

REVIEW

Histamine receptors and
cancer pharmacologyVanina A. Medina^{1,2} and Elena S. Rivera¹

¹Laboratory of Radioisotopes, School of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina, and ²National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

Correspondence

Professor Elena S. Rivera,
Laboratorio de Radioisótopos,
Facultad de Farmacia y
Bioquímica, Universidad de
Buenos Aires, Junín 956, Buenos
Aires 1113, Argentina. E-mail:
erivera@ffyb.uba.ar

Keywords

histamine; histamine H₄ receptor;
cancer pharmacology; breast
cancer; melanoma; colon cancer;
histamine H₄ receptor ligands;
anticancer drugs; cell
proliferation; malignancy

Received

1 April 2010

Revised

14 June 2010

Accepted

1 July 2010

Considerable evidence has been collected indicating that histamine can modulate proliferation of different normal and malignant cells. High histamine biosynthesis and content together with histamine receptors have been reported in different human neoplasias including melanoma, colon and breast cancer, as well as in experimental tumours in which histamine has been postulated to behave as an important paracrine and autocrine regulator of proliferation. The discovery of the human histamine H₄ receptor in different tissues has contributed to our understanding of histamine role in numerous physiological and pathological conditions revealing novel functions for histamine and opening new perspectives in histamine pharmacology research. In the present review we aimed to briefly summarize current knowledge on histamine and histamine receptor involvement in cancer before focusing on some recent evidence supporting the novel role of histamine H₄ receptor in cancer progression representing a promising molecular target and avenue for cancer drug development.

LINKED ARTICLES

BJP has previously published a *Histamine* themed issue (2009). To view this issue visit <http://dx.doi.org/10.1111/bph.2009.157.issue-1>

Abbreviations

$\Delta\psi_m$, mitochondrial transmembrane potential; H₁R, histamine H₁ receptor; H₂R, histamine H₂ receptor; H₃R, histamine H₃ receptor; H₄R, histamine H₄ receptor; HDC, L-histidine decarboxylase; MAPK, mitogen-activated protein kinase; TUNEL, TdT-mediated UTP-biotin Nick End labelling

Introduction

Cancer continues to be a major health problem for those in developed countries being a leading cause of death worldwide and accounting for 7.9 million deaths in 2007. That number is slated to increase to 11.5 million by the year 2030. Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year (Parkin *et al.*, 2005; Mathers and Loncar, 2006).

A large body of literature indicates that tumorigenesis in humans is a multistep process and that these steps reflect genetic and epigenetic alterations that drive the progressive transformation of normal cells into highly malignant derivatives. More than

100 distinct types of cancer have been described and subtypes of tumours can be found within specific organs representing added challenges to cancer treatments (Hanahan and Weinberg, 2000; Frank and Knowles, 2005; Hall and Giaccia, 2006).

Surgery and radiation therapy are by far the most widely used local treatments for cancer and remain mainstays of the effective treatment of cancer to remove the primary tumour or by combining these treatments with chemotherapy, a systemic drug therapy, which are aimed to eradicate micrometastatic disease. The term chemotherapy, in its broadest definition, covers any therapeutic intervention utilizing chemicals and includes the use of any pharmaceutical compounds. In this fashion,

chemotherapeutic agents comprise the traditional cytotoxic drugs, immunotherapy, hormonal therapy, monoclonal antibodies, signal transduction inhibitors, antiangiogenic drugs and differentiating drugs. The ideal chemotherapeutic drug would target and destroy only cancer cells however; most drugs exhibit several toxic effects resulting in serious adverse effects to patients (Camidge and Jodrell, 2005; Fentiman, 2005). Anticancer drug discovery, development and administration are changing in the post-genomics era. Advances in the understanding of cancer biology and the molecular basis of response and resistance to treatments are helping to create novel drugs that can contribute to improve efficacy. The war against cancer might be far from being won, but the era of molecular-targeted treatments could prove to be one of the most important turning points in determining the outcome. Pharmaceuticals are now screened against these targets rather than looking for crude cell turnover or tumour growth effects straightaway (Camidge and Jodrell, 2005; Fentiman, 2005).

A huge number of molecules involved in cell proliferation, a key event in tumour development and progression, have been extensively investigated including histamine (Rivera *et al.*, 2000; Darvas *et al.*, 2003; Pócs *et al.*, 2004). Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous biogenic amine widely distributed throughout the organism and is known since long to be a pleiotropic mediator in different (patho) physiological conditions (Kahlson and Rosengren, 1968; Hill *et al.*, 1997; Dy and Schneider, 2004; Pócs *et al.*, 2004; De Esch *et al.*, 2005).

Notably, most malignant cell lines and experimental tumours express the histamine-synthesizing enzyme, L-histidine decarboxylase (HDC, EC 4.1.1.22) and contain high concentration of endogenous histamine that can be released to the extracellular media and via a paracrine or autocrine regulation, histamine may regulate diverse biological responses related to tumour growth (Bartholeyns and Fozard, 1985; Garcia-Caballero *et al.*, 1994; Engel *et al.*, 1996; Rivera *et al.*, 2000; Falus *et al.*, 2001; Pócs *et al.*, 2004). These events include angiogenesis, cell invasion, migration, differentiation, apoptosis and modulation of the immune response, indicating that histamine may be a crucial mediator in cancer development and progression. Since the first report in 1984 (Bartholeyns and Bouclier, 1984) showing that the inhibition of HDC with monofluormethylhistidine resulted in antitumoural effects on experimental tumours in rodents, a large body of experimental evidence has supported the critical role of HDC and histamine in cellular proliferation. The employment of specific HDC antisense oligo-

nucleotides suppressed melanoma cell proliferation (Hegyesi *et al.*, 2001), and the overexpression of the enzyme with an up-regulated histamine production in murine melanoma cells enhanced metastatic capacity and induced the expression of a more aggressive phenotype (Pócs *et al.*, 2005). In addition, in diverse human tumours histamine concentration showed to be higher compared with surrounding normal tissue including melanomas, colon and breast cancer (Garcia-Caballero *et al.*, 1994; Reynolds *et al.*, 1997; Hegyesi *et al.*, 2001; Sieja *et al.*, 2005; von Mach-Szczypiński *et al.*, 2009). In a high number of human cell lines derived from different neoplasias, as well as in tumoural tissues, the expression of histamine receptors with the ability to regulate cell proliferation has been demonstrated to support the role of histamine as a growth factor (Tilly *et al.*, 1990; Davio *et al.*, 1993; 1996; Rivera *et al.*, 1993; Cricco *et al.*, 1994; Lemos *et al.*, 1995; Wang *et al.*, 1997; Falus *et al.*, 2001; Molnár *et al.*, 2001; 2002; Cianchi *et al.*, 2005; Hegyesi *et al.*, 2005; Medina *et al.*, 2006; Cricco *et al.*, 2008; Davenas *et al.*, 2008; Medina *et al.*, 2008). Histamine receptors in numerous malignant cell types can be associated with multiple signalling pathways. The regulation of receptor density at cell surface can strongly affect the receptor ability to functionally couple and regulate different signal transduction pathways (Mitsubishi *et al.*, 1989; Davio *et al.*, 1995; Fitzsimons *et al.*, 2002).

Furthermore, the discovery of the histamine H₄ receptor (H₄R) with functional presence in a wide range of tissues including tumours revealed novel functions for histamine leading to reconsideration of new perspectives in histamine pharmacology research (Huang and Thurmond, 2008; Leurs *et al.*, 2009; Tiligada *et al.*, 2009; Zampeli and Tiligada, 2009).

In the present review we aimed to briefly summarize current knowledge on histamine and histamine receptor involvement in cancer before focusing on some recent evidence supporting the novel role of H₄R in cancer progression representing a promising therapeutic target for cancer drug development.

Characteristics of H₄R and its ligands

The identification by genomics-based approach of the human H₄R by several groups has helped refine our understanding of histamine roles. It appeared to have a selective expression pattern restricted to medullary and peripheral haematopoietic cells including eosinophils, mast cells, dendritic cells, T cells and monocytes. Therefore, growing attention

Table 1

Compounds most widely used in H₄R investigation

Compound	Chemical name	Human H ₄ R Ki (nmol·L ⁻¹)
Histamine	2-(1H-imidazol-5-yl)ethanamine	16
Imetit	2-(1H-imidazol-5-yl)ethyl carbamimidothioate	1.6
Clobenpropit	3-(1H-imidazol-5-yl)propyl N'-[(4-chlorophenyl)methyl]carbamimidothioate	13
OUP-16	(-)-2-cyano-1-methyl-3-((2R,5R)-5-[1H-imidazol-4(5)-yl]tetrahydrofuran-2-yl)methyl-guanidine	125
4-Methylhistamine	2-(5-methyl-1H-imidazol-4-yl)ethanamine	50
Clozapine	3-chloro-6-(4-methylpiperazin-1-yl)-5H-benzo[c][1,5]benzodiazepine	625
VUF8430	2-(2-guandinoethyl)isothiourea	32
Thioperamide	N-cyclohexyl-4-(1H-imidazol-5-yl)piperidine-1-carbothioamide	125
JN]7777120	1-[(5-chloro-1H-indol-2-yl)carbonyl]-4-methylpiperazine	4
VUF6002	(5-chloro-1H-benzo[d]imidazol-2-yl)(4-methylpiperazin-1-yl)methanone	26
A-987306	cis-4-(Piperazin-1-yl)-5,6,7a,8,9,10,11,11a-octahydrobenzofuro[2,3-h]quinazolin-2-amine	6
A-940894	4-piperazin-1-yl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-ylamine	71

Values (Ki) are taken from Leurs *et al.* (2009) except for imetit (Wulff *et al.*, 2002) and A-940894 (Strakhova *et al.*, 2009). More detailed information on these and other H₄R compounds is reviewed at Lim *et al.* (2005), Leurs *et al.* (2009), Lim *et al.* (2009), Smits *et al.* (2009), Koenig *et al.* (2010) and Smits *et al.* (2010).

H₄R, histamine H₄ receptor.

is directed towards the therapeutic development of H₄R ligands for inflammation and immune disorders. In addition, H₄R was reported to be present on other cell types including intestinal epithelium, spleen, lung, stomach, central nervous system, nerves of nasal mucosa, enteric neurons and interestingly in cancer cells (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Coge *et al.*, 2001; Liu *et al.*, 2001a; Morse *et al.*, 2001; Nguyen *et al.*, 2001; Zhu *et al.*, 2001; Cianchi *et al.*, 2005; Medina *et al.*, 2006; Connelly *et al.*, 2009; Leurs *et al.*, 2009). The significance of the H₄R presence in various human tissues remains to be elucidated and therefore, new roles of H₄R are still unrevealed (Leurs *et al.*, 2009; Zampeli and Tiligada, 2009). The H₄R cDNA was finally identified in the human genome database on the basis of its overall homology (37%, 58% in transmembrane regions) to the H₃R sequence and it has a similar genomic structure. On the other hand, the homology with H₁R and H₂R is of approximately 19%. The human H₄R gene that mapped to chromosome 18 is interrupted by two large introns and encodes a protein of 390 amino acids (Coge *et al.*, 2001; Dy and Schneider, 2004; De Esch *et al.*, 2005; Akdis and Simons, 2006; Leurs *et al.*, 2009). H₄R is coupled to G $\alpha_{i/o}$ proteins, therefore inhibiting forskolin-induced cAMP formation (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Dy and Schneider, 2004; De Esch *et al.*, 2005). Additionally, stimulation of H₄R leads to activation of mitogen-activated protein kinase and also increased calcium mobilization via *Pertussis*

toxin-sensitive pathway (Morse *et al.*, 2001; Hofstra *et al.*, 2003; Akdis and Simons, 2006; Leurs *et al.*, 2009).

Isoforms have been described for the H₄R, which have different ligand binding and signalling characteristics. H₄R splice variants [H₄R (67) and H₄R (302)] have a dominant negative effect on H₄R (390) functionality, being able to retain it intracellularly and to inactivate a population of H₄R (390) presumably via hetero-oligomerization (van Rijn *et al.*, 2008; Leurs *et al.*, 2009). In addition, H₄R dimeric structures that include homo- and hetero-oligomer formation and post-translational changes of the receptor might contribute to added pharmacological complexity for H₄R ligands (van Rijn *et al.*, 2006; 2008; Leurs *et al.*, 2009).

In accordance with the homology between the two receptors, various H₃R ligands are recognized by the H₄R, albeit with different affinities. Initially compounds contain an imidazole heterocycle and have H₃R and H₄R dual activity. They include the H₃R and H₄R agonist, imetit; and the H₃R antagonist and H₄R agonist, clobenpropit (Lim *et al.*, 2005; Leurs *et al.*, 2009) (Table 1). The H₄R selective agonists include compounds such as OUP-16 and 4-methylhistamine (Hashimoto *et al.*, 2003; Lim *et al.*, 2005; Leurs *et al.*, 2009) (Table 1). The antipsychotic agent clozapine was the first non-imidazole H₄R agonist; however, it has affinity for numerous G-protein coupled receptors (Oda *et al.*, 2000; Leurs *et al.*, 2009). VUF8430 is a non-imidazole full

agonist at human H₄R and is considered a new useful tool to evaluate H₄R pharmacology (Leurs *et al.*, 2009; Lim *et al.*, 2009) (Table 1).

The first H₄R antagonist was also an imidazole compound with H₃R and H₄R dual activity such as thioperamide that behaves as an inverse agonist at the H₄R (Hofstra *et al.*, 2003; Damaj *et al.*, 2007; Leurs *et al.*, 2009). After subsequent medicinal chemistry efforts by Johnson and Johnson Pharmaceuticals the selective non-imidazole neutral antagonist JNJ7777120 was discovered and it became an H₄R reference antagonist with more than a thousand fold selective over other histamine receptor subtypes (Jablonowski *et al.*, 2003; Leurs *et al.*, 2009). Recently, other compounds such as A-987306 and A-940894 that have shown to exhibit good pharmacokinetic properties including oral bioavailability and half-life have been reported by Abbot Laboratories (Liu *et al.*, 2008; Strakhova *et al.*, 2009) (Table 1).

Moreover, differences in pharmacological activities of H₄R ligands have been described between different species restricting the preclinical development of future H₄R drugs (Liu *et al.*, 2001b; Lim *et al.*, 2008; 2010; Leurs *et al.*, 2009).

Histamine receptors and breast cancer

Breast cancer is the most common neoplastic disease in women, accounting for over one-fifth of the estimated annual 4.7 million cancer diagnoses in women and continues to rise in incidence (Bray *et al.*, 2004; Parkin *et al.*, 2005). Despite advances in early detection and continuous contributions to the understanding of the molecular bases of breast cancer biology, about 30% of patients with early-stage breast cancer have recurrent disease, which is metastatic in most cases and whose cure is very limited showing a 5 year survival rate of 20% (Gonzalez-Angulo *et al.*, 2007).

The identification of genes and biochemical pathways involved in breast carcinogenesis are of utmost importance for the development of rational molecularly based preventive and therapeutic approaches that offer increased efficacy and low toxicity (Camidge and Jodrell, 2005; Fentiman, 2005).

Considerable evidence has been accumulated indicating that histamine can modulate proliferation of different normal and malignant cells (Tilly *et al.*, 1990; Wang *et al.*, 1997; Rivera *et al.*, 2000; Falus *et al.*, 2001; Pócs *et al.*, 2004). Histamine plays a critical role in the pathological and physiological aspects of the mammary gland. Histamine is involved in growth regulation, differentiation and functioning during development, pregnancy and

lactation (Malinski *et al.*, 1993; Davio *et al.*, 1994; Kierska *et al.*, 1997; Wagner *et al.*, 2003). In addition, histamine is increased in plasma and cancerous tissue derived from breast cancer patients compared with healthy group, which is associated with an imbalance between synthesis and degradation of this monoamine (Garcia-Caballero *et al.*, 1994; Reynolds *et al.*, 1998; Sieja *et al.*, 2005; von Mach-Szczyński *et al.*, 2009). A pilot study revealed that in samples of the same invasive ductal carcinoma patient, histamine peripheral blood levels tended to be reduced post-operatively (Kyriakidis *et al.*, 2009). Further studies support the role of histamine in breast cancer development. It was reported that in experimental mammary carcinomas, histamine becomes an autocrine growth factor capable of regulating cell proliferation via H₁R and H₂R, as one of the first steps responsible for the onset of malignant transformation. In this light, the *in vivo* treatment with H₂R antagonists produced the complete remission of 70% of experimental tumours (Rivera *et al.*, 1993; 2000; Cricco *et al.*, 1994; Davio *et al.*, 1995). Although many reports indicate the presence of H₁R and H₂R in normal and malignant tissues as well as in different cell lines derived from human mammary gland (Davio *et al.*, 1993; 1996; Lemos *et al.*, 1995), the clinical trials that have been carried out with H₂R antagonists in cancer patients demonstrated controversial results for breast cancer (Bolton *et al.*, 2000; Parshad *et al.*, 2005) (Table 2).

Recently, it was demonstrated that H₃R and H₄R are expressed in cell lines derived from human mammary gland (Medina *et al.*, 2006). Histamine is capable of modulating cell proliferation exclusively in malignant cells while no effect on proliferation or expression of oncogenes related to cell growth is observed in non-tumorigenic HBL-100 cells (Davio *et al.*, 2002; Medina *et al.*, 2006). Furthermore, histamine modulated the proliferation of MDA-MB-231 breast cancer cells in a dose-dependent manner producing a significant decrease at 10 $\mu\text{mol}\cdot\text{L}^{-1}$ concentration whereas at lower concentrations increased proliferation moderately. The negative effect on proliferation was associated with the induction of cell cycle arrest in G2/M phase, differentiation and a significant increase in the number of apoptotic cells (Medina *et al.*, 2006). Accordingly, by using pharmacological tools, results demonstrated that histamine increased MDA-MB-231 cell proliferation and also migration via H₃R. In contrast, clobenpropit and VUF8430 treatments significantly decreased proliferation to 45.5% \pm 14.8% and to 76.7% \pm 5.3% respectively. This outcome was associated with an induction of apoptosis assessed after 48 h of H₄R agonist treatment. Clobenpropit and

Table 2

Expression and functional characteristics of histamine receptors in different cancer types

Cancer type	Histamine receptor expression and function	References
Breast cancer	H ₁ R and H ₂ R expression in experimental tumours. H ₂ R antagonist inhibited proliferation.	Cricco <i>et al.</i> (1994); Rivera <i>et al.</i> (2000)
	H ₁ R and H ₂ R expression in human benign and malignant lesions. No correlation between H ₂ R and hormone or EGF receptors.	Davio <i>et al.</i> (1993); Lemos <i>et al.</i> (1995)
	H ₃ R and H ₄ R expression in human benign and malignant lesions. Correlation between H ₃ R and proliferation marker and histamine production.	Medina <i>et al.</i> (2008)
	H ₁ R and H ₂ R expression in human non-tumorigenic (MCF-10A, HBL-100) and tumorigenic (MCF-10T, MCF-7, MDA-MB-231) cell lines. Histamine did not modulate proliferation of HBL-100. H ₁ R and H ₂ R agonist decreased proliferation of MCF-7 and MDA-MB-231 cells.	Davio <i>et al.</i> (1996; 2002); Medina <i>et al.</i> (2006; 2008)
	H ₃ R and H ₄ R expression in HBL-100, MCF-7 and MDA-MB-231 cell lines. H ₃ R agonists increased MDA-MB-231 cell growth and migration. H ₄ R agonists inhibited proliferation, increasing cell apoptosis and senescence of MCF-7 and MDA-MB-231 cells.	Medina <i>et al.</i> (2006; 2008; unpubl. data)
Melanoma	H ₂ R expression in syngeneic or xenogenic melanoma grafts in mice. H ₂ R antagonists inhibited tumour growth.	Szincsaák <i>et al.</i> (2002a,b); Tomita <i>et al.</i> (2005)
	H ₁ R, H ₂ R and H ₃ R expression in human melanoma cell lines (WM35, WM983/B, HT-168, HT-168/M1). H ₁ R agonist reduced proliferation in all cell lines. H ₂ R agonist increased proliferation and Ets-1 expression in WM35 cells.	Hegyesi <i>et al.</i> (2005); Molnár <i>et al.</i> (2001; 2002)
	H ₂ R expression in B16-C3 mouse and A375P and C32 human melanoma cells. H ₂ R antagonists inhibited proliferation while stimulated melanogenesis only in B16-C3 cells.	Uçar (1991)
Colon cancer	H ₂ R expression in syngeneic or xenogenic colon cancer grafts in mice. H ₂ R antagonists inhibited tumour growth by inhibiting angiogenesis and by attenuating antitumour cytokine expression in the tumour microenvironment.	Adams <i>et al.</i> (1994); Takahashi <i>et al.</i> (2001); Tomita <i>et al.</i> (2003); Tomita and Okabe (2005)
	H ₁ R, H ₂ R and H ₄ R expression in human normal colon mucosa and tumour tissue. Decreased H ₁ R and H ₄ R expression in tumours compared with normal colonic mucosa.	Boer <i>et al.</i> (2008); Cianchi <i>et al.</i> (2005)
	H ₁ R, H ₂ R and H ₄ R expression in human colon cancer cells (HT29, Caco-2 and HCT116). H ₂ R and H ₄ R antagonists suppressed histamine-induced proliferation of the three cell lines while reduced histamine-induced COX-2 and VEGF expression in HT29 and Caco-2 cells. H ₁ R antagonist inhibited growth and radiosensitized HT29 cells.	Cianchi <i>et al.</i> (2005); Soule <i>et al.</i> (2010)
Pancreatic cancer	H ₁ R and H ₂ R expression in Panc-1 human cancer cell line. Histamine inhibited proliferation through the H ₁ R and H ₂ R, which was associated with a partial differentiation. Through the H ₂ R histamine induced G0/G1 phase arrest, modulation of MAPK and Bcl-2 family proteins.	Cricco <i>et al.</i> (2000; 2004; 2006); Martín <i>et al.</i> (2002)
	H ₃ R and H ₄ R expression in Panc-1 cells. H ₃ R agonist increased while H ₄ R agonist decreased proliferation.	Cricco <i>et al.</i> (2008)

EGF, epidermal growth factor; Ets-1, v-ets erythroblastosis virus E26 oncogene homolog 1; COX-2, cyclooxygenase-2; VEGF, vascular endothelial growth factor; MAPK, mitogen-activated protein kinase; Bcl-2, B-cell lymphoma 2.

VUF8430 produced a threefold increase in the number of apoptotic cells determined by Annexin-V staining and this effect was blocked by the specific H₄R antagonist JNJ7777120. This result was additionally confirmed by TdT-mediated UTP-biotin Nick End labelling (TUNEL) assay. In accordance to this, clobenpropit produced the disruption of the mitochondrial transmembrane potential ($\Delta\psi_m$, 81.5%) that is associated with apoptosis, and also exerted a 2.5-fold increase in the cell senescence

while reduced migration (Medina *et al.*, 2008). The biological responses triggered by histamine in a more differentiated breast cancer cell line (MCF-7) were further investigated. Results showed that histamine at all doses tested, decreased the proliferation of MCF-7 breast cancer cells through the stimulation of the four histamine receptor subtypes exhibiting a higher effect through the H₄R. Treatment of MCF-7 cells with the H₄R agonists, inhibited proliferation by 50% increasing the exponential

doubling time from 32.6 to 47.2 h and 44.1 h in clobenpropit and VUF8430 treated cells respectively. This negative effect on proliferation was related to an increase in Annexin-V and TUNEL positive cells ($P < 0.01$), a decrease in the $\Delta\psi_m$ (59.5%) and a twofold increase in cell senescence (Medina *et al.*, unpubl. data). These results represent the first report about the expression of H₃R and H₄R in human breast cells and interestingly show that the H₄R is involved in the regulation of breast cancer cell proliferation, apoptosis and senescence.

In agreement with this, recent data indicate that H₃R and H₄R are expressed in human biopsies of benign lesions and breast carcinomas being the level of their expression significantly higher in carcinomas, confirming that H₃R and H₄R are present not only in cell lines but also in the human mammary tissue. Furthermore, the expression of H₃R is highly correlated with proliferation and histamine production in malignant lesions while the 50% of malignant lesions expressed H₄R, all of them

corresponding to metastases or high invasive tumours (Medina *et al.*, 2008) (Figure 1).

Recent results obtained with the orthotopic xenograft tumours of the highly invasive human breast cancer line MDA-MB-231 in immune deficient nude mice xenotransplanted tumours indicate that the H₄R was the major histamine receptor expressed in the tumour. Remarkably, *in vivo* JNJ777120 treatment (10 mg·kg⁻¹, p.o., daily administration) significantly decreased lung metastases indicating that H₄R may be involved in the metastatic process (Medina *et al.*, unpubl. data).

The identification of H₄R and the elucidation of its role in the development and growth of human mammary carcinomas may represent an essential clue for advances in breast cancer treatment. The presented evidences contribute to the identification of molecules involved in breast carcinogenesis and confirm the role of H₄R in the regulation of breast cancer growth and progression representing a novel molecular target for new therapeutic approach.

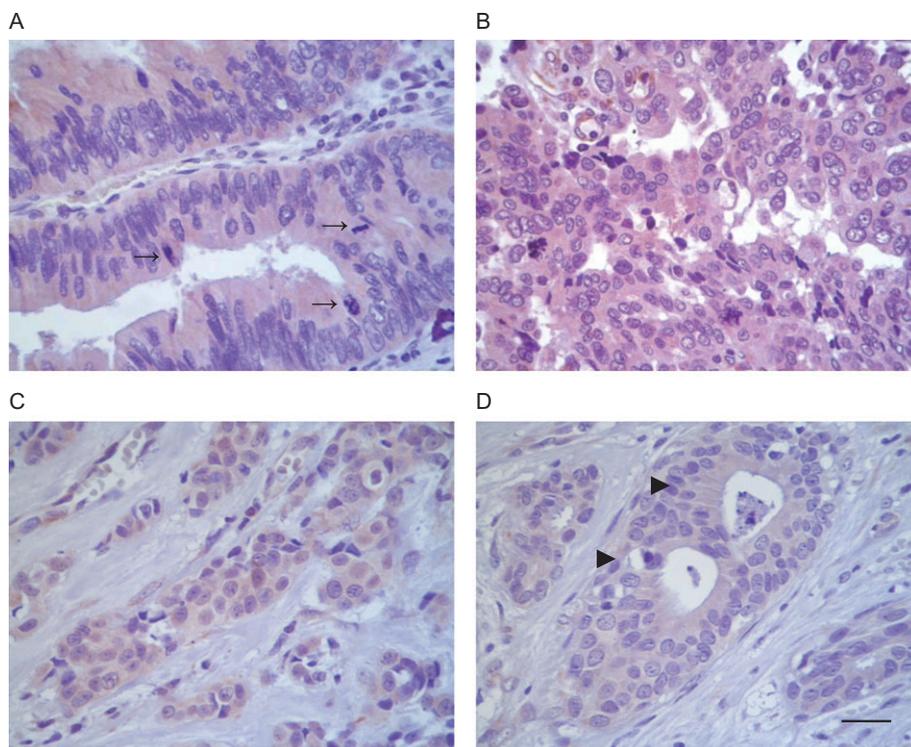


Figure 1

Immunological evidence for the presence of histamine H₄ receptor (H₄R) in human cancers. Fixed specimens were permeabilized and subjected to immunohistochemical analysis as described in Medina *et al.* (2008), probed with rabbit anti-H₄R antibodies (Alpha Diagnostic, 10 μg·mL⁻¹). (A) Atypical glands from a gallbladder adenocarcinoma showing multistratified nuclei with frequent mitosis (→) and marked cytoplasmic positive staining for H₄R. (B) Malignant glands of a lymph node metastasis from ovary adenocarcinoma exhibiting atypical nuclei, and very strong cytoplasmic positive staining for H₄R. (C) Infiltrating lobular carcinoma cells displaying positive immunoreactivity for H₄R. (D) Atypical ducts (▶) derived from a ductal breast adenocarcinoma with positive staining for H₄R. Magnification ×630; scale bar = 20 μm.

Histamine receptors and melanoma

Malignant melanoma is an aggressive, therapy-resistant malignancy of melanocytes. The incidence of melanoma has been steadily growing worldwide, resulting in an increasing public health problem (Markovic *et al.*, 2007). In its early stages malignant melanoma can be cured by surgical resection, but once it has progressed to the metastatic stage it is extremely difficult to treat and does not respond to current therapies. Thus, the development of effective treatments is imperative in order to improve survival and quality of life of melanoma patients (Gray-Schopfer *et al.*, 2007; Cashin *et al.*, 2008). The immunoactivating cytokine interleukin 2 is employed in the treatment of stage IV melanoma in many European countries and in the USA and induces complete regression of melanoma metastases in 3%–5% of treated patients. However, toxicity limits its use. Clinical trials are being performed with the cytokine alone or combined with histamine dihydrochloride suggesting that the combined treatment may specifically prolong the survival of melanoma patients with liver metastases (Mitchell, 2003; Agarwala *et al.*, 2004; Galmarini, 2004).

Melanoma cells and tissues but not normal melanocytes express HDC and contain large amounts of histamine, present histamine receptors, and also both endogenous and exogenous histamine have the ability to regulate melanoma cell growth suggesting the existence of autocrine and paracrine regulation mediated by histamine (Tilly *et al.*, 1990; Reynolds *et al.*, 1996; Haak-Frendscho *et al.*, 2000; Hegyesi *et al.*, 2001; 2005; Molnár *et al.*, 2001; Darvas *et al.*, 2003).

Numerous *in vivo* studies employing animal models bearing syngeneic or xenogenic melanoma grafts demonstrated that both endogenous and exogenous histamine have the ability to stimulate tumour growth while H₂R antagonists (e.g. cimetidine, famotidine, roxatidine) inhibited this effect (Uçar, 1991; Szincsaák *et al.*, 2002a,b; Pócs *et al.*, 2005; Tomita *et al.*, 2005). Overexpression of HDC markedly accelerated tumour growth and increased metastatic colony-forming potential along with rising levels of local histamine production that was correlated with tumour H₂R and rho-C expression in mouse melanoma (Pócs *et al.*, 2005). Additionally, H₂R antagonists stimulated melanogenesis and inhibited proliferation in B16-C3 mouse melanoma cells (Uçar, 1991) (Table 2).

Accordingly, it was previously described that histamine exerts a dual effect on proliferation of the human primary melanoma cell line, WM35, increasing proliferation at low concentrations through the

H₂R receptor while decreasing it at higher concentrations (10 µmol·L⁻¹) via the H₁R, and no evidence of mitogenic signalling through the H₃R has been demonstrated (Falus *et al.*, 2001; Molnár *et al.*, 2001; 2002; Hegyesi *et al.*, 2005). The inhibitory effect of histamine on proliferation was associated with the stimulation of the production of hydrogen peroxide and the induction of senescence of WM35 cells (Medina *et al.*, 2009).

In this line, a number of small clinical trials have investigated the effects of cimetidine alone or in combination with other agents, such as leukocyte interferon, on malignant melanoma with debatable results (Siegers *et al.*, 1999).

Recently, the expression of H₄R and its associated biological responses in the human malignant melanoma cell lines, WM35 (primary melanoma) and M1/15 (derived from liver metastasis), were investigated. Results demonstrated that melanoma cells express H₄R at the mRNA and protein level. By using histamine agonists and antagonists it was shown that the inhibitory effect of histamine on proliferation was in part mediated through the stimulation of the H₄R (clobenpropit IC₅₀ = 1.7 µmol·L⁻¹; VUF8430 IC₅₀ = 1.66 µmol·L⁻¹ in WM35 cells, and clobenpropit IC₅₀ = 4.7 µmol·L⁻¹; VUF8430 IC₅₀ = 4.8 µmol·L⁻¹ in M1/15 cells). Treatment with a specific H₄R antagonist, JNJ7777120, blocked the decrease in proliferation triggered by the H₄R agonists. Furthermore, the decrease in proliferation exerted by H₄R agonists was associated with a twofold induction of cell senescence and an increase in melanogenesis that is a differentiation marker on these cells (Massari *et al.*, unpubl. data).

Current studies indicate that the H₄R is expressed in human melanoma biopsies, confirming that the H₄R is present not only in these cell lines but also in human melanoma tissue (Massari *et al.*, unpubl. data). The identification of H₄R and the clarification of its role in human malignant melanoma progression may contribute for advances in the treatment of this disease.

Histamine receptors and colon cancer

Colorectal cancer is one of the leading causes of cancer death among both men and women worldwide. Mortality has remained constant during the past decades even though the incidence in fact has increased (Parkin *et al.*, 2005). Surgery remains the mainstay of treatment for colon cancer and resulting in 5 year survival in more than 60% of patients (Jemal *et al.*, 2003).

It has been shown that HDC enzymatic activity is significantly increased in colorectal carcinoma

compared with normal mucosa (Garcia-Caballero *et al.*, 1988; Reynolds *et al.*, 1997; Cianchi *et al.*, 2005). Furthermore, it was reported that the activity of the histamine catabolizing enzymes, diamine oxidase or histamine N-methyltransferase, was significantly lower in adenoma tissue than in healthy mucosa in the same patients (Kuefner *et al.*, 2008). These studies suggest that histamine may be involved in tumour development and progression. In this line, loratadine, an H₁R antagonist, inhibited growth and enhanced the effect of radiation of human colon carcinoma cell lines (Soule *et al.*, 2010). Furthermore, earlier studies demonstrated that histamine induced *in vitro* and *in vivo* cell proliferation and this outcome could be blocked by H₂R antagonists (Adams *et al.*, 1994; Cianchi *et al.*, 2005). This effect could be associated with the attenuation of antitumour cytokine expression in the tumour microenvironment exerted by histamine, thus resulting in stimulated colorectal cancer growth (Takahashi *et al.*, 2001; Tomita and Okabe, 2005). In addition, H₂R antagonist significantly suppressed the growth of tumour implants in mice by inhibiting angiogenesis via reducing vascular endothelial growth factor (VEGF) expression (Tomita *et al.*, 2003). Accordingly, some beneficial effects of cimetidine and other H₂R antagonists on survival in colorectal cancer patients have been clinically demonstrated (Adams and Morris, 1994; Kelly *et al.*, 1999; Kapoor *et al.*, 2005) (Table 2).

More recently, the expression of H₄R not only in cell lines but also in tissue derived from colon carcinoma was described (Cianchi *et al.*, 2005; Boer *et al.*, 2008). Interestingly, the H₄R antagonist, JNJ777120, prevented the cell growth-promoting activity of histamine in three colon cancer cell lines without affecting the basal growth of the cells and also inhibited the histamine-mediated increase in VEGF in two cell lines. Combination treatment with zolantidine (an H₂R antagonist) and JNJ777120 determined an additive effect on reducing the histamine-induced VEGF production and histamine-stimulated proliferation (Cianchi *et al.*, 2005). Furthermore, a significant decrease in H₄R levels in neoplastic samples compared with normal colonic tissue was demonstrated, suggesting the involvement of H₄R in colon carcinogenesis (Boer *et al.*, 2008).

Histamine receptors and pancreatic and other cancers

As in other human neoplasias, HDC expression and histamine content have been reported in pancreatic cancer (Rivera *et al.*, 2000; Tanimoto *et al.*, 2004).

Furthermore, it was previously reported that H₁R and H₂R are expressed and associated with cell proliferation in Panc-1, a cell line derived from a human ductal pancreatic carcinoma. Histamine concentrations higher than 1 $\mu\text{mol}\cdot\text{L}^{-1}$ inhibited clonogenic growth through the H₁R and H₂R. On the other hand, nanomolar histamine doses stimulated cell proliferation (Cricco *et al.*, 2000). The anti-proliferative effect exerted by histamine through the H₂R is associated with a G0/G1 phase arrest, a decrease in phosphoactivated ERK1/ERK2 and an increase in phosphoactivated P38 expression, and also a modulation of Bcl-2 family proteins. However, apoptosis is not significantly induced while a partial cell differentiation was associated with this inhibitory action (Cricco *et al.*, 2000; 2004; 2006; Martín *et al.*, 2002).

More recently, it was described the expression of H₃R and H₄R in Panc-1 cells. Proliferation studies indicated that the H₃R and H₄R are involved in pancreatic carcinoma cell growth, being proliferation augmented through H₃R and diminished by H₄R (Cricco *et al.*, 2008) (Table 2).

Moreover, histamine content increased unequivocally in other human cancer types such as ovarian, cervical and endometrial carcinoma in comparison with their adjoining normal tissues suggesting the participation of histamine in carcinogenesis. Besides, exogenous histamine, at micromolar concentration, stimulated proliferation of human ovarian cancer cell line SKOV-3 (Batra and Fadeel, 1994; Chanda and Ganguly, 1995). Preliminary results show that H₄R is expressed in primary and metastatic ovarian carcinoma and also in gallbladder cancer (Figure 1).

Conclusions and perspectives

A significant body of research has contributed to the elucidation of the functional capacities of histamine in tumour cell growth and development. The discovery of the human H₄R has helped to refine our understanding of histamine role in (patho) physiological conditions.

Recent findings indicate that H₄R is expressed in human breast tissues and cell lines exhibiting a key role in histamine-mediated biological processes such as cell proliferation, senescence, apoptosis and metastatic potential in malignant cells. Similar responses were observed in the human cell lines of pancreatic carcinoma and melanoma where histamine, via H₄R, inhibits proliferation and modulates cell differentiation and migration. In addition, H₄R was detected in both colorectal cancer and adjacent normal colonic specimens, and in human colon

cancer cell lines in which histamine exerts both a proliferative and a proangiogenic effect via H₂R/H₄R activation. Although these reports make unquestionably the presence of functional H₄R in human cancer tissues, the precise role of H₄R in cell proliferation seems to be cancer type dependent and must be further investigated. The presented data suggest a novel and complex role of H₄R in carcinogenesis that might represent a new molecular target and avenue potentially useful for the design of more specific and effective therapies for cancer; however, further investigation is needed to fully understand its function in the diverse types of tumours. Therefore, the identification of H₄R with functional presence in different cancers opens new perspectives in histamine pharmacology research aimed to develop a new generation of antihistamines targeting H₄R that may contribute for advances in the treatment of cancer.

Acknowledgements

This work has been supported by grants from the University of Buenos Aires B061, from the National Agency of Scientific and Technological Promotion PICT-2007-01022 and from the EU-FP7 COST Action BM0806 (recent advances in histamine receptor H₄R research). We thank Miss Natalia Rivera for proof-reading the manuscript.

Conflict of interest

The authors state no conflict of interest.

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