase in the levels of reactive oxygen species (ROS) and an imbalance in the activity of the enzymes implicated on their metabolism (18). In contrast, in MCF-7 cells histamine decreased proliferation at all doses tested and all the 4 histamine receptor subtype agonists reduced proliferation. Interestingly, histamine was incapable of inducing proliferation via the H_3R in these cells as compared with the more undifferentiated MDA-MB-231 breast cancer cells, suggesting that a different isoform expression, protein-protein interaction, or signaling pathways could be responsible for the variation in histamine responses (33) (Table 1). In this regard, H_3R agonists decreased the cAMP formation producing a maximal inhibition of forskolin-induced cAMP accumulation of 40% in MDA-MB-231 breast cancer cells while they were unable to modify cAMP levels in MCF-7 cells. In line with *in vitro* data, *in vivo* administration of the JNJ10181457 (H_3R antagonist), produced a decrease in the volume of xenograft tumors of the highly invasive breast cancer cell line MDA-MB-231 established in immune deficient nude mice (34) (Table 1).

It is important to point out that the H_3R is expressed in human biopsies of benign lesions and breast carcinomas, being the level of its expression significantly higher in carcinomas. Furthermore, the expression of H_3R is highly correlated with a proliferation marker (PCNA) and histamine production in malignant lesions (32).

4.2. Role of histamine H_4 receptor in biological processes associated with cancer progression

The identification of the human H_4R more than 10 years ago by several groups has helped refine our understanding of histamine roles in cancer progression (6). It was previously demonstrated that the H_4R is expressed in MDA-MB-231 and MCF-7 breast cancer cell lines. By means of the use of pharmacological compounds it was demonstrated that the main receptor subtype involved in the histamine-induced inhibitory response on proliferation was the H_4R (32,33). The effect of clobenpropit (H_4R agonist and H_3R antagonist), the putative H_4R agonist VUF8430 and/or the combined treatment with the specific antagonist JNJ7777120 on proliferation and apoptosis of MDA-MB-231 cells was evaluated. Both agonists reduced the incorporation of BrdU, induced cell cycle arrest and increased cell apoptosis and senescence while the treatment with JNJ7777120 reversed the histamine inhibitory effect on cell proliferation and senescence (32,33) (Table 2). To further confirm the involvement of H_4R in the reduction of proliferation, H_4R small interfering RNA (siRNA) was employed to knock-down the H_4R expression resulting in the blockade of the inhibitory effect of histamine on proliferation (34). Furthermore, histamine differentially regulated the expression and activity of matrix metalloproteinases, cell migration and invasiveness through H_2R and H_4R in MDA-MB-231 cells modulating H_2O_2 intracellular levels (35). In addition, histamine decreased the proliferation of a more differentiated breast cancer cell line, MCF-7, through the stimulation of the four histamine receptor subtypes, exhibiting a higher effect through the H_4R. Treatment of MCF-7 cells with H_4R agonists induced an augment in the number of cells in the G0/G1 phase of the cell cycle and also exerted an anti-proliferative effect, augmenting the number of apoptotic and senescent cells (33) (Table 2). In line with these results, it was newly shown that the synthetic nuclear bile acid receptor (FXR) agonist GW4064 also activated the H_4R and induced apoptosis of MCF-7 breast cancer cells (36).

These results represent the first report about the functional expression of H_4R in human breast cells and interestingly show that the H_4R is involved in the regulation of breast cancer cell proliferation, apoptosis, senescence, migration and invasion.

In the context of the complexity of cancer disease processes, future anti-cancer treatments will have to take into account the tumor microenvironment and aim to target the different cellular and molecular participants encompassed in a tumor, as well as their specific interactions (1). In this regard, it was recently reported the expression of H_4R in CCD-1059Sk fibroblasts. Conditioned media derived from fibroblasts induced epithelial to mesenchymal transition (EMT) phenotypic changes in MCF-7 and MDA-MB-231 breast cancer cells. These effects were reversed when breast cancer cells were cultured with conditioned media from fibroblasts treated with histamine (20 μM), indicating that histamine may prevent the EMT process, which is essential in cancer progression (37). In agreement with these results, H_4R agonists suppressed human cholangiocarcinoma progression by disruption of EMT processes, decreasing invasion potential and tumor growth (38) and also produced anti-EMT effects in non-small cell lung cancer cell lines and xenograft tumors (39).

Recent findings show the presence of polymorphisms of the human H_4R gene in a Chinese Han population. Variants of rs623590, rs11662595 and rs1421125 genotypes of H_4R gene were significantly associated with the risk and malignant degree of breast cancer (Table 2). Although further studies in a larger sample size as well as in other human races are needed to confirm the clinical relevance, the aforementioned results suggest that changes in the expression or function of H_4R due to the polymorphisms probably have certain impact on the pathogenesis and the clinicopathological characteristics of breast cancer (40).

5. THERAPEUTIC POTENTIAL OF HISTAMINE H_4 RECEPTOR LIGANDS IN BREAST CANCER

The TNBC are undeniably one of the most relevant subgroups of breast cancer given their lack of targeted therapies and their aggressive clinical behavior (7,9,41). Therefore, in order to better understand the role of H_4R in breast cancer and to explore novel therapeutic approaches that could offer increased efficacy with low toxicity, the anti-tumoral effects of the endogenous ligand histamine and other H_4R agonists (clozapine and JNJ28610244) were evaluated *in vitro* and *in vivo* in a human TNBC model. Clozapine is an atypical antipsychotic being used for a long time, clinically available and approved to be use in humans, which showed to fully activate the H_4R with moderate affinity (42-46). JNJ28610244 compound has excellent potency and selectivity for the H_4R, being a useful pharmacological tool for exploring and better understand the H_4R function (47). Results indicate that treatments with clozapine or JNJ28610244 also produced a concentration dependent inhibitory effect on MDA-MB-231 cells proliferation and the anti-proliferative action of these H_4R agonists was fully blocked with the combined treatment with the H_4R antagonist JNJ7777120. Xenograft tumors of the TNBC cell line MDA-MB-231 in immune deficient nude mice exhibited moderate expression of H_4R, high expression of a proliferation marker (PCNA) and reduced apoptotic cells. In agreement with the results described above, *in vivo* treatments with histamine (5 mg/kg, subcutaneous (s.c.), daily administration) or the H_4R agonists (clozapine, 1 mg/kg; JNJ28610244, 10 mg/kg, s.c., daily administration) significantly diminished the tumor growth rate, evidenced by an increase in the exponential doubling time. This effect was associated with a decrease in the PCNA expression levels, and also a reduced intra-tumoral vessels in histamine and clozapine treated mice. Histamine also significantly increased median survival and tumoral apoptosis (34) (Table 2). Results demonstrate the functional expression of H_4R in a breast cancer experimental model and show the anti-tumor properties of H_4R agonists. Consistent with these results, the H_4R agonist 4-methylhistamine significantly decreased the tumor volume and increased survival of mice bearing xenograft non-small cell lung cancer tumors (39). Also, histamine and clozapine significantly increased median survival and decreased tumor volume *in vivo* in a human melanoma experimental model (48).

In addition, previous data indicate that the H_4R is expressed in malignant lesions derived from the human mammary gland, being the level of its expression higher in carcinomas compared to benign lesions, confirming that the H_4R is present not only in cell lines but also in the human breast tissue (32) and in this way, these findings open new perspectives in histamine pharmacology research aimed to develop a new generation of anti-histamines targeting the H_4R that may contribute for advances in the treatment of cancer.

It is important to highlight that histamine not only exhibits an anti-tumoral action but also is able to synergize the ionizing radiation effects in breast cancer cells. Histamine through different histamine receptor subtypes produced a radiosensitizing action involving enhanced radiation-induced oxidative DNA damage in both human estrogen-dependent MCF-7 cells and estrogen-independent MDA-MB-231 cells. Furthermore, in MDA-MB-231 cells these effects correlated with the increased intracellular ROS and inhibition of antioxidant enzymatic activity, decreasing antioxidant defense (18). On the other hand, *in vivo* studies show that histamine was also safely used in different experimental models as a radioprotective agent of normal radiosensitive tissues, including small intestine, salivary glands and bone marrow (49-52). Therefore, the combined use of histamine with radiation could be an attractive strategy to enhance the efficacy of radiotherapy for both estrogen-dependent and estrogen-independent breast cancers and clinical trials are warranted.

6. CONCLUSIONS AND PERSPECTIVES

The identification of histamine receptor subtypes and the elucidation of their role in the development and progression of human breast cancer may represent an essential clue for advances in novel therapeutics. The presented evidences demonstrate the functional expression of H_4R in human breast cancer tissues and cell lines, exhibiting a key role in histamine-mediated biological processes such as cell proliferation, senescence and apoptosis, and suggest novel functions for histamine in the carcinogenic process. The polymorphisms of the H_4R gene, which could probably result in altered expression and function of H_4R and their association with breast cancer risk and malignancy, reinforce the critical (patho)physiological role of H_4R in breast cancer. Although further studies are needed to fully investigate the possible clinical application of the H_4R ligands for breast cancer treatment, the finding that H_4R agonists display anti-tumoral effects may point towards a novel approach to treat breast cancer targeting the H_4R, leading to reconsideration of new perspectives in histamine pharmacology research.

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Abbreviations: H_1R: histamine receptor 1; H_2R: histamine receptor 2; H_3R: histamine receptor 3; H_4R: histamine receptor 4; ER: estrogen receptor; cAMP: cyclic adenosine monophosphate; BrdU: 5-bromo-2'-deoxyuridine; GPCR: G-protein coupled receptors; PCNA: proliferating cell nuclear antigen; sc: subcutaneous; siRNA: small interfering RNA; H_2O_2: hydrogen peroxide; TNBC: triple-negative breast cancer; HER2: epidermal growth factor 2 receptor; HDC: histidine decarboxylase; DAO: diamine oxidase; HMT: histamine N-methyltransferase; NMU: N-nitro-N-methylurea; Th: T helper; PLC: phospholipase C; ROS: reactive oxygen species; PI: phosphoinositide; 3F-MPHA: 2-(3-(trifluoromethyl)phenyl)histamine; Rα-MeH: Rα-methylhistamine; nM: nanomolar; μM: micromolar; FXR: synthetic nuclear bile acid receptor; EMT: epithelial to mesenchymal transition

Key Words: Human Breast Cancer, Histamine H_4 Receptor, Proliferation, H_4R ligands, Experimental Tumor, Histamine, Review

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