Histamine as a Potential Adjuvant to Immuno and Radiotherapy for Cancer Treatment: Discovering New Functions for the Oldest Biogenic Amine

Vanina A. Medina[1,2] and Elena S. Rivera[*,1]

[1]*Laboratorio de Radioisótopos, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Argentina*

[2]*Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina*

Abstract: Since histamine discovery in 1910, it has been recognized as a major mediator in gastric acid secretion and inflammation that is a main pathophysiological characteristic of allergy. For many years, drug development and therapeutic application of histamine antagonists were mainly focused on the allergic and gastrointestinal diseases. At present, it is one of the monoamines (2-(imidazol-4-yl)ethylamine) with the broadest spectrum of activities in various physiological and pathological situations. Thus, it has been shown to be involved in aminergic neurotransmission and numerous brain functions including learning, memory, sleep/wakefulness, locomotor activity, nociception, food intake, secretion of pituitary hormones, and regulation of gastrointestinal and circulatory functions, as well as modulation of immunity and hematopoiesis. A significant body of research has contributed to the elucidation of the functional capacities of histamine in tumor cell growth and development. Evidences for multiple cellular sources of histamine, the discovery of a novel histamine receptor (H4R) and the demonstration of a histamine–cytokine cross-talk have modified the perspective which suggests new potential therapeutic uses of histamine and its receptor ligands. The involvement of histamine in cancer immunotherapy has been a subject of interest for more than a decade. Histamine dihydrochloride is being safely used in clinical trials as an adjuvant for the potential treatment of different cancers, improving efficacy by increasing survival benefit and exhibiting no unexpected or irreversible side effects. Interleukin-2 and interferon-alpha have been used as therapeutic options for the treatment of certain malignancies such as metastatic malignant melanoma, myelogenous leukemia, renal cell carcinoma and chronic hepatitis C. Combination therapy with histamine has two key advantages over cytokine therapy alone, namely improved cytotoxicity against a greater range of cancer types, and improved quality-of-life as a consequence of lower dose administration of the cytokines. Furthermore, radiation therapy is a well recognized treatment modality for cancer. Although effective, adverse effects due to radiotherapy are unavoidable, even with localized delivery techniques. Regardless of many years of research, there are surprisingly few radiation protectors in use today, whose clinical use is limited due to their toxicity; thus, the development of effective and nontoxic agents is yet a challenge for oncologists and radiobiologists. We have recently reported that histamine significantly protects two of the most radiosensitive tissues, small intestine and bone marrow, from high doses of radiation. In addition, histamine has the ability to prevent functional and histological alterations of salivary glands exerted by ionizing radiation. These features make histamine a suitable candidate for its use as an adjuvant for cancer immunotherapy and also as a selective radioprotector for patients undergoing radiotherapy. In the present review we aimed to briefly summarize some general notions on histamine functions before focusing on some recent evidence supporting the novel role of histamine in the immune function and the potential application as an adjuvant to tumor immunotherapy and radiotherapy.

Keywords: Histamine, immunotherapy, radioprotection, histamine receptors, cancer treatment, immune system.

INTRODUCTION

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 [1-3]. Since its discovery by Sir Henry Dale at the beginning of the 20th century [4], there has been a long-standing effort to precisely describe its role in physiologic and pathological processes. Among other functions, it is implicated in allergy, inflammatory responses, gastric acid secretion, bone loss, aminergic neurotransmission and brain functions including sleep/awake control, food intake, learning, and emotion as well as brain diseases [5-8].

Histamine is produced in different cells and tissues by L-Histidine decarboxilase (HDC) (EC. 4.1.1.22), which is the only enzyme responsible for histamine synthesis in mammals [9]. HDC activity is detected not only in the specialized histamine-producing cell types such as mast cells, basophils, entherocromaffin-like cells (ELC) in the stomach and tuberomamillary neurons, but also in a wide variety of tissues and cells [10]. In spite of its ubiquitous presence, levels of HDC are generally low and the enzyme itself is highly unstable. Histamine is further metabolized either by diamine oxidase (DAO) (EC 1.4.3.6) [11, 12] or by histamine N-methyltransferase (HNMT) (EC 2.1.1.8) [13], both enzymes presenting different cell and tissue specific distribution patterns.

*Address correspondence to this author at the Laboratory of Radioisotopes, School of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956, 113 - Buenos Aires, Argentina; Tel: 54 - 11 - 4964-8277/8202; Fax: 54 - 11 - 4964-8277/8202; E-mail: erivera@ffyb.uba.ar

1573-3955/10 $55.00+.00

Mast cells and basophils store histamine in granules that can be released in large amounts in response to diverse immunological and non-immunological stimuli. Other cellular sources of histamine have been reported in cells that express high HDC activity and where the amine is immediately released after synthesis. This neo-synthesized histamine, also called nascent histamine, is present in different cells and tissues where its production through HDC is modulated by different cytokines, mitogenic factors or hormones [14-16]. It is noteworthy that, within minutes of release, histamine level is further controlled by the catabolizing enzymes DAO and HNMT [17], thus it is likely that histamine usually influences events at or near the site of release as a paracrine or autocrine factor.

The observation that histamine synthesis can be induced and made available in an unstored diffusible form in growing or regenerating tissues, suggested that it may have a role beyond its traditional pharmacological properties. The hypothesis that histamine could be involved in cell proliferation was first postulated in 1960 and, since then, a large amount of experimental data regarding this effect has been presented [18, 19]. Cell proliferation is one of the most common phenomena and represents the key step in a great number of vital biological processes such as: reproduction, growth, differentiation, functional and structural repair, hematopoiesis, regeneration and immune response. Furthermore, cell proliferation is crucial for tumor development and progression, and in this line, the involvement of histamine in cancer has been extensively investigated [18-20].

HISTAMINE RECEPTORS

It is generally acknowledged that histamine is an important mediator of many (patho) physiological conditions and exerts its actions through the interaction with four histamine receptor subtypes. All these receptors belong to the family of heptahelical G-protein coupled receptors (GPCR) and they are the H1, H2, H3 and H4 histamine receptors (H1R, H2R, H3R, H4R). The first two histamine receptors were proposed in 1966 by Ash and Schild and in 1972 by Black *et al*., based on the classical pharmacological analysis [21, 22]. Using a similar strategy in 1983 a new H3R subtype mediating a negative feedback on the release of histamine from rat brain slices was described by Arrang *et al*. [23]. The cloning of this receptors, the H1R and H2R in 1991 and the H3R in 1999, contributed to a huge increase in the knowledge of their molecular pharmacology and biochemistry [24-27]. It was not until 2000-2001 that by using the H3R DNA sequence, several independent research groups identified the novel H4R highly expressed in immune cells [28-33]. Like most other GPCR, histamine receptors exist as equilibrium between their inactive and active conformations. Constitutive activity has now been shown for all four types of histamine receptors, leading to the reclassification of some antagonists as inverse agonists. Agonists with a preferential affinity for the active state of the receptor stabilize the receptor in its active conformation leading to a continuous activation signal. On the contrary, inverse agonists (antagonists in the old terminology), with a preferential affinity for the inactive state, stabilize the receptor in this conformation and consequently induce an inactive state, which is characterized by blocked signal transduction. These members of the GPCR family may exist as homo- and hetero-oligomers at the cell surface, which could have different pharmacological and physiological effects [34-41]. Moreover, the affinity of histamine binding to different histamine receptors varies significantly. Thus, the effects of histamine and receptor ligands upon receptor stimulation are rather complex [35, 41, 42].

Pharmacologic agents are summarized in Table **1**.

Histamine H1R

The H1R is the main histamine receptor subtype involved in the pathological process of allergy such as allergenic rhinitis, conjunctivitis, atopic dermatitis, urticaria, asthma and anaphylaxis, and acute inflammatory disorders. In the lung, it mediates bronchoconstriction and increased vascular permeability. The H1R is expressed in a wide variety of tissues, including airway and vascular smooth muscle, endothelia, gastrointestinal tract, liver, genitourinary and cardiovascular systems, central nervous system (CNS), adrenal medulla, chondrocytes and in various immune cells including neutrophils, monocytes, eosinophils, dendritic cells (DC), as well as T and B lymphocytes, in which it mediates the various biological manifestations of allergic responses. The coding sequence of the human H1R is intronless and is located in the chromosome 3 [2, 35, 43-49]. The human H1R

Table 1. Human Histamine Receptor Comparisons

	Expression	G Protein Coupling and Main Effectors	Agonists	Antagonists/Inverse Agonists
H1R	Ubiquitous	$G\alpha_q$, calcium influx, cGMP, NFκB	Histaprodifens, 2-(3-trifluoromethylphenyl) histamine	Mepyramine, cetirizine, diphenhydramine, loratadine
H2R	Ubiquitous	$G\alpha_s$, increase in cAMP, c-Fos, c-Jun, PKC	Dimaprit, amthamine, impromidine	Famotidine, ranitidine, cimetidine
H3R	CNS, eosinophils, DC, monocytes	$G\alpha_{i/o}$, inhibition of cAMP, MAPK, PKB	R-(α)-methylhistamine, imetit, immepip	Clobenpropit, thioperamide, iodoproxyfan
H4R	Bone marrow and peripheral hematopoietic cells, eosinophils, DC, neutrophils, T cells, basophils, mast cells, neurons, spleen, small intestine	$G\alpha_{i/o}$, inhibition of cAMP, MAPK, calcium influx	Clobenpropit, VUF 8430, 4-methylhistamine, R-(α)-methylhistamine,	Thioperamide, JNJ7777120, VUF 6002

contains 487 amino acids and is a Gαq/11-coupled protein with a very large third intracellular loop and a relatively short C-terminal tail. The most important signal induced by ligand binding is the activation of phospholipase C-generating inositol 1, 4, 5-triphosphate (Ins (1, 4, 5) P3) and 1, 2-diacylglycerol leading to increased cytosolic calcium. In addition to the inositol signaling system, H1R activation could lead to additional secondary signaling pathways. This rise in intracellular calcium levels seems to account for the various pharmacological activities promoted by the receptor, such as nitric oxide production, vasodilatation, liberation of arachidonic acid from phospholipids and increased cyclic GMP (cyclic guanosine-3', 5'-monophosphate). Additionally, it was reported that H1R can directly increase the cAMP (cyclic adenosine-3', 5'-monophosphate) levels. H1R also activates NF-kB through Gαq11 and Gβγ upon agonist binding, while constitutive activation of NF-kB occurs only through the Gβγ [2, 35, 44, 47, 49, 50].

Histamine H2R

The H2R principal action from a clinical point of view is its role in stimulating gastric acid secretion. The human H2R intronless gene, which is located on chromosome 5, encodes a protein of 359 amino acids. The H2R has a ubiquitous expression as the H1R. It is expressed in gastric parietal cells, heart, endothelial cells, nerve cells, airway and vascular smooth muscle, hepatocytes, chondrocytes, and immune cells, such as neutrophils, monocytes, eosinophils, DC, and T and B lymphocytes [2, 35, 43, 45-46]. The H2R is coupled both to adenylate cyclase *via* a GTP-binding protein G_s, and phosphoinositide second messenger systems by separate GTP-dependent mechanisms. However, H2R-dependent effects of histamine are predominantly mediated by cAMP that activates protein kinase A (PKA) enzymes phosphorylating a wide variety of proteins involved in regulatory processes. Activation of H2R is also associated with other additional signal transduction pathways including activation of c-Fos, c-Jun, protein kinase C and p70S6kinase [2, 35, 37, 47, 48, 51, 52].

Histamine H3R

The H3R has initially been identified in both central and peripheral nervous system as a presynaptic receptor controlling the release of histamine and other neurotransmitters (dopamine, serotonine, noradrenalin, γ-aminobutyric acid and acetylcholine). The H3R has gained pharmaceutical interest as a potential drug target for the treatment of various important disorders like obesity, myocardial ischemia, migraine, inflammatory diseases and several CNS disorders like Alzheimer's disease, attention-deficit hyperactivity disorder and schizophrenia. The human H3R gene consists of either three exons and two introns, or four exons and three introns spanning 5.5 kb on chromosome 20. Alternatively, the most 3' intron has been proposed to be a pseudo-intron as it is retained in the hH3R(445) isoform, but deleted in the hH3R(413) isoform. Overall similarity between the H3R and the H1R and H2R amounts to only 22% and 20%, respectively [2, 24, 35, 38, 45, 46, 53-59].

The cloning of the human H3R has led to the discovery of many H3R isoforms generated through alternative splicing of the H3R mRNA and several signal transduction pathways that are modulated by the H3R. H3R can activate several signal transduction pathways including Gi/o-dependent inhibition of adenylyl cyclase that leads to inhibition of cAMP formation, activation of mitogen activated protein kinase pathway (MAPK), phospholipase A2, and Akt/protein kinase B, as well as the inhibition of the Na+/H+ exchanger and inhibition of K+-induced Ca2+ mobilization. A negative coupling to phosphoinositide turnover in the human gastric cell line HGT has also been described. Moreover, at least 20 isoforms of the human H3R have been described and they vary in the length of the third intracellular loop, their distinct central nervous system localization, differential signaling pathways and ligand binding affinity, which contribute to the heterogeneity of H3R pharmacology [2, 35, 38, 54-62].

Histamine H4R

The identification of the human H4R by several groups has helped refine our understanding of histamine roles including the modulation of immune function. It appeared to have a selective expression pattern restricted to medullary and peripheral hematopoietic cells including eosinophils, mast cells, DC, T cells and monocytes. Therefore, growing attention is directed toward the therapeutic development of H4R ligand for inflammation and immune disorders [7, 28-33, 35, 41, 43, 45, 46]. In addition, H4R was reported to be present on other cell types including intestinal epithelium, CNS, nerves of nasal mucosa, enteric neurons and also in cancer cells [63-70]. 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. In accordance with the homology between the two receptors, various H3R ligands are recognized by the H4R, albeit with different affinities. On the other hand, the homology with H1R and H2R is of approximately 19%. The human H4R gene that mapped to chromosome 18, encodes a 390 amino acid. Isoforms have been described also for the H4R which have different ligand binding and signaling characteristics. H4R splice variants 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. H4R are coupled to Gi/o, initiating various transduction pathways such as inhibition of forskolin-induced cAMP formation, increased calcium influx and MAPK activation [28-33, 35, 41, 43, 45-47, 71-73].

HISTAMINE IN PROLIFERATION AND CANCER DEVELOPMENT

Considerable evidence has been accumulated indicating that histamine can modulate proliferation of different normal and malignant cells by acting through the specific membrane receptors [18-20]. High histamine biosynthesis and content has been reported in a wide number of human and experimental tumors [74, 75], and in diverse human tumors histamine concentration showed to be higher compared to surrounding normal tissue including melanomas, colon carcinoma, and breast cancer [76-79]. Histamine receptors are expressed in multiple malignant cell types, with the

additional finding that they can be associated to multiple signaling pathways. The regulation of receptor density at cell surface can strongly affect the receptor ability to functionally couple and regulate different signal transduction pathways [48, 51, 52, 67].

In addition, H3R and H4R can express diverse isoforms, and it is likely that the different isoforms have diversity in their signaling pathways [38, 54, 56, 57]. In mammary gland, histamine plays a critical role in growth regulation, differentiation and functioning during development, pregnancy and lactation [80, 81]. We have recently reported the expression of the H3R and H4R in human benign and malignant lesions of the mammary gland. Furthermore, the expression of H3R is highly correlated with proliferation and histamine production in malignant lesions [68], and preliminary results obtained with xenotransplanted tumors in nude mice indicate that the H4R may be involved in the metastastatic process (unpublished data). In a high number of human cell lines derived from different neoplasias, as well as in tumoral tissues, the expression of histamine receptors with the ability to regulate cell proliferation has been demonstrated [82]. It has recently been shown that histamine regulates proliferation of McA-RH7777 hepatoma cells by interacting with autoinhibitory H3R [83]. Moreover, histamine exerts both a proproliferative and a proangiogenic effect *via* H2R/H4R activation in colon cancer cells [69].

Notably, most malignant cell lines express HDC 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 tumor growth. 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 [84] showing that the inhibition of HDC with monofluormethylhistidine (MFMH) resulted in antitumoral effects on experimental tumors 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 suppressed melanoma cell proliferation [76], 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 [85]. Similarly, the identification of histamine receptors in a large number of malignant cell lines, as well as in biopsies of human tumors, supported the role of histamine as a growth factor, and the discovery of the H4R with functional presence in a wide range of tissues revealed novel functions for histamine, leading to reconsideration of new perspectives in histamine pharmacology research.

HISTAMINE AND THE IMMUNE SYSTEM

It is well-documented that histamine influences basic physiological and patho-physiological immunological processes, playing critical roles in the modulation of immune response and hematopoiesis as well as inflammatory and allergic reactions [35, 45, 46]. Immune response and hematopoiesis are controlled by a complex network of cytokines and chemokines. A large body of experimental data supports the idea that histamine participates in a complex interactive network with cytokines that influence the outcome of the immune response. The diverse effects of histamine on immune regulation and hematopoiesis appear to be due to differential expression and regulation of the four histamine receptor subtypes and their distinct intracellular signals that determine the biological effects of histamine. A bidirectional link between histamine and cytokines is observed since histamine modulates immune cell functions and cytokines control histamine synthesis and release, as well as histamine receptor expression. On the one hand, histamine synthesis in various hematopoietic populations is subject to regulation by cytokines like interleukin (IL)-3, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1, IL-18, IL-12, tumor necrosis factor alpha (TNFα) and also corticosteroids. On the other hand, histamine modulates the production of cytokines by T cells, DC, and macrophages [45, 86-91].

Mast cells and basophils are the major sources of histamine in normal tissues. They can store the biogenic amine in specific cytosolic granules, which is released by exocytosis in large amounts during degranulation following immunological or non-immunological activation. Other cells can also produce histamine and in the absence of specific granules for storage, this "neosynthesized'' or ''nascent' histamine is secreted immediately after synthesis. Neosynthesized histamine produced by monocytes, lymphocytes, hematopoietic progenitors, macrophages, platelets, DC and other histamine-producing cells is thought to play a role in modulation of immune system by modulating the cytokine profile and the functions of antigen-presenting cells (APC), and its production is modulated by cytokines [35, 45, 46, 92, 93].

Histamine and Th1-Th2 Cytokine Profile

The T-helper cell polarization is an essential event in the adaptive immune system which is regulated by the cytokine network. On the one hand, Th1 cells produce mainly IL-2, IL-12, and interferon gamma (IFNγ), and promote a cellular/cytotoxic T-cell response. On the other hand, Th2 cells produce IL-4, IL-6, IL-10 and IL-13 and enhance the humoral responses. Until recently, it was generally accepted that histamine promotes Th2 response by inhibiting IL-12 production by APC and stimulating that of IL-10. However, histamine can exert a differential effect on these subsets depending on the differential pattern of expression of H1R and H2R on Th1 and Th2 cells that determine the reciprocal T cell response upon histamine stimulation. The H1R subtype is predominant in the Th1 population, while the H2R subtype is preferential in Th2 cells. Histamine enhances Th1-type responses by triggering the H1R, whereas both Th1 and Th2 responses are negatively regulated through H2R. Histamine acts as a pro-Th2, anti-Th1 mediator during Th differentiation by modulating cytokine production by APC such as increasing IL-10 [45, 46, 88, 91].

In addition, histamine hinders Th2 activity of differentiated cells *via* H2R which acts as the negative regulator of proliferation, IL-4 and IL-13 production and can also stimulate Th1 proliferation *via* H1R, preferentially expressed on Th1 cells, thus providing an additional anti-Th2 signal *via* increased IFNγ production. The H1R

knockout mice showed a suppression of IFN and a dominant Th2 type cytokines (IL-4 and IL-13) while the H2R knockout mice demonstrated an up-regulation of Th1 and Th2 cytokines compared to the wild type counterparts. Therefore, histamine seems to enhance and to suppress both Th1 and Th2 responses depending on the cell receptor subtype. Furthermore, histamine directly affects antibody production, acting as a co-stimulatory receptor on B cells. Histamine H1R predominantly expressed on Th1 cells may suppress humoral immune responses by enhancing Th1 type cytokine IFN-γ. In contrast, through H2R, histamine potentiates humoral immune responses. Allergen-specific immunoglobulin-epsilon (IgE) and IgG1, IgG2b and IgG3 production is increased in H1R receptor-deficient mice compared with mice lacking H2R [35, 45, 94-97].

The diverse findings regarding the immune modulatory actions of histamine during Th1/Th2 differentiation appear to be due to the complexity of the system, which involves the four histamine receptor subtypes with distinct functions and intracellular signaling, the expression of which is modified with the microenvironment and the differentiation cell stage. Furthermore, the latest discovered H4R, mainly expressed in hematopoietic and immunocompetent cells such as mast cells, basophils, eosinophils, T lymphocytes, monocytes and DC, adds more complexity and invites for exhaustive investigation [30, 32, 63, 98-102].

The involvement of H4R in DC activation and T cell differentiation was recently reported, indicating its immunomodulatory action. An *in vitro* study indicated that blockade of the H4R on DC by genetic or pharmacological tools, leads to a decrease in cytokine and chemokine production and limits their ability to direct the Th2 polarization of T cells. These suggest that the H4R in DC originates the Th2-promoting environment by suppressing IL-12p70 and stimulating pro-inflammatory cytokines such as IL-6 and TNF-α production [63, 103, 104]. In CD8+ T cells histamine induced IL-16 production through the H2R and H4R. Therefore, histamine may have an indirect effect on T-cell recruitment by regulating the levels of this chemoattractant [98].

The interaction between histamine and the cytokines is bidirectional, since some cytokines were found to modulate the production and release of histamine as well. The effect of cytokines is especially potent on neosynthesized histamine by cells differing from mature basophils or mast cells. HDC activity is modulated in response to cytokines like IL-3, GM-CSF, IL-1, IL-18, IL-12, macrophage colony-stimulating factor (M-CSF) and TNFα [45, 88, 105-108]. Basophil precursors generate histamine upon exposure to IL-3, IL-5, GM-CSF [3, 45, 88, 109].

Histamine and Functions of Antigen-Presenting Cells (APC)

Histamine has been shown to regulate several essential events in the antigen-specific immune response development. Specialized or professional APC such as DC, macrophages and B lymphocytes, capture extracellular protein antigens, internalize and process them, and display histocompatibility complex (HMC)-associated peptides to naïve T cells during the recognition phase of the immune response to initiate these responses. They also present antigens to differentiated effector T cells during the effector phase to trigger the mechanisms that eliminate the antigens [110]. Their differentiation process includes increased display of co-stimulatory molecules and cytokine production.

DC are APC that mature from monocytic and lymphoid precursors and acquire dendritic cell 1 and dendritic cell 2 phenotypes depending on the stimulus, which in turn facilitates the development of Th1 and Th2 cells, respectively [35]. Endogenous histamine is actively synthesized during cytokine-induced DC differentiation, which acts in autocrine and paracrine fashion and modifies DC markers such as CD45 and CD40 [111]. In addition, histamine increases the expression of co-stimulatory molecule CD86 and alters chemokine production [46, 112, 113].

Histamine modulates functions and activity of DC precursors as well as their immature and mature forms that express all four histamine receptors [98, 112-114]. In the differentiation process of dendritic cell 1 from monocytes, H1R and H3R induce proinflammatory cytokine production and Th1 priming activity, and increase APC capacity. On the other hand, H2R suppresses APC capacity, enhances IL-10 production inducing Th2 cells [113, 115, 116].

Histamine induces intracellular calcium increase and chemotaxis in immature DC due to stimulation of H1R and H3R. Mature DC lose these responses and histamine stimulates IL-10 while it inhibits IL-12 production *via* H2R [115]. In agreement with these observations, histamine inhibits the production of pro-inflammatory IL-1-like activity, TNF-α, IL-12 and IL-18 but enhances IL-10 secretion, through H2R in monocytes stimulated with Toll-like receptor-triggering bacterial products [116-119]. Moreover, histamine *via* H2R inhibited the LPS-induced TNFα production through the regulation of intracellular adhesion molecule (ICAM)-1 and B7.1 expression [120]. In plasmacytoid DC (pDC), another professional APC, histamine regulates cytokine production through the H2R [121]. In contrast with the observations in other DC, human epidermal Langerhans cells do not express H1R or H2R mainly because of the effect of transforming growth factor (TGF)-β [122].

The H4R is expressed on the surface of monocytes and is up-regulated by IFN-γ, and also in the presence of neutralizing antibody to IL-10 [33, 123]. Histamine mediated effects through the H4R on APCs involved the IL-12 downregulation and chemotaxis induction in human monocytes derived DCs [104], and CCL2 downregulation in human monocytes [123]. Additionally, human inflammatory dendritic epidermal cells express a functionally active H4R that was upregulated by IFNγ, which upon stimulation leads to downregulation of the Th2-linked chemokine CCL2 and the Th1 cytokine IL-12 [124].

Among the several functions of the natural killer (NK) cells is the regulation of the adaptive immune response by secreting cytokines like IFNγ, shaping the innate immune system by interacting with DC, defending against viral infection, and destroying tumor cells [125]. Damaj *et al*. demonstrated that H4R protein is expressed in IL-2-activated

NK cells and that this receptor mediates cell chemotaxis induced by histamine [126]. The finding that H4R expression can be modulated by cytokines is suggestive of a possible implication in the regulation of immune responses.

Histamine in Hematopoiesis

It is well documented that histamine participates in the regulation of hematopoiesis by stimulating both primitive multipotent and more lineage-restricted myeloid progenitors. The role of histamine in hematopoiesis was first proposed by Byron, who reported in 1977 that exogenous histamine could promote the entry of colony-forming units in the spleen (CFU-S) into cell cycle *via* the H2R [127]. Even at low concentrations (10^{-8}M) histamine when added during *in vitro* cultures was able to enhance granulocyte precursor proliferation and colony forming unit activity (CFU-C), resulting in an increased number of differentiated neutrophils [128]. In addition, the cells involved in the regulation of hematopoiesis express histamine receptors and secrete histamine [102, 129]. Endogenous histamine is produced in hematopoietic progenitors in response to IL-3 and GM-CSF in the hematopoietic microenvironment being a requisite for bone marrow-derived CFU-S cell cycling in response to IL-3 or GM-CSF plus IL-1 [18, 45, 46, 129-131]. Dy *et al*. proposed that histamine may be involved in inducible hematopoiesis rather than maintaining bone marrow homeostasis, satisfying the increased requirements of an efficient host defense, considering that histamine is synthesized exclusively in response to hematopoietic growth factors generated during the immune response (IL-3, GM-CSF and IL-1). Therefore, it is not surprising that in HDC-deficient mice only mast cells, which synthesize histamine constitutively, appear to be abnormal, exhibiting altered morphology and reduced granular content [132]. Moreover, it was reported that a faster bone marrow repopulation was observed in wild type in comparison with HDC -/- knockout mice and that HDC and histamine content in regenerating bone marrow populations increased after total-body irradiation in wild type mice [133]. Furthermore, bone marrow-derived mast cell differentiation is strongly reduced in HDC knockout, histamine-free mice suggesting that the effect of histamine on the IL-3-dependent mast cell differentiation during the early period is crucial and irreplaceable taking into account that exogenously added histamine is unable to substitute the endogenously missing histamine [134].

Reports on side effects including agranulocytosis and neutropenia by H2R antagonists or H4R agonist clozapine further support a positive role of histamine in hematopoiesis [135-140]. The most recently identified H4R preferentially expressed in the bone marrow, raised questions regarding its role during hematopoiesis. It was recently reported that both murine and human progenitor cell populations express H4R and respond to its agonists by reduced growth factor-induced cell cycle progression leading to decreased myeloid, erythroid and lymphoid colony formation [141].

Histamine in Inflammatory and Allergic Reactions

Histamine is considered one of the most important mediators that orchestrates allergic and inflammatory responses. The majority of available data support the concept that histamine increases the secretion of pro-inflammatory cytokines and chemokines, thus inducing the evolvement of inflammatory responses [88]. Histamine influences several immune/inflammatory and effector functions in addition to its dominant role in type I hypersensitivity reactions [102, 142].

This biogenic amine is one of the major inflammatory mediators of allergic disease and exerts an important role mediating the cardinal signs of allergic rhinoconjunctivitis (sneezing, itching, nasal discharge, and mucosal edema), urticaria (vasodilatation, pruritus, and increased vascular permeability), anaphylaxis (vasodilatation, flushing, increased vascular permeability, tachycardia, and smooth muscle contraction) and bronchial asthma (bronchial smooth muscle contraction, mucosal edema, and mucus secretion). Histamine is released from mast cells and basophils after their activation by interaction of allergens with surface IgE. The most characteristic roles for H1R activation are smooth muscle contraction and increases in vascular permeability. Many of its functions contribute to allergic responses and therefore, H1R antagonists (commonly referred to as antihistamines) have been very successful drugs for the treatment of allergies [21, 35, 91, 143, 144]. During an allergic response, histamine produced by mast cells degranulation causes vascular permeability, and drives the infiltration and mediator production of inflammatory cells. Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines such as IL-1α, IL-1β, IL-6 and also chemokines such as regulated upon activation normal T-cell expressed and secreted (RANTES), IL-8, or IL-16 in several cell types and local tissues [35, 88, 119, 145-148]. In explant cultures of human nasal mucosa histamine induces the CC chemokines, monocyte chemotactic protein (MCP) 1 and 3, RANTES, and eotaxin *via* H1R, suggesting a prolonged inflammatory cycle in the histamine-MCP axis in allergic rhinitis [149]. In monocytes from non-atopic healthy individuals, histamine prevents the generation of CD1a+CD14- DC and induces CD1a-CD14+ DC *via* H2R, in GMCSF and IL-4-driven differentiation. This effect results from the histamine-induced secretion of IL-10 and therefore may contribute to the exacerbation of allergic diseases [150].

Histamine is a major mast cell-derived mediator that causes endothelial cell contraction and increased vascular permeability. Histamine regulates the expression of its own receptors on endothelial cells, and *via* H1R increases the expression of adhesion molecules such as ICAM-1, vascular cellular adhesion molecule (VCAM-1) and P-selectin potentiating the chemoattractant-induced leukocyte adhesion. Initial leukocyte recruitment after mast cell activation in the rat mesentery is critically dependent on histamine release [35, 43, 151-153]. Histamine possesses all the properties of a classical leukocyte chemoattractant, including: agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape, and up-regulation of adhesion molecule expression. Histamine is a chemoattractant for eosinophils and mast cells [35, 93, 100, 154]. On the other hand, histamine inhibits neutrophil chemotaxis and activation due to histamine H2R activation. This was further confirmed in HDC-deficient mice

demonstrating that histamine plays significant roles in the negative regulation of neutrophil infiltration *via* H2R in allergic inflammation [155, 156].

In addition to its well-characterized effects in the acute inflammatory and allergic responses, histamine has been shown to affect chronic inflammation. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and effector functions leading to chronic inflammation. On the other hand, histamine acting through its H2R positively interferes with the peripheral antigen tolerance induced by T regulatory (Treg) cells in several pathways [101, 102, 142, 157].

Atopic asthma is a chronic inflammatory disorder characterized by hyperresponsiveness and chronic inflammation of the airways upon exposure to allergens. Although many cell types are involved, Th2 T cells, which produce IL-4, IL-5, and IL-13 in the airways, are thought to be most important for disease perpetuation. Histamine plays an important role in the pathogenesis of atopic asthma through differential regulation of T helper lymphocytes. Histamine enhances the secretion of Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 and inhibits the production of Th1 cytokines IL-2 and IFNγ and monokine IL-12. It has been shown that the Jak-STAT (Janus kinase-signal transducers and activators of transcription) pathway is involved in histamine-mediated regulation of cytokines [101, 144, 158, 159].

The standard treatment of asthma consists of beta-adrenergic receptor agonists and inhaled corticosteroids. Although H1R antagonists have been used to treat allergies, offering symptomatic relief of several physiological events in allergic rhinitis, such as edema and vasodilatation, they do not substantially ameliorate early or late phase bronchoconstrictive events in the asthmatic airway in response to allergen challenge, suggesting that histamine receptors other than the H1R may be more important in the pathology of asthma [45, 63, 101, 158]. The importance of histamine in asthma and chronic pruritus may have been underestimated. The discovery of a fourth histamine receptor and its expression on numerous immune and inflammatory cells has motivated a re-evaluation of the actions of histamine on immune system. H4R is primarily expressed on eosinophils, T cells, DC, basophils, and mast cells, cell types intimately involved with development and perpetuation of allergic responses [71, 103, 160]. This receptor has been shown to mediate mast cell, eosinophil, and DC chemotaxis and can modulate cytokine production from DC and T cells denoting its role in immunomodulation. Histamine acts through the H4R to mediate calcium mobilization, upregulation of adhesion molecules like CD11b and CD54, rearrangement of actin cytoskeleton and cell shape change leading to eosinophils migration. The H4R also mediates histamine-induced chemotaxis and calcium mobilization of mast cells without affecting degranulation in mice, which is blocked by antagonists of the H4R and is not observed in mast cells derived from H4R-deficient mice. Similarly, DC chemotaxis and actin polymerization can also be regulated by H4R; therefore, blocking the H4R on inflammatory cells might be a promising anti-inflammatory, immunomodulatory strategy [7, 31, 63, 71, 98, 100, 103, 104, 143, 161-163]. It was recently reported that H4R-deficient mice and mice treated with H4R antagonists exhibited decreased allergic lung inflammation, with decreases in infiltrating lung eosinophils and lymphocytes, and decreases in Th2 responses. The T cells restimulation ex vivo showed decreased levels in IL-4, IL-5, IL-13, IL-6, and IL-17. In addition, the blockade of the H4R on DC *in vitro* leads to decreases in cytokine and chemokine production and limits their ability to induce Th2 responses in T cells, suggesting that the H4R can modulate allergic responses *via* its influence on T cell activation [103, 160]. The available data from *in vitro* studies, experiments using genetically modified mice and pharmacological studies using H4R antagonists, such as JNJ7777120 and H4R agonists like 4-methylhistamine, in numerous animal models strongly implicated the H4R in inflammatory conditions such as asthma, allergic disorders and autoimmune diseases. The H4R is postulated as a novel target for the pharmacological modulation of histamine-mediated immune signals and offers potential therapeutic exploitation of this promising new drug target in inflammatory and allergic disorders. Also suggested were the possible synergistic effects between H1R and H4R antagonists in targeting various inflammatory conditions such as acute asthma, which indicates that the development of dual H1R/H4R antagonists is a meaningful and technically possible goal for the treatment of type-I allergic reactions [Reviewed at 7, 63, 160].

HISTAMINE AS AN ADJUVANT IN CANCER IMMUNOTHERAPY

The potential for treating cancer patients by immunologic approaches has held great promise for immunologists and cancer biologist for much of this century. The main reason for interest in an immunologic approach is that current therapies for cancer are still highly toxic and non-specific and rely on drugs that kill dividing cells or block cell division. Therefore, these therapies have severe effects on normal proliferating cells in cancer patients, leading to associated side effects. As a result, the treatment of cancers causes significant morbidity and mortality. Immunotherapy for tumors is aimed at augmenting the weak host immune response to tumors (active immunity) or at administering tumor-specific antibodies or T cells, a form of passive immunity [110, 164]. Combinations of different types of immunotherapy and of immunotherapy and chemotherapy have been tested, with enough suggestions of improved efficacy to encourage further clinical trials [165]. Much of the current practice of immunotherapy is based on treatment with cytokines such as IL-2 or IFNα. These cytokines enhance the ability of human NK cells and cytotoxic T-lymphocytes to kill cancerous or hepatitis C virus (HCV)-infected cells. The focus on IL-2 has arisen from *in vitro* demonstration of enhancement of tumor-specific cytotoxic T-lymphocyte and NK-cell activity after cytokine activation [166]

However, the results obtained in clinical trials with these cytokines have proved disappointing in many forms of cancer. NK cells and T cells are the primary targets of cytokines used in cancer immunotherapy. Nevertheless, these tumoricidal lymphocytes are frequently dysfunctional or apoptotic when residing within solid cancers, effect that is

poorly understood and conceivably limits the efficiency of strategies aiming at activating lymphocyte-mediated antitumor immunity. Recent studies imply that reactive oxygen species (ROS) and local secretion of inhibitory substances, produced by tumor-infiltrating monocyte/macrophages, may contribute to blocking the cytokine-dependent stimulation of T- and NK-cell production and activity in neoplastic tissue, and thus treatment with IL-2 and/or IFNα becomes ineffective [167, 168].

Agents capable of modulating cytotoxic effector function have been identified, including histamine dihydrochloride. The potential role of histamine in cancer immunotherapy has been a subject of interest for more than a decade. Histamine has been shown to act as an inhibitor of cellular-mediated free-radical production by monocytes/macrophages that contribute to tumor immunosuppression. ROS can cause down-regulation of the CD3ζ transduction antigen in NK and T cells along with significant NK-cell and T-cell apoptosis. *In vitro* evidence shows that histamine inhibits the ROS formation and release by monocytes/macrophages during respiratory burst; *via* H2R suppressing the activity of a key enzyme in oxygen radical formation, the NADPH oxidase; and in this way protects impaired NK and T cells functions produced by oxidative damage. Histamine has the potential to optimize cytokine-induced activation of T cells and NK cells restoring their antineoplastic, cytotoxic capabilities; therefore, the addition of histamine to cytokine treatment may improve treatment efficacy [166-174].

Clinical trials in solid tumors and in acute myeloid leukemia (AML) have demonstrated the potential to improve treatment outcome when histamine dihydrochloride is combined with immunotherapy. Maxim is developing a subcutaneous formulation of histamine dihydrochloride (Ceplene, formerly known as Maxamine, licensed by Maxim Pharmaceuticals Inc., CA, USA) for use as an adjuvant to immunotherapy. Administered as an outpatient treatment; histamine dihydrochloride (subcutaneous) was designed to offer the benefits of improved clinical efficacy, reduced toxicity and lower treatment cost. The two key advantages of combination therapy over cytokine therapy alone proposed are enhanced cytotoxicity against a greater range of cancer types, and improved quality-of-life as a consequence of lower dose administration of the cytokines. Clinically, histamine dihydrochloride (subcutaneous) is being evaluated in clinical trials for malignant stage melanoma, AML, renal cell carcinoma (RCC) and also hepatitis C [Reviewed at 167-169, 173].

The immunoactivating cytokine IL-2 is employed in the treatment of stage IV melanoma in many European countries and in the United States. IL-2 therapy induces complete regression of melanoma metastases in 3–5% of treated patients, but the toxicity of many IL-2 regimens limits its use. In addition to significant constitutional side effects, high doses IL-2 can result in dose-limiting hypotension, renal impairment, and pulmonary edema. The available data of phase III trials (M01, M0102) suggest that administration of IL-2 combined with histamine dihydrochloride may specifically prolong the survival of melanoma patients with liver metastases [168;175]. In addition, treatment of patients with stage IV melanoma with histamine in combination with IL-2 (MP104) increases type 1 T-cell responses and may promote induction of melanoma-specific T cells [176]. Single-agent IFNα as well as IL-2 treatment, yields response rates of approximately 15% in metastatic melanoma with infrequent long-term responders and occasional long-term survivors. Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with IL-2, IFN-α2b and histamine dihydrochloride *vs* dacarbazine in patients with stage IV melanoma showed that, although not statistically significant, median survival was longer for patients receiving histamine/IL-2/IFN (271 days) than for patients receiving dacarbazine (231 days) and that the combined regimen was safely administered on an outpatient basis [177, 178].

AML is the most common acute leukemia in adults. Despite successful chemotherapeutic remission induction and the introduction of more efficacious consolidation regimens, a worryingly large proportion of AML patients in complete remission will still suffer from recurrent and refractory disease and subsequently experience relapses which are associated with poor long-term survival. A recent randomized trial in AML demonstrated a statistically significant improvement in long-term leukemia-free survival, preventing relapse for patients treated post-consolidation with histamine and IL-2 compared with the no-treatment control patients. The addition of histamine in IL-2 therapy aims at protecting cytotoxic lymphocytes from myeloid cell-induced suppression and apoptosis. The combination of histamine/IL-2 is the first postconsolidation immunotherapy to prevent AML relapse in a randomized phase III trial and exhibits tolerable toxicity [166, 167, 173, 179, 180].

Less promising results were reported for histamine dihydrochloride added to cytokines in patients with other solid tumors; especially in advanced or metastatic RCC (mRCC) which produces a median survival of 8 to 12 months. Traditionally, surgery has been the treatment of choice for mRCC. Initial interest has focused on two cytokines, IFN-α and IL-2, with response rates ranging from 15% to 20%. Expansion of activated T cells in blood during treatment with these two cytokines seems to relate to clinical efficacy in patients with RCC. It was recently reported in two randomized phase II trials that circulating monocytes and neutrophils are powerful negative prognostic factors for IL-2- based immunotherapy and establish a biological rationale for the potential use of histamine in conjunction with IL-2 in mRCC. The potential benefit of histamine as an adjuvant to immunotherapy for mRCC should be the focus of further investigation [168, 169, 181-183].

Results published thus far indicate that administration of histamine dihydrochloride (subcutaneous) has been generally well tolerated in trials to date, being safe, feasible, and potentially efficacious, and it deserves further investigation in randomized trials [166, 168, 171, 173].

HISTAMINE AS A POTENTIAL ADJUVANT TO RADIOTHERAPY

Radiation therapy is a well recognized treatment modality for cancer, especially for localized disease that has not spread. Although effective, ionizing radiation is toxic not only to tumour cells but also to healthy tissues, producing

unavoidable adverse effects, even with localized delivery techniques [184-186]. The ratio of tumour response to normal-tissue damage is called the therapeutic index and can be manipulated by dose fractionation or by the use of drugs that preferentially either increase the tumour response (radiosensitizers) or reduce the biological effects of radiation, increasing the tolerance of normal tissues (radioprotectors). Despite many years of research there are surprisingly few radiation protectors in use today, whose clinical use is limited due to their toxicity; thus, the development of effective and nontoxic agents is yet a challenge for oncologists and radiobiologists [185-191].

The acute effects of irradiation result from the death of a large number of cells in tissues with a rapid rate of turnover. These include effects in the epidermal layer or skin, gastrointestinal epithelium, and hematopoietic system, in which the response is determined by a hierarchical cell lineage, composed of stem cells and their differentiating offspring. In clinical radiotherapy, the tolerance of normal tissues for radiation depends on the ability of clonogenic cells to maintain a sufficient number of mature cells suitably structured to preserve organ function [190, 191]. During radiotherapy for intraabdominal and pelvic cancers, radiation seriously affects radiosensitive tissues such as small intestine and bone marrow [191, 192]. We have previously demonstrated that histamine treatment (daily subcutaneous injection, 0.1 mg/kg) significantly protects mouse small intestine against radiation-induced toxicity ameliorating histological injury and improving trophism of enterocytes [193]. Histamine completely prevented the decrease in the number of crypts evoked by whole body irradiation (132±9 *vs* 85±5 in untreated and irradiated animals) which is vital for small intestine restoration since the intestinal crypt contains a hierarchy of stem cells that preserve the potential to regenerate the stem cell population and the tissue after cytotoxic exposure [193-196]. Histamine radioprotective effect on small intestine was related to an increased rate of proliferation as evidenced by the enhanced proliferation markers in crypts [5-bromo-2'-deoxyuridine (BrdU)-positive cells per crypt: 2.0±0.3 *vs* 0.1±0.1 in untreated and irradiated mice]. Additionally, this outcome was accompanied by a reduction in the number of apoptotic cells per crypt (0.2±0.1 *vs* 2.0±0.7 in untreated and irradiated mice). The latter effect was associated with a modification of antioxidant enzyme levels that could lead to enhance the antioxidant capacity of intestinal cells [193].

The bone marrow pluripotent stem cells, such as erythroblast, are particularly radiosensitive and, after whole body irradiation, an important grade of aplasia is observed increasing the possibility of haemorrhage and/or infection occurrence that could be lethal. The survival of stem cells determines the subsequent repopulation of bone marrow after irradiation [190, 191]. We further investigated the capability of histamine to prevent ionizing radiation-induced toxicity on bone marrow. Our results demonstrated that histamine (0.1 mg/kg) significantly reduced the grade of aplasia, ameliorating the oedema and vascular damage produced by ionizing radiation while eliciting a significant conservation of the medullar progenies on bone marrow in mouse and rat species increasing the number of megakaryocytes (14.0±1.0 *vs* 7.3±1.0 in mice; and 9.9±1.3 *vs* 4.1±1.0 in rats) and also myeloid (253.4±37.6 *vs* 7.8±1.5 in mice; and 52.0±3.7 *vs* 31.8±3.1 in rats), lymphoid (97.4±6.5 *vs* 19.8±1.6 in mice; and 23.4±0.9 *vs* 11.7±2.5 in rats) and erythroid cells (165.0±9.1 *vs* 8.8±2.8 in mice; and 27.3±2.3 *vs* 15.6±3.5 in rats) per mm^2. The histamine effect is mediated at least in part by an increase in the rate of proliferation, as evidenced by the enhanced PCNA protein expression and BrdU incorporation, and is associated with an enhanced HDC expression in irradiated bone marrow cells [197]. In this line, it was reported that a faster bone marrow repopulation was observed in wild type in comparison with HDC-deficient mice and that intracellular HDC and histamine content in regenerating bone marrow populations in HDC+/+ mice increased after total-body irradiation [133].

Irradiation is a major treatment modality administered for head and neck cancer. Despite improvements in the technology for delivering therapeutic radiation, salivary glands are inevitably irradiated, causing devastating side-effects which results in salivary hypofunction and consequent xerostomia [191, 198-202]. Salivary glands of rat are quite similar to human salivary glands in which salivary flow is rapidly reduced after ionizing radiation exposure [198]. Therefore, we additionally investigated the potential radioprotective effect of histamine against ionizing radiation induced damage on rat submandibular gland. Recent results demonstrated that histamine markedly prevented radiation injury on submandibular gland, ameliorating the histological and morphological alterations. Radiation significantly decreased salivation by approximately 35-40%, which was associated with a reduction of submandibular gland wet weight relative to body weight (35%) and an alteration of epithelial architecture with lower cylindrical cells, vacuolization of acinar cells, partial loss of eosinophilic secretor granular material, and anisokaryosis. It is worth noting that histamine treatment (0.1 mg/kg) completely reversed the reduced salivation induced by radiation, preserving glandular function and mass with normal structure organization of acini and ducts. Results also revealed that histamine radioprotective effect on submandibular gland was associated with maintenance of tissue homeostasis, increasing the rate of proliferation while decreasing the apoptotic index in irradiated submandibular gland (Medina V, submitted manuscript).

To sum up, histamine treatment can selectively modulate cellular damage produced by ionizing radiation, thus preventing radiation induced damage on small intestine, bone marrow and salivary glands, and in addition, increasing radiosensitivity of human breast cancer cells [67, 193, 197]. Histamine radioprotective effect was demonstrated in two different rodent species, which suggests that histamine could exert a radioprotective action in other mammals.

Based on the presented evidences, we can conclude that histamine is a potential candidate as a safe radioprotective agent that might increase the therapeutic index of radiotherapy for intraabdominal, pelvic, and head and neck cancers, and enhance patient quality of life by protecting normal tissue from radiation injury. However, the efficacy of histamine needs to be carefully investigated in prospective clinical trials.

CONCLUSION

Throughout this review we tried to compile the most recent knowledge regarding novel functions of histamine focusing on the role on immune system and some recent evidence supporting the potential application of histamine as an adjuvant to tumor immunotherapy and radiotherapy.

For more than 50 years diverse functions have been postulated as possible mechanisms responsible for the clinical and experimental evidence of histamine involvement in cancer development, and the connection with the immune system was initially proposed as one of the most important. Nowadays, we have to conclude that almost all the hypothesis postulated were valid: histamine high biosynthesis and content, release, autocrine and paracrine regulation through the four receptors subtypes, modulation of tumor cell proliferation, differentiation, apoptosis, invasion and migration, angiogenesis, and a role as a messenger in inflammatory and immune response, are all tightly related to cancer development and progression.

The discovery of H4R with a selective expression pattern in medullary and peripheral hematopoietic cells have modified the perspective of histamine pharmacology, suggesting new potential therapeutic uses of H4R ligands for inflammation and immune disorders. The presented evidence reinforces the hypothesis of a key role for histamine on immune function that is mainly related to the potential adjuvant use of histamine as an adjuvant in cancer treatment. One century after the discovery of this small molecule, the oldest biogenic amine, it still contributes to the identification of molecular targets potentially useful for the design of more specific and effective therapies for cancer and other multifaceted disorders that involve the immune system.

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 form the EU-KP7 COST programme BM0806 (Histamine H4R network). We thank Miss Natalia Rivera for proof reading the manuscript.

REFERENCES

[1] Kahlson G, Rosengren E. New approaches to the physiology of histamine. Physiol. Rev. 1968; 48: 155-96.

[2] Hill SJ, Ganellin CR, Timmerman H, *et al*. International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev 1997; 49: 253-84.

[3] Watanabe T, Timmerman H, Yanai K, Eds. Histamine research in the new millennium. Amsterdam, Elsevier Science 2001.

[4] Barger G, Dale HM. The presence in ergot and physiological activity of B.iminazoylethylamine. J Physiol Paris 1910; 40: 38-40.

[5] Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev 2008; 88(3): 1183-241.

[6] Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci 2003; 4: 121-30.

[7] Zampeli E, Tiligada E. The role of histamine H4 receptor in immune and inflammatory disorders. Br J Pharmacol 2009; 157: 24-33.

[8] Ohtsu H, Tanaka S, Terui T, Watanabe T. Falus A. Mice lacking histidine decarboxilase exhibit abnormal mast cells. FEBS Letters 2001; 502: 53-6.

[9] Watanabe T, Nakamura H, Liang LY, Yamatodani A, Wada H. Partial purification and characterization of L-Histidine decarboxilase from fetal rat. Biochem Pharmacol. 1979; 28: 1149-55.

[10] Falus A. In: Falus A Ed. Histamine and inflammation. Austin, RG Landes Company. 1994; 33-60.

[11] Buffoni F. Histaminase and related amino oxidases. Pharmacol Rev 1966; 18: 1163-99.

[12] Schwelberger H. In: Falus A Ed, Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 43-52.

[13] Schwelberger. In: Falus A Ed, Histamine: Biology and Medical Aspects. Budapest, Hungary: SpringMed Publishing 2004; 53-9.

[14] Middleton RJ, Martin SA, Bulfield GA. New regulatory gene in the histidine decarboxylase gene complex determines the responsiveness of the mouse kidney enzyme to testosterone. Genet Res 1987; 49: 61-7.

[15] Zahnow CA, Panula P, Yamatodani A, Millhorn DE. Glucocorticoid hormones downregulate histidine decarboxylase mRNA and enzyme activity in rat lungAm J Physiol 1998; 275: L407-13.

[16] Darvas Z, Falus A. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 31-42.

[17] Abe Y, Ogino S, Irifune M, Imamura J, Fukui M, Wada H. Histamine content, synthesis and degradation in human nasal mucosa. Clin Exp Allergy 1993; 23: 132-6.

[18] Pós Z, Hegyesi H, Rivera ES. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 199-217.

[19] Garcia-Caballero M, Brandes L, Hosoda S Eds. Histamine in normal and cancer cell proliferation. Adv. in Bioscience 89. Oxford, Pergamon Press 1993.

[20] Rivera E, Cricco G, Engel N, Fitzsimons C, Martin G, Bergoc R. Histamine as an autocrine growth factor: an unusual role for a widespread mediator. Semin Cancer Biol 2000; 10: 15-23.

[21] Ash AS, Schild HO. Receptors mediating some actions of histamine. Br J Pharmacol Chemother 1966; 27: 427-39.

[22] Black JW, Duncan WA, Durant CJ, Ganellin CR, Parsons EM. Definition and antagonism of histamine H2-receptors. Nature 1972; 236: 385-90.

[23] Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature 1983; 302: 832-7.

[24] Lovenberg TW, Roland BI, Wilson SJ, *et al.* Cloning and functional expression of the human histamine H3 receptor. Mol Pharmacol 1999; 55: 1101-7.

[25] Yamashita M, Fukui H, Sugama K, *et al*. Expression cloning of a cDNA encoding the bovine histamine H1 receptor. Proc Natl Acad Sci U S A 1991; 88: 11515-9.

[26] Gantz I, Munzert G, Tashiro T, *et al*. Molecular cloning of the human histamine H2 receptor. Biochem Biophys Res Commun. 1991; 178: 1386-92.

[27] Gantz I, Schäffer M, DelValle J, *et al*. Molecular cloning of a gene encoding the histamine H2 receptor. Proc Natl Acad Sci U S A. 1991; 88: 429-33.

[28] Nakamura T, Itadani H, Hidaka Y, Ohta M, Tanaka K. Molecular cloning and characterization of a new human histamine receptor, HH4R. Biochem Biophys Res Commun 2000; 279: 615-20.

[29] Nguyen T, Shapiro DA, George SR, *et al*. Discovery of a novel member of the histamine receptor family. Mol Pharmacol 2001; 59: 427-33.

[30] Liu C, MA XJ, Jiang X, *et al*. Cloning and pharmacological characterization of a fourth histamine receptor (H4) expressed in bone marrow. Mol Pharmacol 2001; 59: 420-6.

[31] Oda T, Morikawa N, Saito Y, Masuho Y, Matsumoto S. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. J Biol Chem 2000; 275: 36781-6.

[32] Zhu Y, Michalovich D, Wu H, *et al*. Cloning, expression, and pharmacological characterization of a novel human histamine receptor. Mol Pharmacol 2001; 59: 434-41.

[33] Morse KL, Behan J, Laz TM, *et al*. Cloning and characterization of a novel human histamine receptor. J Pharmacol Exp Ther 2001; 296: 1058-66.

[34] Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy 2002; 32: 489-98.

[35] Akdis CA, Simons FER. Histamine receptors are hot in immunopharmacology. Eur J Pharmacol 2006; 533: 69-76.

[36] van Rijn RM, Chazot PL, Shenton FC, Sansuk K, Bakker RA, Leurs R. Oligomerization of recombinant and endogenously expressed human histamine H(4) receptors. Mol Pharmacol. 2006; 70: 604-15.

[37] Fukushima Y, Asano T, Saitoh T, *et al*. Oligomer formation of histamine H2 receptors expressed in Sf9 and COS7 cells. FEBS Lett 1997; 409: 283-6.

[38] Bongers G, Bakker RA, Leurs R. Molecular aspects of histamine H3 receptor. Biochem Pharmacol 2007; 73: 1195-204.
[39] Bakker RA, Dees G, Carrillo JJ, *et al*. Domain swapping in the human histamine H1 receptor. J Pharmacol Exp Ther 2004; 311: 131-8.
[40] Jablonowski JA, Grice CA, Chai W, *et al*. The first potent and selective non-imidazole human histamine H4 receptor antagonists. J Med Chem 2003; 46: 3957-60.
[41] Leurs R, Chazot PL, Shenton FC, Lim HD, de Esch IJ. Molecular and biochemical pharmacology of the histamine H4 receptor. Br J Pharmacol 2009; 157: 14-23.
[42] Gbahou F, Vincent L, Humbert-Claude M, Tardivel-Lacombe J, Chabret C, Arrang JM. Compared pharmacology of human histamine H3 and H4 receptors: structure-activity relationships of histamine derivatives. Br J Pharmacol 2006; 147: 744-54.
[43] Igaz P, Hegyesi H. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 69-77.
[44] Bakker RA, Schoonus SBJ, Smit MJ, Timmerman H, Leurs R. Histamine H1-receptor activation of nuclear factor-κB; roles for G gamma- and G alpha/11 subunits in constitutive and agonist-mediated signaling. Mol Pharmacol 2001; 60: 1133-42.
[45] Dy M, Schneider E. Histamine-cytokine connection in immunity and hematopoiesis. Cytokine Growth Factor Rev 2004; 15: 393-410.
[46] Schneider E, Rolli-Derkinderen M, Arock M, Dy M. Trends in histamine research: new functions during immune responses and hematopoiesis. Trends Immunol 2002; 23: 255-63.
[47] Lázár-Molnár E. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 89-96.
[48] Davio CA, Cricco GP, Bergoc RM, Rivera ES. H1 and H2 histamine receptors in experimental carcinomas with an atypical coupling to signal transducers. Biochem Pharmacol 1995; 50: 91-6.
[49] Leurs R, Smits MJ, Timmerman H. Molecular pharmacological aspects of histamine receptors. Pharmacol Ther 1995; 66: 413-63.
[50] Smit MJ, Hoffmann M, Timmerman H, Leurs R. Molecular properties and signaling pathways of the histamine H1 receptor. Clin Exp Allergy 1999; 29: 19-28.
[51] Fitzsimons C, Engel N, Policastro L, Durán H, Molinari B, Rivera E. Regulation of phospholipase C activation by the number of H(2) receptors during Ca(2+)-induced differentiation of mouse keratinocytes. Biochem Pharmacol 2002; 63: 1785-96.
[52] Mitsuhashi M, Mitsuhashi T, Payan D. Multiple signaling pathways of histamine H2 receptors. Identification of an H2 receptor-dependent Ca2+ mobilization pathway in human HL-60 promyelocytic leukemia cells. J Biol Chem 1989; 264: 18356-62.
[53] Tardivel-Lacombe J, Morisset S, Gbahou F, Schwartz JC, Arrang JM. Chromosomal mapping and organization of the human histamine H3 receptor gene. Neuroreport 2001; 12: 321-4.
[54] Coge F, Guenin SP, Audinot V, *et al*. Genomic organization and characterization of splice variants of the human histamine H3 receptor. Biochem J 2001; 355: 279-88.
[55] Wellendorph P, Goodman MW, Burstein ES, Nash NR, Brann MR, Weiner DM. Molecular cloning and pharmacology of functionally distinct isoforms of the human histamine H3 receptor. Neuropharmacol 2002; 42: 929-40.
[56] Leurs R, Bakker RA, Timmerman H, de Esch IJP. The histamine H3 receptor: from gene cloning to H3 receptor drugs. Nature Rev 2005; 4: 107-22.
[57] Bakker RA. Histamine H3 receptor isoforms. Inflamm Res 2004; 53: 509-16.
[58] Bakker RA, Lozada AF, Van Marle A, *et al*. Discovery of naturally occurring splice variants of the rat histamine H3 receptor that act as dominant-negative isoforms. Mol Pharmacol 2006; 69: 1194-206.
[59] Hancock AA, Esbenshade TA, Krueger KM, Yao BB. Genetic and pharmacological aspects of histamine H3 receptor heterogeneity. Life Sci 2003; 73: 3043-72.
[60] Hancock AA. The challenge of drug discovery of a GPCR target: analysis of preclinical pharmacology of histamine H3 antagonists/inverse agonists. Biochem Pharmacol 2006; 71: 1103-13.
[61] Krueger KM, Witte DG, Ireland-Denny L, *et al*. G protein-dependent pharmacology of histamine H3 receptor ligands: evidence for heterogeneous active state receptor conformations. J Pharmacol Exp Ther 2005; 314: 271-81.
[62] Cherifi I, Pigeon C, Le romancer M, Bado A, Reyl-Desmars F, Lewin MJM. Purification of a histamine H3 receptor negatively coupled to phosphoinositide turnover in the human gastric cell line HGT1. J Biol Chem 1992; 267: 25315-20.
[63] Huang JF, Thurmond RL. The new biology of histamine receptors. Curr Allergy Asthma Rep 2008; 8: 21-7.
[64] Sander LE, Lorentz A, Sellge G, *et al*. Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract. Gut 2006; 55: 498-504.
[65] Connelly WM, Shenton FC, Lethbridge N, *et al*. The histamine H4 receptor is functionally expressed on neurons in the mammalian CNS. Br J Pharmacol 2009; 157: 55-63.
[66] Breunig E, Michel K, Zeller F, Seidl S, Weyhern CW, Schemann M. Histamine excites neurons in the human submucous plexus through activation of H1, H2, H3 and H4 receptors. J Physiol 2007; 583: 731-42.
[67] Medina V, Cricco G, Nuñez M, *et al*. Histamine-mediated signaling processes in human malignant mammary cells. Cancer Biol Ther 2006; 5: 1462-71.
[68] Medina V, Croci M, Crescenti E, *et al*. The role of histamine in human mammary carcinogenesis: H3 and H4 receptors as potential therapeutic targets for breast cancer treatment. Cancer Biol Ther 2008; 7: 28-35.
[69] Cianchi F, Cortesini C, Schiavone N, *et al.* The role of cyclooxygenase-2 in mediating the effects of histamine on cell proliferation and vascular endothelial growth factor production in colorectal cancer. Clin Cancer Res 2005; 11: 6807-15.
[70] Tiligada E, Zampeli E, Sander K, Stark H. Histamine H3 and H4 receptors as novel drug targets. Expert Opin Investig Drugs 2009; 18: 1519-31.
[71] De Esch JP, Thurmond RL, Jongejan A, Leurs R. The histamine H4 receptor as a new therapeutic target for inflammation. Trends Pharmacol Sci 2005; 26: 462-9.
[72] Coge F, Guenin SP, Rique H, Boutin JA, Galizzi JP. Structure and expression of the human histamine H4-receptor gene. Biochem Biophy Res Commun 2001; 284: 301-9.
[73] van Rijn RM, van Marle A, Chazot PL, *et al*. Cloning and characterization of dominant negative splice variants of the human histamine H4 receptor. Biochem J 2008; 414: 121-31.
[74] Bartholeyns J, Fozard J. Role of histamine in tumor development. Trends Pharmacol Sci 1985: 6: 123-25.
[75] Engel N, Cricco G, Davio C, *et al*. Histamine regulates the expression of histidine decarboxylase in NMU-induced tumors in rats. Inflamm Res 1996; 45: 64-5.
[76] Hegyesi H, Somalí B, Varga VL, *et al.* Suppression of melanoma cell proliferation by histidine decarbolxylase specific antisense oligonucleotides. J Investigative Dermatol 2001; 117: 151-3.
[77] Reynolds JL, Akhter J, Adams WJ, Morris DL. Histamine content in colorectal cancer. Are there sufficient levels of histamine to affect lymphocyte function? Eur J Surg Oncol 1997; 23: 224-7.
[78] Sieja K, Stanosz S, Von Mach-Szczypinski J, Olewniezak S, Stanosz M. Concentration of histamine in serum and tissues of the primary ductal breast cancer in women. Breast 2005; 14: 236-41.
[79] Garcia-Caballero M, Neugebauer E, Campos R, Nuñez de Castro I, Vara-Thorbeck C. Histamine synthesis and content in benign and malignant breast tumors. Surg Oncol 1994; 3: 167-73.
[80] Kierska D, Fogel W, Malinski C. Histamine concentration and metabolism in mouse mammary gland during strous cycle. Inflamm Res 1997; 46: 63-4.
[81] Wagner W, Ichikawa A, Tanaka S, Panula P, Fogel WA. Mouse mammary epithelial histamine system. J Physiol Pharm 2003; 54: 211-23.
[82] Wang LD, Hoeltzel M, Butler B, *et al.* Activation of the human histamine H2 receptor is linked to cell proliferation and c-fos gene transcription. Am J Physiol 1997; 273: C2037-45.
[83] Davenas E, Rouleau A, Morisset S, Arrang JM. Autoregulation of McA-RH7777 hepatoma cell proliferation by histamine H3 receptors. J Pharmacol Exp Ther 2008; 326: 406-13.
[84] Bartholeyns J, Bouclier M. Involvement of histamine in growth of mouse and rat tumors: antitumoral properties of monofluormethylhistidine, an enzyme-activated irreversible inhibitor of histidine decarbolxylase. Cancer Res 1984; 44: 639-45.
[85] Pós Z, Sáfrány G, Müller K, Tóth S, Falus A, Hegyesi H. Phenotypic profiling of engineered mouse melanomas with manipulated histamine production identifies histamine H2 receptor and Rho-c as histamine-regulated melanoma progression markers. Cancer Res 2005; 65: 4458-66.

[86] Kitamura Y, Das AK, Murata Y, *et al*. Dexamethasone suppresses histamine synthesis by repressing both transcription and activity of HDC in allergic rats. Allergol Int 2006; 55: 279-86.

[87] Ohgoh M, Yamamoto J, Kawata M, Yamamura I, Fukui T, Ichikawa A. Enhanced expression of the mouse L-histidine decarboxylase gene with a combination of dexamethasone and 12-O-tetradecanoylphorbol-13-acetate. Biochem Biophys Res Commun 1993; 196: 1113-9.

[88] Igaz P, Falus A. In: Falus A Ed, Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 112-7.

[89] Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. J Allergy Clin Immunol 2003; 112: 15-22.

[90] Marone G, Granata F, Spadaro G, Genovese A, Triggiani M. The histamine–cytokine network in allergic inflammation. J Allergy Clin Immunol 2003; 112: S83-8.

[91] Jutel M, Watanabe T, Akdis M, Blaser K, Akdis CA. Immune regulation by histamine. Curr Opin Immunol 2002; 14: 735-40.

[92] Watt AP, Ennis M. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 99-111.

[93] Xie H, He SH. Roles of histamine and its receptors in allergic and inflammatory bowel diseases. World J Gastroenterol 2005; 11: 2851-7.

[94] Banu Y, Watanabe T. Augmentation of antigen receptor-mediated responses by histamine H1 receptor signaling. J Exp Med 1999; 189: 673-82.

[95] Jutel M, Watanabe T, Klunker S, *et al*. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. Nature 2001; 413: 420-4.

[96] Jutel M, Blaser K, Akdis CA. The role of histamine in regulation of immune responses. Chem Immunol Allergy 2006; 91: 174-87.

[97] Jutel M, Klunker S, Akdis M, *et al*. Histamine upregulates Th1 and downregulates Th2 responses due to different patterns of surface histamine 1 and 2 receptor expression. Int Arch Allergy Immunol 2001; 124: 190-2.

[98] Gantner F, Sakai K, Tusche MW, Cruikshank WW, Center DM, Bacon KB. Histamine H(4) and H(2) receptors control histamine-induced interleukin-16 release from human CD8(+) T cells. J Pharmacol Exp Ther 2002; 303: 300-7.

[99] O'Reilly M, Alpert R, Jenkinson S, *et al*. Identification of a histamine H4 receptor on human eosinophils - role in eosinophil chemotaxis. J Recept Signal Transduct Res 2002; 22: 431-48.

[100] Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther 2003; 305: 1212-21.

[101] Jutel M, Blaser K, Akdis CA. Histamine in chronic allergic responses. J Investig Allergol Clin Immunol 2005; 15: 1-8.

[102] Jutel M, Blaser K, Akdis CA. Histamine receptors in immune regulation and allergen-specific immunotherapy. Immunol Allergy Clin North Am 2006; 26: 245-59.

[103] Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL. The Histamine H4 Receptor Mediates Allergic Airway Inflammation by Regulating the Activation of CD4+ T Cells. J Immunol 2006: 176: 7062-70.

[104] Gutzmer R, Diestel C, Mommert S, *et al*. Histamine H4 receptor stimulation suppresses IL-12p70 production and mediates chemotaxis in human monocyte-derived dendritic cells. J Immunol 2005; 174: 5224-32.

[105] Dy M, Schneider E, Gastinel LN, Auffray C, Mermod JJ, Hamburger J. Histamine-producing cell-stimulating activity. A biological activity shared by interleukin 3 and granulocyte-macrophage colony stimulating factor. Eur J Immunol 1987; 17: 1243-8.

[106] Schneider E, Pollard H, Lepault F, Guy-Grand D, Minkowski M, Dy M. Histamine-producing cell-stimulating activity: interleukin 3 and granulocyte-macrophage colony-stimulating factor induce de novo synthesis of histidine decarboylase in hemopoietic progenitor cells. J Immunol 1987; 139: 3710-7.

[107] Yamaguchi K, Motegi K, Endo Y. Induction of histidine decarboxylase, the histamine-forming enzyme, in mice by interleukin-12. Toxicology 2000; 156: 57-65.

[108] Yamaguchi K, Motegi K, Kurimoto M, Endo Y. Induction of the activity of the histamine-forming enzyme, histidine decarboxylase, in mice by IL-18 and by IL-18 plus IL-12. Inflamm Res 2000; 49: 513-9.

[109] Schneider E, Lemoine F, Breton-Gorius J, *et al*. IL-3-induced coexpression of IL-4, IL-6 and histidine decarboxylase mRNA in basophilic myelocytes enriched in sorted-Rh-bright bone marrow cells. Exp Haematol 1999; 27: 1010-8.

[110] Abbas AK, Lichtman AH, Pober JS, Eds. Cellular and molecular immunology. Philadelphia: WB Saunders Company; 2000.

[111] Szeberényi JB, Pállinger E, Zsinkó M, *et al*. Inhibition of effects of endogenously synthesized histamine disturbs *in vitro* human dendritic cell differentiation. Immunol Lett 2001; 76: 175-82.

[112] Idzdo M, La Sala A, Ferrari D, *et al*. Expression and function of histamine receptors in human monocyte-derived dendritic cells. J Allergy Clin Immunol 2002; 109: 839-46.

[113] Caron G, Delneste Y, Roelandts E, *et al*. Histamine induces CD86 expression and chemokine production by human immature dendritic cells. J Immunol 2001; 166: 6000-6.

[114] Gutzmer R, Langer K, Lisewski M, *et al*. Expression and function of histamine receptors 1 and 2 on human monocyte-derived dendritic cells. J Allergy Clin Immunol 2002; 109: 524-31.

[115] Mazzoni A, Young HA, Spitzer JH, Visintin A, Segal DM. Histamine regulates cytokine production in maturing dendritic cells, resulting in altered T cell polarization. J Clin Invest 2001; 108: 1865-73.

[116] van der Pouw Kraan TC, Snijders A, Boeije LC, *et al*. Histamine inhibits the production of interleukin-12 through interaction with H2 receptors. J Clin Invest 1998; 102: 1866-73.

[117] Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL. Histamine potently suppresses human IL-12 and stimulates IL-10 production *via* H2 receptors. J Immunol 1998; 161: 2586-93.

[118] Takahashi HK, Iwagaki H, Mori S, Yoshino T, Tanaka N, Nishibori M. Histamine inhibits lipopolysaccharide-induced interleukin (IL)-18 production in human monocytes. Clin Immunol 2004; 112: 30-4.

[119] Vannier E, Dinarello CA. Histamine enhances interleukin (IL)-1-induced IL-1 gene expression and protein synthesis *via* H2 receptors in peripheral blood mononuclear cells. Comparison with IL-1 receptor antagonist. J Clin Invest 1993; 92: 281-7.

[120] Morichika T, Takahashi HK, Iwagaki H, *et al*. Histamine inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production in an intercellular adhesion molecule-1- and B7.1-dependent manner. J Pharmacol Exp Ther 2003; 304: 624-33.

[121] Mazzoni A, Leifer CA, Mullen GED, Kennedy MN, Klinman DM, Segal DM. Cutting edge: histamine inhibits IFN-a release from plasmacytoid dendritic cells. J Immunol 2003; 170: 2269-73.

[122] Ohtani T, Aiba S, Mizuashi M, Mollah ZU, Nakagawa S, Tagami H. H1 and H2 histamine receptors are absent on Langerhans cells and present on dermal dendritic cells. J Invest Dermatol 2003; 121: 1073-9.

[123] Dijkstra D, Leurs R, Chazot P, *et al*. Histamine downregulates monocytes CCL2 production through the histamine H4 receptor. J Allergy Clin Immunol 2007; 120: 300-7.

[124] Dijkstra D, Stark H, Chazot PL, *et al*. Human inflammatory dendritic epidermal cells express a functional histamine H4 receptor. J Invest Dermatol 2008; 128: 1696-703.

[125] Maghazachi AA, Al-Aoukaty A. Chemokines activate natural killer cells through heterotrimeric G-proteins: implications for the treatment of AIDS and cancer. FASEB J 1998; 12: 913-24.

[126] Damaj BB, Barrena Becerra C, Esber HJ, Wen Y, Maghazachi AA. Functional Expression of H4 Histamine Receptor in Human Natural Killer Cells, Monocytes, and Dendritic Cells. J Immunol 2007; 179: 7907-15.

[127] Byron JW. Mechanism for histamine H2-receptor induced cell-cycle changes in the bone marrow stem cell. Agents Actions 1977; 7: 209-13.

[128] Nakaya N, Tasaka K. The influence of histamine on precursor of granulocytic leukocytes in murine bone marrow. Life Sci 1999; 42: 999-1010.

[129] Scheneider E, Dy M. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 226-39.

[130] Schneider E, Piquet-Pellorce C, Dy M. New role for histamine in interleukin-3 induced proliferation of hematopoietic stem cells. J Cell Physiol 1990; 143: 337-43.

[131] Piquet-Pellorce C, Schneider E, Dy M. GM-CSF in association with IL-1 triggers day-8 CFU-S into cell cycle: role of histamine. J Cell Physiol 1991; 149:18.

[132] Ohtsu H, Tanaka S, Terui T, *et al*. Mice lacking histidine decarboxylase exhibit abnormal mast cells. FEBS Lett 2001; 502: 53-6.

[133] Horvath Z, Pallinger E, Horvath G, Jelinek I, Falus A, Buzas EI. Histamine H1 and H2 receptors but not H4 receptors are upregulated during bone marrow regeneration. Cell Immunol 2006; 244: 110-5.

[134] Wiener Z, Andrásfalvy M, Pállinger E, *et al*. Bone marrow-derived mast cell differentiation is strongly reduced in histidine decarboxylase knockout, histamine-free mice. Int Immunol 2002; 14: 381-7.

[135] Aglietta M, Stacchini A, Sanavio F, Piacibello W. H2 receptor antagonists and human granulopoiesis. Experientia 1985; 41: 375-6.

[136] Fitchen JH, Koeffler HP. Cimetidine and granulopoiesis: bone marrow culture studies in normal man and patients with cimetidine-associated neutropenia. Br J Haematol 1980; 46: 361-6.

[137] Byron JW. Pharmacodynamic basis for the interaction of cimetidine with the bone marrow stem cells (CFUS). Exp Hematol 1980; 8: 256-63.

[138] Aymard JP, Aymard B, Netter P, Bannwarth B, Trechot P, Streiff F. Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol Adverse Drug Exp 1988; 3: 430-48.

[139] Opgen-Rhein C, Dettling M. Clozapine-induced agranulocytosis and its genetic determinants. Pharmacogenomics 2008; 9: 1101-11.

[140] Ghaznavi S, Nakic M, Rao P, *et al*. Rechallenging with clozapine following neutropenia: treatment options for refractory schizophrenia. Am J Psychiatry 2008; 165: 813-8.

[141] Petit-Bertron AF, Machavoine F, Defresne MP, *et al.* H4 histamine receptors mediate cell cycle arrest in growth factor-induced murine and human hematopoietic progenitor cells. PLoS One 2009; 4:e6504.

[142] Akdis CA, Jutel M, Akdis M. Regulatory effects of histamine and histamine receptor expression in human allergic immune responses. Chem Immunol Allergy 2008; 94: 67-82.

[143] Thurmond RL, Desai PJ, Dunford PJ, *et al*. A Potent and Selective Histamine H4 Receptor Antagonist with Anti-Inflammatory Properties. JPET 2004; 309: 404-13.

[144] Herjavecz I, Hirschberg A. In: Falus A Ed. Histamine: Biology and Medical Aspects. Budapest, SpringMed Publishing 2004; 140-58.

[145] Bayram H, Devalia JL, Khair OA, *et al*. Effect of loratadine on nitrogen dioxide-induced changes in electrical resistance and release of inflammatory mediators from cultured human bronchial epithelial cells. J Allergy Clin Immunol 1999; 104: 93-9.

[146] Jeannin P, Delneste Y, Gosset P, *et al*. Histamine induces interleukin-8 secretion by endothelial cells. Blood 1994; 84: 2229-33.

[147] Meretey K, Falus A, Taga T, Kishimoto T. Histamine influences the expression of the interleukin-6 receptor on human lymphoid, monocytoid and hepatoma cell lines. Agents Actions 1991; 33: 189-91.

[148] Igaz P, Novák I, Lázaár E, Horváth B, Héninger E, Falus A. Bidirectional communication between histamine and cytokines. Inflamm Res. 2001; 50: 123-8.

[149] Fujikura T, Shimosawa T, Yakuo I. Regulatory effect of histamine H1 receptor antagonist on the expression of messenger RNA encoding CC chemokines in the human nasal mucosa. J. Allergy Clin Immnol 2001; 107: 123-8.

[150] Katoh N, Soga F, Nara T, Masuda K, Kishimoto S. Histamine Induces the Generation of Monocyte-Derived Dendritic Cells that Express CD14 but not CD1a. J Invest Dermatol 2005; 125: 753 - 60.

[151] Kubes P, Kanwar S. Histamine induces leukocyte rolling in post-capillary venules. A P-selectin-mediated event. J Immunol 1994; 152: 3570-7.

[152] Yamaki K, Thorlacius H, Xie X, Lindbom L, Hedqvist P, Raud J. Characteristics of histamine-induced leukocyte rolling in the undisturbed microcirculation of the rat mesentery. Br J Pharmacol 1998; 123: 390-9.

[153] Schaefer U, Schmitz V, Schneider A, Neugebauer E. Histamine induced homologous and heterologous regulation of histamine receptor subtype mRNA expression in cultured endothelial cells. Shock 1999; 12: 309-15.

[154] Clark RA, Sandler JA, Gallin JI, Kaplan AP. Histamine modulation of eosinophil migration. J Immunol 1977; 118: 137-45.

[155] Seligmann BE, Fletcher MP, Gallin JI. Histamine modulation of human neutrophil oxidative metabolism, locomotion, degranulation, and membrane potential changes. J Immunol 1983; 130: 1902-9.

[156] Hirasawa N, Ohtsu H, Watanabe T, Ohuchi K. Enhancement of neutrophil infiltration in histidine decarboxylase-deficient mice. Immunology 2002; 107: 217-21.

[157] Jutel M, Blaser K, Akdis CA. Histamine in allergic inflammation and immune modulation. Int Arch Allergy Immunol 2005; 137: 82-92.

[158] Packard KA, Khan MM. Effects of histamine on Th1/Th2 cytokine balance. Int Immunopharmacol 2003; 3: 909-20.

[159] Brightling CE, Bradding P. The re-emergence of the mast cell as a pivotal cell in asthma pathogenesis. Curr Allergy Asthma Rep 2005; 5: 130-5.

[160] Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. Nat Rev Drug Discov 2008; 7:41-53.

[161] Bäumer W, Wendorff S, Gutzmer R, *et al*. Histamine H4 receptors modulate dendritic cell migration through skin-immunomodulatory role of histamine. Allergy 2008; 63: 1387-94.

[162] Buckland KF, Williams TJ, Conroy DM. Histamine induces cytoskeletal changes in human eosinophils *via* the H4 receptor. Br J Pharmacol 2003; 140:1117-27.

[163] Ling P, Ngo K, Nguyen S, *et al*. Histamine H4 receptor mediates eosinophil chemotaxis with cell shape change and adhesion molecule upregulation. Br J Pharmacol 2004; 142: 161-71.

[164] Leszczyniecka M, Roberts T, Dent P, Grant S, Fisher P. Differentiation therapy of human cancer: basic science and clinical applications. Pharmacol Ther 2001; 90: 105-56.

[165] Mitchell MS. Immunotherapy as part of combinations for the treatment of cancer. Int Immunopharmacol 2003; 3: 1051-9.

[166] Stadtmauer EA. Histamine dihydrochloride and interleukin-2 in the treatment of acute myeloid leukemia. Semin Oncol 2002; 29: 47-51.

[167] Hellstrand K. Histamine in cancer immunotherapy: a preclinical background. Semin Oncol 2002; 29: 35-40.

[168] Galmarini CM. Histamine dihydrochloride (subcutaneous) Maxim. Curr Opinion Investig Drugs 2004; 5: 1298-310.

[169] Perz JB, Ho AD. Histamine dihydrochloride for the treatment of acute myeloid leukemia, malignant melanoma and renal cell carcinoma. Future Oncol 2008; 4: 169-77.

[170] Agarwala SS, Sabbagh MH. Histamine dihydrochloride: inhibiting oxidants and synergising IL-2-mediated immune activation in the tumour microenvironment. Expert Opinion Biol Ther 2001; 1: 869-79

[171] Naredi P. Histamine as an adjunct to immunotherapy. Semin Oncol 2002; 29: 31-4.

[172] Hellstrand K, Hansson M, Hermodsson S. Adjuvant histamine in cancer immunotherapy. Semin Cancer Biol 2000; 10: 29-39.

[173] Romero AI, Thoren FB, Aurelius J, Askarieh G, Brune M, Hellstrand K. Post-consolidation immunotherapy with histamine dihydrochloride and interleukin-2 in AML. Scand J Immunol 2009; 70: 194-205.

[174] Hellstrand K, Brune M, Dahlgren C, *et al*. Alleviating oxidative stress in cancer immunotherapy: a role for histamine? Med Oncol 2000; 17: 258-69.

[175] Agarwala SS, Hellstrand K, Gehlsen K, Naredi P. Immunotherapy with histamine and interleukin 2 in malignant melanoma with liver metastasis. Cancer Immunol Immunother 2004; 53: 840-1.

[176] Asemissen AM, Scheibenbogen C, Letsch A, *et al*. Addition of histamine to interleukin 2 treatment augments type 1 T-cell responses in patients with melanoma *in vivo*: immunologic results from a randomized clinical trial of interleukin 2 with or without histamine (MP 104). Clin Cancer Res 2005; 11: 290-7.

[177] O'Day SJ, Agarwala SS, Naredi P, Kass CL, Gehlsen KR, Glaspy J. Treatment with histamine dihydrochloride and interleukin-2 in patients with advanced metastatic malignant melanoma: a detailed safety analysis. Melanoma Res 2003; 13: 307-11.

[178] Middleton M, Hauschild A, Thomson D, *et al*. Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with interleukin-2, interferon-{alpha}2b and histamine dihydrochloride *vs* dacarbazine in patients with stage IV melanoma. Ann Oncol 2007; 18: 1691-7.

[179] Thorén FB, Romero AI, Brune M, Hellstrand K. Histamine dihydrochloride and low-dose interleukin-2 as post-consolidation immunotherapy in acute myeloid leukemia. Expert Opin Biol Ther 2009; 9: 1217-23.

[180] Brune M, Castaigne S, Catalano J, *et al*. Improved leukemia-free survival after postconsolidation immunotherapy with histamine

dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood 2006; 108: 88-96.

[181] Donskov F, Hokland M, Marcussen N, Torp Madsen HH, von der Maase H. Monocytes and neutrophils as 'bad guys' for the outcome of interleukin-2 with and without histamine in metastatic renal cell carcinoma--results from a randomised phase II trial. Br J Cancer 2006; 94: 218-26.

[182] Donskov F, Middleton M, Fode K, *et al*. Two randomised phase II trials of subcutaneous interleukin-2 and histamine dihydrochloride in patients with metastatic renal cell carcinoma. Br J Cancer 2005; 93: 757-62.

[183] Donskov F, von der Maase H, Henriksson R, *et al*. Outpatient treatment with subcutaneous histamine dihydrochloride in combination with interleukin-2 and interferon-alpha in patients with metastatic renal cell carcinoma: results of an open single-armed multicentre phase II study. Ann Oncol 2002; 13: 441-9.

[184] Barcellos-Hoff MH, Park C, Wright EG. Radiation and the microenvironment tumorigenesis and therapy. Nature 2005; 5: 867-74.

[185] Grdina DJ, Murley JS, Kataoka Y. Radioprotectans: current status and new directions. Oncology 2002; 63: 2-10.

[186] Hall EJ, Giaccia AJ. In: Hall EJ, Giaccia AJ, Eds, Radiobiology for radiobiologists. Philadelphia, Lippincott Williams and Wilkins 2006; 129-34.

[187] Dziegielewski J, Baulch JE, Goetz W, *et al*. WR-1065, the active metabolite of amifostine, mitigates radiation-induced delayed genomic instability. Free Radic Biol Med 2008; 45: 1674-81.

[188] Weichselbaum R. Radiation's outer limits. Nat Med 2005; 11: 477-8.

[189] Hall EJ, Giaccia. In: Hall EJ, Giaccia AJ, Eds. Radiobiology for radiobiologists. Philadelphia, Lippincott Williams and Wilkins 2006; 303-326.

[190] Betzen SM, Overgaard J. In: Steel GG, Ed, Basic Clinical Radiobiology. New York, Oxford University press, Inc. 1997; 87-97.

[191] Hall EJ, Giaccia AJ. In: Hall EJ, Giaccia AJ, Eds, Radiobiology for radiobiologists. Philadelphia, Lippincott Williams and Wilkins 2006; 327-348.

[192] Emami B, Lyman J, Brown A, *et al*. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109-22.

[193] Medina V, Croci M, Mohamad N, *et al*. Mechanisms underlying the radioprotective effect of histamine on small intestine. Int J Radiat Biol 2007; 83: 653-63.

[194] Potten CS, Wilson JW, Booth C. Regulation and significance of apoptosis in the stem cells of the gastrointestinal epithelium. Stem Cells 1997; 15: 82-93.

[195] Potten CS. Stem cells in gastrointestinal epithelium: numbers, characteristics and death. Philos Trans R Soc Lond B Biol Sci 1998; 353: 821-30.

[196] Potten CS, Owen G, Booth D. Intestinal stem cells protect their genome by selective segregation of template DNA strands. J Cell Sci 2002; 115: 2381-8.

[197] Medina V, Croci C, Carabajal E, Bergoc RM, Rivera ES. Histamine protects bone marrow against cellular damage induced by ionizing radiation. Int J Radiat Biol 2010; 86: 283-90.

[198] Nagler RM. The enigmatic mechanism of irradiation-induced damage to the major salivary glands. Oral Dis 2002; 8: 141-6.

[199] Valdez IH, Atkinson JC, Ship JA, *et al*. Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. Int J Radiat Oncol Biol Phys 1993; 25: 41-7.

[200] Vissink A, Jansma J, Spijkervet FKL, *et al*. Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med 2003; 14: 199-212.

[201] Burlage FR, Coppes RP, Meertens H, *et al*. Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. Radiother Oncol 2001; 31: 271-3.

[202] Burlage FR, Roesink JM, Kampinga HH, *et al*. Protection of salivary function by concomitant pilocarpine during radiotherapy: a double-blind, randomized, placebo-controlled study. Int. J. Radiat Oncol Biol Phys 2008; 70: 14-22.

Received: September 22, 2009 Revised: September 25, 2009 Accepted: October 8, 2009