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INVITED REVIEW

Histamine in cancer immunology and immunotherapy. Current status and new perspectives

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Abstract

Cancer is the second leading cause of death globally and its incidence and mortality are rapidly increasing worldwide. The dynamic interaction of immune cells and tumor cells determines the clinical outcome of cancer. Immunotherapy comes to the forefront of cancer treatments, resulting in impressive and durable responses but only in a fraction of patients. Thus, understanding the characteristics and profiles of immune cells in the tumor microenvironment (TME) is a necessary step to move forward in the design of new immunomodulatory strategies that can boost the immune system to fight cancer. Histamine produces a complex and fine-tuned regulation of the phenotype and functions of the different immune cells, participating in multiple regulatory responses of the innate and adaptive immunity. Considering the important actions of histamine-producing immune cells in the TME, in this review we first address the most important immunomodulatory roles of histamine and histamine receptors in the context of cancer development and progression. In addition, this review highlights the current progress and foundational developments in the field of cancer immunotherapy in combination with histamine and pharmacological compounds targeting histamine receptors.

KEYWORDS
adaptive immunity, anti-tumor immunity, breast cancer, histamine receptors, immunotherapy, innate immunity, leukemia

Abbreviations: AC, adenylate cyclase; AML, acute myeloid leukemia; AOM, azoxymethane; APCs, professional antigen-presenting cells; Bregs, regulatory B cells; cAMP, cyclic adenosine monophosphate; cDCs, conventional DCs; CML, chronic myeloid leukemia; CNS, central nervous system; CR, complete remission; CRC, colorectal cancer; CREB, cAMP response element-binding protein; CTLA-4, cytotoxic T lymphocyte antigen 4; CXCL1, C-X-C motif chemokine ligand 1; CXCL10, C-X-C motif chemokine ligand 10; CXCL2, C-X-C motif chemokine ligand 2; DAO, diamine oxidase; DCs, dendritic cells; DSS, dextran sulfate sodium; EPO, eosinophil peroxidase; ErbB-2, human epidermal growth factor receptor 2; FcεRI, receptor for immunoglobulin E; FoxP3, transcription factor forkhead box P3; GTP, guanosine triphosphate; H_4 receptor KO, H_4 receptor knockout mice; HDC, histamine dihydrochloride; IFN, interferon; IFNα, interferon alfa; IFNγ, interferon γ; IgE, immunoglobulin E; LFS, leukemia-free survival; MAPK, mitogen-activated protein kinase; MBP, major basic protein; MDSCs, myeloid-derived suppressor cells; MHC I, class 1 major histocompatibility complex; MHC II, class 2 major histocompatibility complex; Mo, monocytes; moDCs, monocyte-derived DCs; MRP, resistance-associated protein; MSI, microsatellite instability; NCR, natural cytotoxicity receptors; NETs, neutrophil extracellular traps; NHL, non-Hodgkin lymphomas; NK, natural killer; NKT, natural killer T cell; OS, overall survival; PC, plasma cell; PD-1, programmed dead 1; pDCs, plasmacytoid DCs; PD-L1, programmed-death 1 ligand; PGD2, prostaglandin D2; PKA, protein kinase A; PLC, phospholipase C; RCC, renal cell carcinoma; ROS, reactive oxygen species; TABE, peripheral blood eosinophilia; TAMs, tumor-associated macrophages; TANs, tumor-associated neutrophils; TATE, tumor-associated tissue eosinophils; T-bet, transcription factor T-box; TDLN, tumor draining lymph nodes; TGFβ, transforming growth factor β; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TNFα, tumor necrosis factor α; Tregs, regulatory T cells; uPA, urokinase plasminogen activator; WT, wild type.

1 | INTRODUCTION

Cancer is the second leading cause of death globally and its incidence and mortality are rapidly increasing worldwide.[1] Although advances in cancer research result in improved anti-tumor targeted therapies, they continue to have variable outcomes, associated with limited response and severe toxicity thus, several patients will suffer from overwhelming morbimortality. Extraordinary advances in the understanding of the interactions between the immune system and cancer cells have been made in the last decade, which led to the development of effective and promising immunotherapies targeting different tumor molecules and their interaction with the tumor microenvironment (TME). Consequently, immune checkpoint inhibitors were developed to successfully enhance anti-tumor T-cell features but resulted in durable responses only in a fraction of patients. The dynamic interaction of immune cells and tumor cells determines the clinical outcome of cancer and it can be reshaped by cancer immunotherapies. One of the most important topics in cancer immunology research today is to understand the characteristics and profiles of immune cells in the TME to design new immunomodulatory strategies that can boost the immune system to fight cancer.

Even though histamine has been the first inflammatory biogenic amine to be characterized, novel functions of histamine are still being described. In this sense, the discovery of the histamine H_4 receptor by several groups in 2000/2001 significantly expanded the research field. Histamine is one of the most widely investigated molecules in biomedicine and all histamine receptor subtypes constitute well-established or promising drug targets.[2,3]

Importantly, histamine is a major mediator responsible for multiple regulatory responses of innate and adaptive immunity[4–6] (Figure 1). Immune cells that are key participants in the TME can synthesize, release and respond to histamine.

Furthermore, there is increasing evidence indicating that histamine can modulate cell proliferation and differentiation of normal and malignant cells. High histamine biosynthesis and content have been found in different human tumors including melanoma, colon, and breast cancer, as well as in experimental cancer models. Histamine can be released to the extracellular medium and through a paracrine or autocrine regulation, it may regulate diverse biological responses related to tumor growth (reviewed in Refs. [4,7]). From cell lines to animal models and human clinical studies, an overwhelming amount of data supports the relevance of histamine receptors in cancer development and progression. Both pro-tumor and

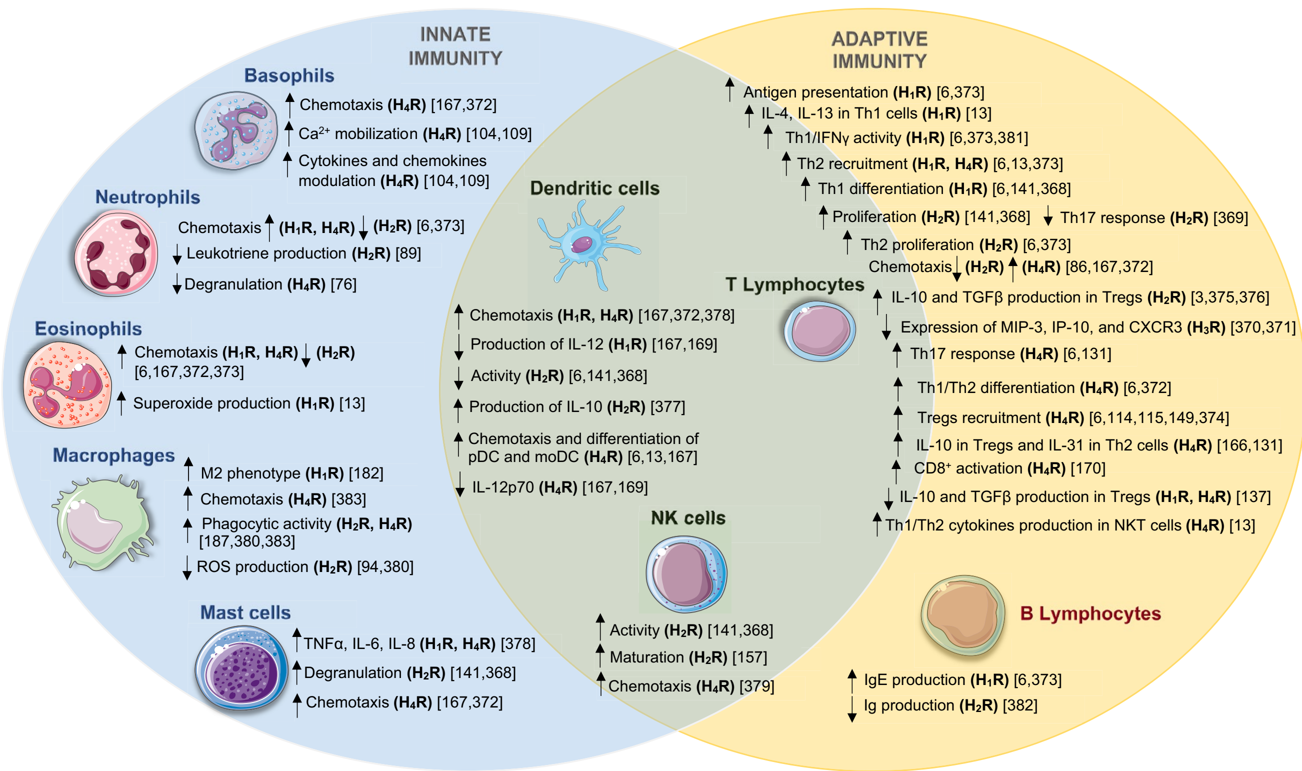


FIGURE 1 Immunomodulatory effects mediated by histamine receptor signaling in innate and adaptive immunity. The binding of histamine to its receptors can modulate the function of the immune cells, including neutrophils, eosinophils, basophils, mast cells, dendritic cells (DCs), natural killer (NK) cells, NKT cells; Th1-, Th2-, Th17-, regulatory $CD4^+$ T-, $CD8^+$ cytotoxic T cells, and B cells. The participation of the different histamine receptor subtypes in each cell subsets was determined through functional assays and the use of pharmacological compounds. CxCR3, C-X-C Motif Chemokine Receptor 3; IL, interleukin; IFNγ, interferon gamma; IP-10, IFN-inducible protein 10; M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages; MIP-3, macrophage inflammatory protein 3; moDC, monocyte-derived dendritic cells; NKT, invariant natural killers T cells; pDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; TGFβ, transforming growth factor-beta; TNFα, tumor necrosis factor-alpha; Tregs, T regulatory cells

anti-tumor effects of histamine receptors have been described depending on the cancer type and other important factors. Differences in histamine metabolism, TME, the concentration of histamine in the tissue, and the activation of histamine receptors may determine the biological responses in diverse neoplasias.[4,7–13] These events include angiogenesis, cell proliferation, invasion, migration, differentiation, apoptosis, and also the modulation of the immune response, indicating that histamine may be a crucial mediator in cancer formation and dissemination.

Additionally, histamine receptors are differentially expressed in benign lesions or healthy tissues compared to malignant lesions in diverse cancers, including melanoma, cholangiocarcinoma, oral, and colorectal cancers.[7,14,15] The expression of different histamine receptor subtypes, such as H_1 and H_4, was associated with clinicopathological characteristics and tumor grade in different neoplasias, reinforcing the role of the histaminergic system in carcinogenesis. Therefore, in addition to a direct effect of histamine through tumor cell-intrinsic mechanisms involving activation of histamine receptors in cancer cells (reviewed in Refs. [4,7,8]), histamine could contribute to the modulation of TME by regulating immune-mediated effects.

The purpose of this review was to address the most recent findings on the immunomodulatory role of histamine and its receptors in the complex anti-tumor immunity. In addition, this review compiles the most up-to-date data supporting the potential use of histamine as an adjuvant to cancer immunotherapy.

2 | HISTAMINE RECEPTORS

Histamine [2-(4-imidazolyl)-ethylamine; β-imidazolylethylamine] is an endogenous biogenic amine that is synthesized by histidine decarboxylase-mediated decarboxylation of the amino acid L-histidine. It is catabolized intracellularly by the histamine N-methyltransferase and extracellularly by the diamine oxidase.[2,16] Histamine is ubiquitously distributed in mammalian cells, and it exerts pleiotropic effects as a result of the existence of four G-protein-coupled histamine receptor subtypes that trigger distinct signaling cascades and are differentially expressed throughout the tissues.

Histamine receptors are named in the order in which they were discovered: H_1, H_2, H_3, and H_4 receptors, and have different histamine-binding affinities.[17–25] All four receptors show a balance between their inactive and active conformation and present constitutive activity, leading to a re-classification of some antagonists into inverse agonists.[25] To add more complexity to the matter, it has been shown that histamine receptors can appear as homo and hetero-oligomers, which influences the repertoire of physiological and pharmacological effects.[26–31]

The H_1 receptor is a Gαq/11-coupled protein receptor, which stimulates the phospholipase C (PLC) to generate inositol 1,4,5-triphosphate and 1,2-DAG leading to an increase in cytosolic Ca^{2+}. Besides, it can produce cyclic adenosine monophosphate (cAMP) accumulation via Gβγ subunits of Gq.[25–32] It is ubiquitously distributed and plays a key role in smooth muscle contraction, stimulates nitric oxide formation, and increases vascular permeability, showing numerous roles in inflammatory processes in allergic disorders.[33] As expected, H_1 receptor antagonists/inverse agonists, including mepyramine, fexofenadine, loratadine, diphenhydramine, and astemizol are widely used for the treatment of allergic diseases.[34,35]

Similar to H_1, H_2 receptor is expressed in almost all peripheral tissues as well as in the central nervous system (CNS). The H_2 receptor is coupled to adenylate cyclase (AC) and its stimulation enhances the amounts of cAMP and downstream effects mediated by protein kinase A (PKA) and the transcription factor cAMP-response element-binding protein (CREB). However, using a different GTP-dependent mechanism, H_2 receptor also modulates phosphoinositide second messenger system.[25,36] Many of the H_1 receptor-mediated effects can be balanced by the H_2 receptor, including the relaxation of smooth muscle cells, causing vasodilation. The H_2 receptor activation causes marked chronotropic and inotropic effects in the heart and induces gastric acid production from parietal cells in the gastric mucosa. Most H_2 receptor antagonists/inverse agonists including cimetidine, famotidine, and nizatidine are clinically used to inhibit histamine-induced gastric acid secretion.[34,35]

It is important to point out that in recombinant and native systems in which H_1 and H_2 receptors are coexpressed, cross-regulation of both pathways including cross-desensitization of the receptors and their responses occurs when cells are exposed to a sustained stimulus with H_1 receptor or H_2 receptor agonists.[37–39]

The H_3 receptor is a Gαi/0-coupled protein receptor, and its activation leads to inhibition of cAMP formation, accumulation of Ca^{2+}, and stimulation of the MAPK pathway.[40,41] Although primarily described in the CNS, it is additionally found in other tissues including some immune cells.[5,42] The H_3 receptor acts as an autoreceptor and heteroreceptor, regulating the release of histamine from histaminergic neurons and of various other neurotransmitters. Thus, the H_3 receptor blocking ligands are promising agents for the treatment of CNS disorders, obesity, sleep disorders, Alzheimer's disease, and schizophrenia.[43–47] Pitolisant is a first-in-class FDA-approved agent for the treatment of daytime sleepiness in adults with narcolepsy by acting as an antagonist/inverse agonist at the H_3 receptor.[34,35,48]

The H_4 receptor is a Gαi/0-coupled protein receptor that is predominantly expressed in cells of the immune system and is involved in immunomodulatory pathways. The expression of H_4 receptor has been detected in various tissues including the spleen, thymus, lung, small and large intestines, and also cancer cells.[8,49–52] Activation of H_4 receptor leads to the inhibition of AC and downstream cAMP-responsive elements as well as the activation of MAPK and PLC with Ca^{2+} mobilization.[25,34,35,41] Numerous in vivo studies have demonstrated that the H_4 receptor plays an important role in inflammation and pruritus. Clinical trials are already in the way to assess the effectiveness of various H_4 receptor antagonists.[8,53–57] In a phase IIa study in Japanese adult patients with moderate atopic dermatitis, JNJ39758979 (100 or 300 mg daily orally administered for 6 weeks) was effective in ameliorating pruritus and eczema but it showed agranulocytosis, a life-threatening side effect, which seemed to be an off-target effect.[53,58] Although toreforant (JNJ38518168), another H_4 receptor antagonist with a different chemical structure to avoid the agranulocytosis-associated side effect, failed to improve uncontrolled, eosinophilic asthma (30 mg per day for 24 weeks),[54,56] it produced a greater response than placebo in patients with moderate-to-severe psoriasis (30 and 60 mg per day).[59] In addition, toreforant (100 mg once daily orally administered for 12 weeks) reduced the signs and the symptoms of rheumatoid arthritis in a phase IIa study, but these could not be confirmed in a phase IIb trial.[60] Recently, the selective H_4 receptor antagonist adriforant (ZPL-3893787, 30 mg administered orally for 8 weeks) was well tolerated and improved eczema and severity in patients with moderate to severe atopic dermatitis.[57,61]

Histamine and its four receptors represent a complex axis with multiple regulatory functions in the innate and adaptive immunity. These functions depend on the receptor subtypes involved and their differential expression and associated signaling. Therefore, in addition to histamine's classical roles in the inflammatory process, it is also recognized as a vital player in immunoregulation, balancing extensive and opposed effects in the immune system.

A summary of the distinct immunoregulatory impacts that histamine produces through its binding to each of the four subtypes of histamine receptors is depicted in Figure 1.

3 | HISTAMINE MODULATION OF THE ANTI-TUMOR IMMUNITY

Cancer is a heterogeneous and multi-faceted disease, characterized by uncontrolled cell proliferation, evasion of growth suppressors and the immune response, avoidance of apoptosis, sustained replicative potential and angiogenesis, reprogramming of energy metabolism, genetic and epigenetic instability, tissue invasion and metastasis, and enhanced inflammation, which collectively dictate tumor progression.[62,63] Besides being a hallmark of cancer, inflammation might also contribute to the establishment of other alterations described by Hanahan and Weinberg. Infiltration of both innate and adaptive immune cells and a molecular network of soluble mediators are two key constituents of cancer-associated inflammation.[62,63] In this regard, the complexity of cancer goes beyond the neoplastic cells and includes the TME, which is defined as the collection of cells, molecules, and vasculature that surrounds the tumor, and it is specifically adapted in response to disease. The composition of TME changes during the tumor evolution affecting the early stages of cancer progression as well as the formation of distant metastasis.

The immune system comprises a dynamic network of cells, tissues, and organs that participate in the two lines of defense called innate and adaptive immunity. Immune cells are important components of the TME because, on the one hand, they can eliminate tumor cells and, on the other hand, they can provide the necessary conditions to facilitate tumor growth and progression, which highlights the dichotomous nature of the immune system.[62,64,65] This process is called immunoediting and refers to the ability of immune cells to intervene in the elimination of tumor cells (immunosurveillance) and, at the same time, shape the immunogenicity of tumors favoring their growth and progression (immunotolerance).[64,66] Cancer immunoediting is a dynamic process that consists of three phases: elimination, equilibrium, and escape.

In the elimination phase, the immune system detects and eliminates tumor cells that develop due to failures in their intrinsic mechanisms of tumor suppression. The elimination can be complete, meaning no tumor cells remain, or incomplete, when only a portion of them is eliminated. In the latter case, tumor cells enter an equilibrium phase, where they evolve and accumulate changes that modulate the expression of tumor antigens. In this phase, the immune system continues to act and eliminate susceptible tumor clones. However, resistant cell variants that could avoid or suppress immunity may develop, leading to the escape phase, thus allowing tumor progression.[62,64,66]

The balance between immunological surveillance and tolerance is determined by a complex interplay between different types of immune cells in the TME that include macrophages, neutrophils, mast cells, natural killer (NK) cells, dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), B cells, and different subtypes of T cells (Table 1).

In the last decades, advances in tumor immunology contributed to shed light on the complex mechanisms regulating cellular immune responses during cancer progression. However, the dynamic relationship between the immune system and tumor cells, which determines the clinical outcome of the disease and how it is reshaped by cancer therapy, is far from being fully understood. New research is necessary to achieve tumor control using multidisciplinary approaches.

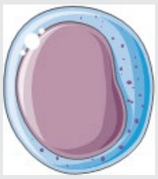
Histamine is considered one of the most important mediators that orchestrate inflammatory responses, and it plays a central role in numerous pathological conditions, including cancer [reviewed in Refs. [4,7]).

Considering the important role of histamine-producing immune cells in the TME, in this section, we summarize the most important immunomodulatory roles of histamine and histamine receptors in the context of cancer development and progression.

3.1 | Effect of histamine on granulocytes and mast cells

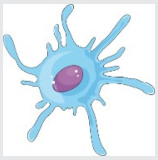
Granulocytes are immune cells that have specialized granules in the cytoplasm that contain a wide variety of substance, which may include histamine, cationic proteins, defensins, heparin, proteolytic enzymes, cathepsin G, lysozyme, and myeloperoxidase, among others. The specific types of granulocytes traditionally include neutrophils, eosinophils, and basophils. Granulocytes and mast cells are produced in the bone marrow through hematopoiesis. The process of cell maturation and proliferation occurs in the bone marrow and requires approximately 7–12 days before their release into the

TABLE 1 Role of immune cell subsets in cancer immunoediting

Immune cell	Tumor effect	References
 T cells	Pro-tumor effects: CD4$^+$ Th2 cells produce IL-4, IL-5, IL-13, and activate eosinophils, basophils, and B cells. Tumors characterized by a Th2 immune infiltrate are associated with a poor prognosis. IL-17 derived from Th17 cells promotes cell migration and invasion Anti-tumor effects: CD4$^+$ Th1 cells produce IFNγ, TNFα, and IL-2. They activate macrophages, NK cells, and CD8$^+$ T cells, and eliminate tumor cells through cytolytic mechanisms or modulating the TME. They optimize DCs in antigen presentation to CD8$^+$ T cells. In lymphoid organs, they increase the action of B cells and CTL response. They are associated with favorable prognosis in renal cell, colorectal, esophageal, and squamous carcinomas CD4$^+$ Th17 cells have anti-tumoral functions, inducing the recruitment of DCs into the tumor and the adjacent lymph nodes and thus, promoting tumor-specific CTL responses CD8$^+$ T cells display MHC I-mediated CTL activation, which produces perforins, granzymes, serine esterases, and IFNγ or TNFα. They are associated with a better prognosis in melanoma, TNBC, ovarian, bladder, and renal cancer	65,115,125–127,149,292–295
 NK cells	Anti-tumor effects: NK cells eliminate malignant cells through perforin and granzyme B, induce target cell apoptosis via Fas/FasL and TRAIL/TRAIL pathways, and secrete cytokines including IFNγ and TNFα. They promote adaptive responses through IFNγ secretion and cDC1 regulation, eliminate immature DCs or facilitate their maturation. They discriminate between "normal and altered self" through MHC I-specific inhibitory receptors and activate receptors that recognize ligands associated with cell stress. NK cells inhibit tumor growth, favor Th1 polarization of CD4$^+$ T cells, and are associated with improved patient prognosis and survival	159,296–302
 Tregs	Pro-tumor effects: Tregs suppress effector functions of immune cells such as CD4$^+$ and CD8$^+$ T cells, NK cells, macrophages, and DCs. Tregs induce tumor progression by the secretion of immunosuppressive mediators IL-10 and TGFβ, the exhaustion of T cell through the expression of LAG-3, TIM-3, and PD-1, and the inhibition of DCs maturation. They inhibit the cytolytic activity on CTL and NK cells by mediators like granzyme B, the TRAIL pathway, galectin-1, and perforin. Tregs modulate the function of DCs through the expression of Nrp-1 and CTLA-4 A decreased ratio of cytotoxic CD8$^+$ T cells to Tregs correlated with poor prognosis in patients with breast, ovarian, and gastric cancers	142,143,303–309
 B cells	Pro-tumor effects: B cells stimulate antibody-mediated activation of immunosuppressive myeloid cells and tumor growth by IL-35 production. Bregs induce apoptosis in CD4$^+$ T cells, suppress IFNγ production by NK and CD8$^+$ cells, exacerbate inflammation, and support cancer growth by IL-10 production. Bregs convert naïve CD4$^+$ T cells into Foxp3$^+$ Tregs, upregulate ROS and NO in MDSCs by TGFβ production. They are associated with a poor prognosis in ovarian cancer, glioblastoma, and clear cell renal carcinoma Anti-tumor effects: B cells induce tumor regression via a direct cytotoxic effect on tumor cells by secreting immunoglobulins (ADCC), and via Fas/FasL, TRAIL/Apo2L, and IFNγ secreted by NK cells. They act as APCs and polarize T cells toward Th1 or Th2 response. They are associated with increased overall survival in patients with melanoma, lung and pancreatic adenocarcinomas, and head and neck squamous cell carcinoma	155,310–320
 MDSCs	Pro-tumor effects: MDSCs inhibit T-cell proliferation by depletion of essential amino acids (L-arginine and tryptophan), production of ROS and RNS, restriction of lymphocyte trafficking (downregulation of L-selectin), and induction of T-cell apoptosis by decreasing Bcl-2 expression and upregulation of FAS. They promote differentiation of CD4$^+$ T cells to Tregs, and induce metastasis, cell migration, invasion (degradation of ECM and promotion of EMT), angiogenesis, and formation of the premetastatic niche In cancer patients, MDSCs' expansion in the peripheral blood is correlated with poor clinical outcomes and with advanced clinical stages	194,321–325

(Continues)

TABLE 1 (Continued)

Immune cell	Tumor effect	References
 Dendritic cells	Pro-tumor effects: pDCs mediate tolerance and immunosuppression, producing IDO and inducing Tregs. pDCs in the TME are associated with poor prognosis in melanoma, head and neck, breast, and ovarian cancers Anti-tumor effects: cDCs attract primed T cells back from the lymph nodes to the tumor. cDC1 s activate $CD8^+$ T-cell responses through peptide cross-presentation on MHC I. cDC2 s activate $CD4^+$ T-cell responses via MHC II-dependent antigen presentation. pDCs participate in immune tolerance, produce and secrete type I interferons. Therapeutic activation of pDCs has shown efficacy in melanoma, basal cell carcinoma, and T-cell lymphoma	165,326–332
 Macrophages	Pro-tumor effects: TAMs with a M2-like phenotype (anti-inflammatory role) have properties correlated with angiogenesis, immunosuppression, and promotion of cancer growth, vascular invasion, metastasis, cancer stemness, and poor prognosis. M2 macrophages produce anti-inflammatory cytokines (e.g., IL-10), upregulate scavenger receptors, such as mannose receptors, and suppress T-cell recruitment and activation. M2 TAMs are associated with resistance to chemotherapy and radiotherapy Anti-tumor effects: TAMs with a M1-like phenotype (pro-inflammatory role) are associated with the early phases of tumor development or with regressing tumors. M1 macrophages mediate anti-microbial and tumoricidal responses by secreting inflammatory cytokines, such as TNFα, IL-12, ROS, and NO, and by upregulating the expression of MHC II and promoting a Th1-type of response	179,180,333–337
 Mast cells	Pro-tumor effects: Mast cells induce the production of pro-angiogenic and pro-lymphangiogenic factors (chymase, tryptase, VEGF, IL-6, PDGF, FGF-2, MMP-9), promote the degradation of ECM and immunosuppression, and stimulate distant metastasis. They are associated with poor prognosis in Hodgkin's lymphoma, melanoma, endometrial, cervical, esophageal, lung, gastric, colorectal, and prostate carcinomas Anti-tumor effects: Mast cells promote activation and recruitment of DCs, NK cells, $CD8^+$, and $CD4^+$ cells. They induce the inhibition of Tregs, MDSCs, and M2 phenotype, and they have cytotoxic activity. The high number of mast cells is associated with a good prognosis in breast cancer	108,110,112,119,338–344
 Eosinophils	Pro-tumor effects: They induce fibroblast and endothelial cell proliferation, polarization to M2 phenotype, and promote metastasis via MMP-9, angiogenesis, and tissue healing. TABE is observed in carcinomas of the kidney, thyroid, liver, gallbladder, pancreas, breast, and Hodgkin's lymphomas and SCCs. Their presence is associated with a poor prognosis Anti-tumor effects: They are recruited by chemoattractants such as IL-5, IL-4, GM-CSF, and CCL11 in numerous types of cancers. TATE is associated with a good prognosis in gastrointestinal and head and neck cancers. They reduce tumor growth, induce recruitment and activation of T and NK cells, and promote cytotoxic activity via degranulation. They induce inhibition and normalization of tumor vessels, polarization to M1 phenotype, and maturation of DCs	97,98,101,102,345–348
 Neutrophils	Pro-tumor effects: N2 TANs promote tumor growth (through the production of growth factors and NE), cell invasion and migration, angiogenesis, and lymphangiogenesis (through the release of VEGFs, MMP-9, and Bv8). They induce inhibition of T and NK cells, ETM, metastasis, Tregs recruitment, and chemoresistance. Neutrophilia is associated with a poor prognosis. High neutrophils/lymphocytes ratio in solid tumors is correlated with poor outcomes Anti-tumor effects: N1 TANs induce T-cell activation by TGFβ inhibition, recruitment of pro-inflammatory macrophages (M1), cytotoxicity through release of ROS and RNS, apoptosis (through the release of TRAIL), and inhibition of angiogenesis (through the release of the anti-angiogenic VEGF-A165b)	349–359

(Continues)

TABLE 1 (Continued)

Immune cell	Tumor effect	References
 Basophils	Pro-tumor effects: They stimulate angiogenesis through the production of VEGF-A, VEGF-B, angiopoietin 1, CXCL8, and HGF. They promote ETM by production of CXCL8 and TNFα, the recruitment of anti-inflammatory macrophages (M2), and they induce ECM degradation and immunosuppression Anti-tumor effects: They have cytotoxic effects via granzyme B and TNFα. Histamine secretion promotes DCs maturation and inhibition of tumor growth	110,173,200,360–367

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; APCs, antigen-presenting cells; Apo2L, apo2 ligand or TRAIL; Bregs, B regulatory cells; Bv8, prokineticin-2 protein; CCL11, CC-chemokine ligand 11; cDC1 s, conventional type-1 dendritic cells; cDC2 s, conventional type-2 dendritic cells; CTL, cytotoxic T lymphocytes; CTLA-4, T-lymphocyte-associated protein 4; CXCL8, C-X-C motif chemokine ligand 8; DCs, dendritic cells; ECM, extracellular matrix; Fas/FasL, Fas receptor/Fas-ligand; FGF-2, fibroblast growth factor 2; GM-CSF, granulocyte-macrophage colony stimulating factor; HGF, hepatocyte growth factor; IDO, indoleamine 2,3-dioxygenase; LAG-3, lymphocyte activation gene-3; MDSCs, myeloid-derived suppressor cells; MHC I: major histocompatibility complex class I; MHC II, major histocompatibility complex class II; MMP-9, metalloproteinase 9; moDCs, monocyte-derived dendritic cells; N1, tumor-associated neutrophils type 1; N2, tumor-associated neutrophils type 2; NE, neutrophil elastase; NK, natural killer; NO, nitric oxide; Nrp1, neuropilin; PD-1, programmed cell death 1; pDCs, plasmacytoid dendritic cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCC, squamous-cell carcinoma; TABE, tumor-associated blood eosinophilia; TANs, tumor-associated neutrophils; TATE, tumor-associated tissue eosinophilia; TGFβ, transforming growth factor beta; TILs, tumor-infiltrating lymphocytes; TIM-3, T-cell immunoglobulin and mucin domain-3; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TNFα, tumor necrosis factor-alpha; TRAIL, TNF-related apoptosis-inducing ligand; Tregs, T regulatory cells; VEGF, vascular endothelial growth factor; VEGF-A165b, anti-angiogenic isoform of vascular endothelial growth factor-A; VEGF-B, vascular endothelial growth factor-B.

bloodstream (circulating leukocytes) and their homing to different tissues (resident leukocytes).[67]

Hematopoietic cells including mast cells, eosinophils, basophils, DCs, and T cells express histamine receptors and their histamine-induced activation produces numerous important functions during immune responses (Figure 1).

It is important to highlight that there are uncertainties around the specificity of the commercially available antibodies used to detect histamine receptors, considering the nonspecific binding effects that have been reported. Therefore, different approaches should be used when checking the specificity of an antibody that include: the use of cells with genetic knockdown of their expression, cells recombinantly expressing closely related receptor subtypes, and/or the use of various antibodies directed against different receptors' epitopes.[34,68–70] The verification of the expression using other identifying techniques, including qRT-PCR, RT-PCR, in situ hybridization, northern blot, and ligand-binding assays, is extremely important to assess the distribution of histamine receptor subtypes.

Numerous studies showed expression of the H_1, H_2, and H_4 receptor but not of the H_3 receptor in human granulocytes and mast cells, using techniques such as RT-PCR, northern blot, immunofluorescence, and ligand-binding assays.[71–77] However, Hofstra et al found no H_4 receptor expression in murine neutrophils evaluated by RT-PCR.[78]

Neutrophils are the most abundant leukocytes in the human circulatory system and are the first responders in acute inflammation. They capture invading micro-organisms through different mechanisms such as phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs).[79] In addition, neutrophils play a pivotal role in chronic inflammatory diseases such as cancer.[67] Although recent evidence suggests an important role of neutrophils in the TME, the pro- or anti-tumor nature of neutrophils in different cancer types is still inconclusive[80] (Table 1).

Recent studies have reported that histamine plays an important role in hematopoietic stem cell proliferation and neutrophil maturation.[81] During inflammatory processes, neutrophils stimulate the production and release of histamine.[82] Histamine seems to have anti-inflammatory properties via the H_2 receptor and cAMP formation, inhibiting activation of neutrophils and HL-60 leukemic cells,[83] leukotriene synthesis, and chemotaxis[5,7,84–89] (Figure 1).

Limited information about the immunomodulatory role of histamine in tumor-associated neutrophils (TANs) is reported. By targeting NADPH-oxidase via the H_2 receptor on monocytes[90] and neutrophils,[91] histamine has been proposed as an anti-phagocyte drug-candidate with the ability to inhibit the formation and release of reactive oxygen species (ROS).[92,93] Thus, histamine treatment potentially improves the efficacy of the immunotherapy with IL-2 for diverse oncological conditions by protecting the anti-tumor immune effector NK and T cells from oxidative stress-induced inhibition and apoptosis, as described in the following section.[94] In vivo treatment with histamine and H_4 receptor agonists (1 mg/kg daily s.c. administration for 30 days) reduced human 1205Lu melanoma tumor growth and neovascular formation while it decreased the neutrophil-to-lymphocyte ratio infiltrate.[10]

Eosinophils are granulocytes that develop during hematopoiesis in the bone marrow and are terminally differentiated after migrating into the blood. They have multiple functions, which include cytotoxicity, inflammatory processes, modulation of innate and adaptive immunity, and anti-tumor responses. Eosinophilic leukocytes respond to different antigenic stimuli (helminths, virus, bacteria, fungi) as well as immunostimulatory ligands (MHC II, CD40, CD80, CD86) through different receptors. They are recruited by chemokines and their function is influenced by cytokines. Together with mast cells and basophils, they control mechanisms associated with allergy and asthma. Eosinophils are characterized by basic granules composed of cationic proteins, including eosinophil cationic protein, eosinophil-derived neurotoxin, major basic protein (MBP), eosinophil peroxidase (EPO), hydrolytic enzymes, and a diverse repertoire of preformed cytokines, chemokines, and numerous growth factors.[67]

Histamine has a dose-dependent effect on chemotaxis of eosinophilic granulocytes[5,95,96] (Figure 1).

Tissue eosinophilia (also termed tumor-associated tissue eosinophils, TATE) and peripheral blood eosinophilia (TABE) have been associated with both favorable and unfavorable anti-tumor response and prognosis[97–102] (Table 1). Transcriptomic and proteomic analyses of TATE revealed an activated eosinophil phenotype associated with IFNγ signaling and suggest that these cells may be targets for immunotherapy.[103]

Mast cells and basophils play several roles in the innate and adaptive immune responses and are mediators of type I allergy.[104–106] Although both immune cell types resemble in terms of morphology and functional properties, basophils arise and mature in the bone marrow and circulate in the bloodstream, whereas mast cells develop from a different precursor in the bone marrow and usually mature in the resident tissues (e.g., skin, lung, and gastrointestinal tract). Therefore, mast cell phenotype and maturation are influenced by the local microenvironment. The activation of the receptor for immunoglobulin E (FcεRI) in mast cells and basophils, which is triggered by the crosslinking with antigen-specific IgE, results in the release of numerous inflammatory mediators in their granule content, which are responsible for the allergic reactions. The released mediators comprise histamine, lipid mediators, proteases, cytokines, and chemokines, which may act locally on other immune cells, vessels and/or smooth muscle.[67,104,106–108]

Mast cells and basophils are the major sources of histamine in healthy tissues, which is stored in specific cytosolic granules, and it is released in large quantities during degranulation following immunological or nonimmunological activation.[85] Both granulocytic immune cells express H_1, H_2, and H_4 receptors and histamine modulates their functions, including their ability to further degranulate[94,104,106,109] (Figure 1).

Infiltration of mast cells has been found in numerous types of human tumors and experimental cancer models, and it was associated either with a good or a poor prognosis depending on the cancer type, tissue localization, and the ability of mast cells to interact with TME.[110–112] Histamine and other secreted mediators could promote invasion and angiogenesis by shaping the TME and inducing stromal remodeling and capillary permeability[112] (Table 1).

The role of histamine in the TME is complex as it can exert different immunobiological effects through the four histamine receptor subtypes.[7,113–115] The human leukemia cell line HMC-1 expresses H_1, H_2, and H_4 receptors evidenced by RT-PCR and western blot, and moderate effects of H_1 receptor and H_2 receptor antihistamines are observed on the secretion of proinflammatory cytokines IL-6, IL-8, and TNFα.[5] It has been recently demonstrated that the treatment with mast cell mediators exert opposite effects on the proliferation of YAC-1 and EL4 cell lines, both derived from murine T cell lymphomas, but of different origin. The result of the co-administration of histamine receptor antagonists and mast cell mediators on these cancer cells suggested a major involvement of H_2 receptor and H_4 receptor in the growth inhibition in YAC-1 cells. On the other hand, the enhanced cell growth in EL-4 cells was mediated by H_1, H_2, and H_4 receptors.[116] In experimental models of non-small-cell lung cancer, a dual effect of mast cells has been described, as they enhance tumor growth in vitro but importantly, they exert anti-tumorigenic effects in mice as it has been shown using the mast cell-deficient mouse Sash model.[117] In some cancer types, enhancing local mast cell degranulation may induce anti-tumor immune mechanisms, which include the recruitment of effector cells, the direct impact of released mediators on tumor cells and the secondary effects on immune regulation.[118,119] In this regard, investigating the role of mast cells in different tumors will improve the knowledge and further identify potential mechanisms involved in the paradoxical role of mast cells in the TME.

Basophils are the less abundant peripheral blood leukocytes and are key players in Th2 immune responses and allergy.[120] Limited information about basophils' role in cancer is available. Recent data show that they can be recruited into the TME by several chemotactic factors secreted by tumors or immune cells, including VEGFs, histamine, prostaglandin D2 (PGD2), urokinase plasminogen activator (uPA), and chemokines. Marked basophilia represents a relevant independent prognostic variable in chronic myeloid leukemia (CML).[121] Recent evidence suggests that basophils may be a useful predictive or monitoring marker for the development of hypersensitivity against oncological treatments. In addition, the activation of basophils may be associated with improved outcomes for ovarian cancer patients.[122]

3.2 | Effect of histamine on lymphocytes

Lymphocytes consist of three major groups: T cells, B cells, and NK cells. The major players in adaptive immunity are T and antibody-producing B cells, which develop in the thymus and bone marrow, respectively, whereas NK cells are part of the innate immunity.[123,124] It is well-documented that histamine through different receptor subtypes plays an important role in the modulation of lymphocytes during immune responses and inflammatory reactions[5,85,88] (Figure 1).

T lymphocytes are one of the most powerful immune cells against cancer and they have been a major target of immunotherapy, which has emerged as a breakthrough in cancer therapeutics. $CD4^+$ T cells, including Th1, Th2, Th17, and Tregs ($CD4^+CD25^+$ regulatory T cells) together with $CD8^+$ cytotoxic T cells are extremely important mediating anti-tumor immunity (Table 1). A positive correlation between the presence of tumor-infiltrating lymphocytes (TILs) and patients' survival has been demonstrated in numerous types of cancer.[125–127]

Jutel et al demonstrated through RT-PCR and flow cytometry assays that H_1 and H_2 receptors are predominantly expressed in Th1 and Th2 cells, respectively.[128,129] mRNA expression studies confirmed the expression of H_1, H_2, and H_4 receptors whereas H_3 receptor mRNA was absent in $CD8^+$, $CD4^+$, and Th17 T cells.[130–132] The expression of H_2 receptor in Tregs from healthy subjects and patients with allergic rhinitis (AR) was demonstrated by flow cytometry.[133] Numerous studies evaluate the important role of histamine receptors using functional assays[114,115,133–138] (Figure 1).

Systemic treatment with histamine (10 mg/kg, twice a day for 21 days beginning the day of tumor implantation) increased Colon 38 tumor growth implants in syngeneic mice by an indirect effect associated with a reduction in the anti-tumor cytokines expression in the TME, dysregulating the balance between Th1 and Th2 cells.[139] Reynolds et al reported the levels of histamine content in 31 colorectal cancer specimens and indicated that they were sufficient to inhibit lymphocyte activity.[140] *Lactobacillus rhamnosus*-derived histamine promotes a regulatory Foxp3-T cell response profile in intestinal Peyer patches while altering Th1 polarization through the H_2 receptor.[141]

The infiltrating cytotoxic cells, mainly $CD8^+$ T lymphocytes and NK cells, are responsible for killing cancer cells. Therefore, immunosuppressive cells' infiltrate such as Tregs and MDSCs, is usually associated with a worse prognosis in cancer patients.

Tregs are a subset of $CD4^+$ T cells characterized by their expression of a master transcription factor forkhead box P3 (FoxP3), which is essential for Tregs' differentiation and function. They play a central role in the maintenance of self-tolerance, homeostasis, and resolution of inflammation through the suppression of the T-cell population, including both $CD4^+$ and $CD8^+$ T cells, DCs, B cells, natural killer T (NKT) cells, Th17 cells, NK cells, monocytes, and macrophages by the secretion of suppressive cytokines like IL-10 and TGFβ, and the expression of the inhibitory surface molecules LAG-3, TIM-3, PD-1, and CTLA-4.[142,143]

In the TME, Tregs are one of the major immune cell types involved in the suppression of anti-tumor immunity, promoting tumor immune evasion (Table 1). Histamine and its receptor ligands are capable of modulating the activity of Tregs in many pathological processes like allergies, autoimmune and inflammatory diseases, and even in various types of cancer (Figure 1). It was shown that histamine released by mast cells reduced the expression of CD25 and the Tregs-specific transcription factor Foxp3 and inhibited Tregs' suppressor function, enhancing the development of protective immunity. These effects were mimicked by the H_1-receptor-specific agonist 2-pyridylethylamine and were reversed by loratadine.[136] On the other hand, several studies indicate that the immunosuppressive activity of Tregs in allergy and asthma is increased through the activation of the H_2 receptor.[144,145] In line with those results, cimetidine, a H_2 receptor antagonist, reduces the regulatory T-cell-mediated immunosuppression.[84,146,147]

In the tumor context, a reduction in the percentage of splenic Tregs was found in histidine decarboxylase-deficient mice compared to wild-type (WT) mice bearing syngeneic mammary-adenocarcinoma LM2 tumors. The lack of histamine upregulated splenic T-bet^+ lymphocytes and the IL-12/IFNγ production.[148]

Recently the role of the H_4 receptor in the anti-tumor immunity was described for the first time, using H_4 receptor deficiency or pharmacological blockade in the experimental murine model of triple-negative breast cancer (TNBC) developed by orthotopic inoculation of 4T1 cells. The effect of systemic treatment with histamine (1 or 5 mg/kg daily s.c. administration for 15 days, starting when tumors became palpable) or specific H_4 receptor pharmacological ligands JNJ7777120 (H_4 receptor antagonist, 10 mg/kg daily s.c. administration for 15 days, starting when tumors became palpable) and JNJ28610244 (H_4 receptor agonist, 1 or 5 mg/kg daily s.c. administration for 15 days, starting when tumors became palpable), on tumor progression and immune response was evaluated. Histamine (5 mg/kg) reduced tumor weight, an effect that was inversely correlated with the presence of TILs. Histamine, used even in a lower concentration (1 mg/kg), was able to enhance the therapeutic effect of ionizing radiation, suggesting that it could be a potential agent to be used in combined therapies. The higher anti-tumor and antimetastatic effects of histamine treatment compared with H_4 receptor agonist's administration could be associated with the multifaceted action of histamine on different receptors and cell types, which on the one hand balanced anti-tumor immunity and on the other hand, by acting directly through the H_4 receptor on 4T1 tumor cells, reduced proliferation (Figure 2). The administered doses of the H_4 receptor's agonist conditioned the outcome of its therapeutic and immunomodulatory effects in vivo. The lowest concentration (1 mg/kg) slightly, but significantly, reduced the tumor size and increased the percentage of $CD4^+$ T cells in the tumor-draining lymph nodes (TDLN), whereas a concentration of 5 mg/kg did not change the tumor weight probably due to an immunosuppressive effect on the TME (Figure 2). The treatment with the H_4 receptor antagonist led to a reduced proportion of tumor-infiltrating $CD4^+$ T cells and Tregs in the TDLN, as it was observed in H_4 receptor-deficient mice (H_4 receptor-KO)[114,149] (Figure 2). H_4 receptor-KO mice showed reduced tumor growth and lung metastases, and $CD4^+$ T cell tumor infiltration, while they exhibited a greater infiltrate of NK cells and $CD19^+$ B lymphocytes compared to tumors developed in WT mice. The TDLN of the H_4 receptor-KO mice showed decreased percentages of the $CD4^+$ T cells and Tregs subpopulations together with a higher percentage of NK cells.

In another model of breast cancer developed in BALB/c mice with LM3 cells (ErbB-2 positive), the percentage of Tregs decreased significantly in TDLN from H_4 receptor-deficient animals, demonstrating that in both breast cancer models the H_4 receptor exhibits an immunosuppressive effect, particularly modulating the compartment of $CD4^+$ T lymphocytes.[114,115,149] In line with these results, intratracheal instillation of the H_4 receptor agonist 4-methylhistamine (10 μg/100 μl) mitigated airway hyperreactivity and inflammation of allergic asthma in a murine model through increasing IL-10 secretion levels and the recruitment of Tregs.[134] Additionally, in an experimental allergic encephalomyelitis model, H_4 receptor-KO mice showed a lower proportion of Tregs in secondary lymphoid organs compared to WT mice, which increased the severity of the disease.[150]

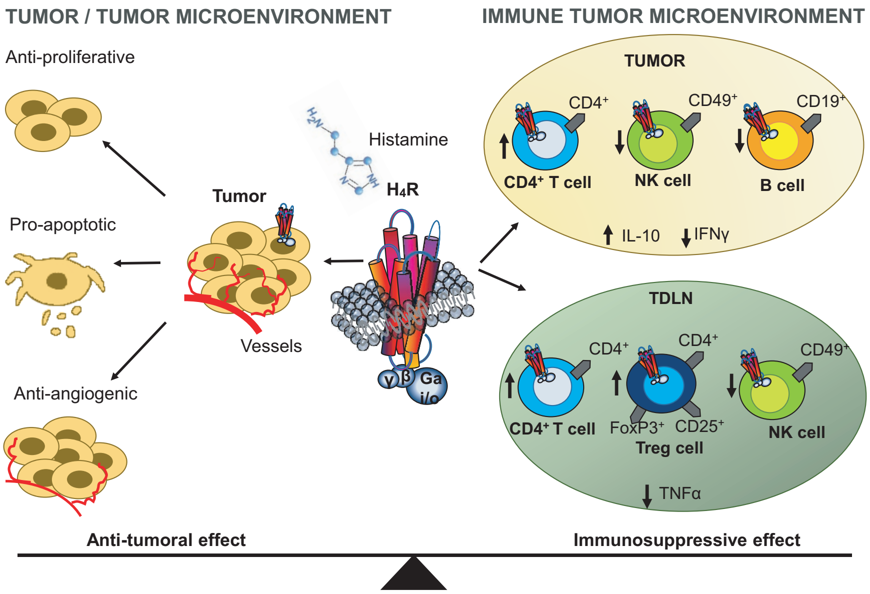


FIGURE 2 Effect of H_4 receptor activation in tumor cells and the tumor microenvironment (TME). Histamine or selective H_4 receptor agonists play important roles at a variety of stages during tumor development and in multiple cell types including cancer and immune cells. On the one hand, H_4 receptor activation exerts a direct in vitro cytotoxic effect on TNBC cells, whereas on the other the H_4 receptor selectively affects the distribution of different immune cell populations in the TME, modulating the local and systemic immune responses. In a TNBC murine model, H_4 receptor stimulation increases the percentage of $CD4^+$ tumor-infiltrating T cells, whereas it decreases the infiltration of NK cells and $CD19^+$ B lymphocytes. In addition, it increases IL-10 secretion levels, whereas decreases IFNγ levels in tumor-conditioned medium from wild-type (WT) mice. Likewise, tumor draining lymph nodes (TDLN) of WT mice show higher proportions of $CD4^+$ T cells and T regulatory cells ($CD4^+$ $CD25^+$ $FoxP3^+$), a reduced percentage of NK cells, and decreased TNFα levels in TDLN compared with H_4 receptor-KO mice, thus suggesting an immunosuppressive effect of H_4 receptor[114,149]

In a phase IV trial, patients with acute myeloid leukemia (AML) who received immunotherapy with histamine dihydrochloride and IL-2 during the initial cycles showed an increase in the peripheral blood Tregs' count[151] (Table 2). Furthermore, it was recently demonstrated that the number and size of tumors and the degree of colonic inflammation, associated with the expression of cyclooxygenase 2 and the production of C-X-C motif chemokine ligand 1 (CXCL1) and CXCL2, are reduced in H_4 receptor-deficient mice compared to WT mice in a chemically induced colorectal cancer model.[152]

B cells are recognized as the main effector cells of humoral immunity because of their ability to produce antibodies (immunoglobulins, Ig). The naïve mature B cells differentiate into activated B cells after the first encounter with the antigen, thus proliferating and becoming plasma cells, which produce and release antibodies. They can be classified according to their location and how they are activated.[153] Regulatory B cells (Bregs) can inhibit T-cell-mediated immunity and are characterized by producing inhibitory cytokines such as IL-10, IL-35, or TGFβ.[154,155]

The tumor-infiltrating B cells exert both pro-tumor and anti-tumor effects depending on their phenotype, the antibodies and cytokines that they produce, and the composition of the TME (Table 1).

Histamine can affect B-cell Ig production (Figure 1). Colorectal cancer patients treated with cimetidine (8.8 or 1.2 g per day oral administration from the day of admission to the 10th postoperative day) showed elevated levels of $CD19^+$ B cells in blood samples, which was associated with an improved local immune response.[156] In line with these results, a recent study demonstrated that treatment with ranitidine, a H_2 receptor antagonist, (8 mg/kg added to drinking water 1 day prior to tumor cell injection and during 21 days) enhanced anti-tumor antibody responses and reduced tumor growth in murine models of breast cancer developed with E0771-GFP and 4T1 cell lines, effects that were mediated by B cells and may have included the participation of NK cells.[157]

Natural killer cells are effector lymphocytes that play a crucial role in the defense against viruses and the surveillance of tumor insurgence. Activation of NK cells in the TME can contribute to anti-tumor immunity through various mechanisms (Table 1).[158,159] Damaj et al evaluated the expression of histamine receptors by immunoblot analysis and staining with anti-histamine receptors' antibodies and flow cytometry, and showed that NK cells, monocytes, and dendritic cells express the H_1 and H_4 receptors but not H_2 and H_3 receptors.[160]

Treatment with histamine enhanced IL-2 and IFNα induced NK cell-mediated killing of human tumor cells in vitro and in tumor-bearing mice by inhibiting phagocyte-derived ROS.[161,162] However, the benefit of histamine does not apply to all tumors and depends on its type and origin.[163] Degranulating mast cells at tumor sites can also augment NK cell function via histamine release.[113] These findings are the fundamental rock for the use of histamine as an adjuvant to cancer immunotherapy, which is described in the next section.

TABLE 2 Clinical trials with histamine or histamine receptor's ligands and immunotherapy

Trial [references]	Phase	Disease	Patients (*N*)	Treatment	Drug indication	Recruitment status
NCT00005038 (*)	II	Kidney cancer	60	IL-2 (Aldesleukin) + histamine dihydrochloride (HDC)	Aldesleukin s.c. once daily and HDC s.c. twice daily (b.i.d.) on days 1–5 of weeks 1–3 followed by 2 weeks of rest	Unknown
NCT00003991 [231,232,239]	III	Leukemia	360	Aldesleukin + HDC	Following consolidation chemotherapy or autologous stem cell transplantation, patients received Aldesleukin (16,400 IU/kg s.c. b.i.d.) followed by HDC (0.5 mg s.c.) over 5–7 min b.i.d. on days 1–21. Treatment was repeated every 6 weeks for 3 courses and then every 9 weeks for 7 courses in the absence of disease relapse or unacceptable toxicity	Completed
NCT01347996 [151,201,214,230,234,235,237,238]	IV	Acute myeloid leukemia	84	HDC (Ceplene®) + IL-2	Ceplene® (0.5 mg s.c. b.i.d.) and IL-2 (1 µg/kg or 16,400 IU/kg b.i.d. for 21 day-cycle followed by 21 days of rest	Completed
NCT03040401 (*)	I/II	Chronic myelomonocytic leukemia	15	Ceplene® + IL-2 (Proleukin®)	Ceplene® and/or Proleukin® s.c. b.i.d. in 3-week periods followed by 3- or 6-week rest periods	Unknown
NCT00039234 (*)	III	Melanoma (skin), metastatic cancer	224	Aldesleukin + HDC	Aldesleukin s.c. b.i.d. on days 1 and 2 of weeks 1 and 3 and days 1–5 of weeks 2 and 4. Patients also received HDC s.c. over 10–30 min on days 1–5 of weeks 1–4	Active, not recruiting
NCT00002733 (*)	II	Kidney cancer, melanoma (skin)	20–30 with melanoma 20–30 with renal cell carcinoma	TILs + cimetidine	TILs infusion once followed by oral cimetidine every 6 h for 4 weeks	Completed
NCT04165096	II	Non-small-cell lung carcinoma	Estimated Enrollment: 90 participants	MK-5890 + pembrolizumab + Diphenhydramine + acetaminophen	On day 1 of each 3-week cycle, participants receive pembrolizumab 200 mg intravenously (i.v.) plus MK-5890 i.v. for a maximum of 35 cycles (approximately 2 years). All participants are premedicated 1.5 h (±30 min) before infusion of MK-5890 with 50 mg oral diphenhydramine (or equivalent dose of anti-histamine), and 500–1000 mg of oral acetaminophen (or equivalent dose of analgesic)	Recruiting

Note: Twice daily (b.i.d.), tumor-infiltrating lymphocytes (TILs), aldesleukin (IL-2), histamine dihydrochloride (HDC), Ceplene® (histamine dihydrochloride), Proleukin® (IL-2), MK-5890 (anti-CD27), pembrolizumab (anti-PD-1 immune checkpoint blocking antibodies), diphenhydramine (H_1 receptor antagonist), intravenously (i.v.). (*) Dosage is not available.

Source: https://www.clinicaltrials.gov/ct2/home.

3.3 | Effect of histamine on dendritic cells

Dendritic cells (DCs) are a heterogeneous population of migratory leukocytes that play a fundamental role in the induction and regulation of innate and adaptive immunity. They are crucial as professional antigen-presenting cells (APCs), activating $CD8^+$ and $CD4^+$ T cells through MHC I and MHC II molecules, respectively, and providing a wide variety of fundamental signals (costimulatory molecules and cytokines) to shape the immune response.[164,165] Three subsets of DCs have been described with specific functions, morphology, and location: conventional DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs). cDCs phagocytose debris from apoptotic tumor cells, and they migrate to TDLN where they present these antigens to naïve $CD4^+$ or $CD8^+$ T cells (Table 1).

In both mature and immature DCs, expression of all histamine receptors has been demonstrated by RT-PCR.[166-168] However, the authors were not able to evaluate the expression of the H_3 and H_4 receptors by western blot and flow cytometry using commercially available polyclonal rabbit antibodies.[167,169] The studies investigating the H_3 receptor mRNA expression in MoDCs are controversial. Some of them detected mRNA presence[167,169] whereas others found only a faint[170] or no signal.[171] Thus, both endogenous and exogenous histamine may influence not only the expression of surface markers but also the function, differentiation, and maturation of DCs.[5,172,173]

Histamine increases the capacity of DCs to induce the polarization of naïve $CD4^+$ T lymphocytes into predominantly Th2 lymphocytes through H_2 receptor-mediated chemotaxis.[174,175] On the other hand, Vanbervliet et al showed in a murine model of atopic dermatitis, a significantly reduced antigen-specific skin inflammation and diminished IL-12 and increased IL-23 and IL-6 production by DCs in H_1 receptor-deficient mice compared to WT mice.[176] Martner et al, demonstrated that the treatment with histamine (75 mg/kg i.p. three times a week for 2 weeks) reduced the growth of murine EL4 lymphomas while increased tumor-infiltrating DCs in WT mice but not in NADPH oxidase type 2 (NOX2)-deficient mice. A positive correlation between accumulation of intra-tumoral DCs and $CD8^+$ T cells paralleled with a reduced tumor size.[173]

3.4 | Effect of histamine on monocytes and macrophages

Monocytes play an important role in the immune defense, inflammation, and homeostasis by sensing their local environment. They circulate in the blood and migrate to inflammatory tissues and differentiate in response to different stimuli into macrophages and monocyte-derived dendritic cells (moDCs). Macrophages can be divided into two main groups designated M1 and M2, which can be identified by cell surface markers and their functional phenotype. M1 macrophages play a critical role in the innate defense of the host and tumor destruction. M2 macrophages have been found to participate in biological processes of angiogenesis, tissue remodeling, wound healing, and anti-inflammatory responses.[177,178] During tumor development and progression through the metastatic cascade, macrophages are involved in shaping the primary, micro-invasive, and premetastatic TMEs.[179] Tumor-associated macrophages (TAMs) include both M1 macrophages that harbor anti-tumor effector functions and M2 macrophages that express tumor-promoting and immunosuppressive factors (Table 1).[179,180]

Several authors have reported that both monocytes and fully differentiated macrophages express histamine receptors, particularly H_1, H_2, and H_4 receptors.[88,181–184] However, others found no evidence of H_1 and H_4 receptor expression in human monocytes.[184,185] Histamine stimulates the exocytosis and the cytokine production in human lung macrophages via the H_1 receptor while increasing phagocytosis by its signaling through the H_2 receptor.[186,187] In both bone marrow-derived macrophages and RAW 264.7 cells, histamine is capable of promoting macrophage differentiation and induces chemotaxis and phagocytic activity by the activation of the H_4 receptor[188,189] (Figure 1). Furthermore, during in vitro differentiation from monocytes to macrophages, the H_4 receptor agonist ST-1006 modified the M1 phenotype by upregulating the macrophage differentiation marker CD68 and downregulating the production of CXCL10.[182]

Cimetidine treatment (400 mg twice daily, given as infusion or tablets depending on the postoperative condition) of patients with gastrointestinal cancer resulted in a better prognosis by increasing the release of the anti-tumor cytokine IL-18 from monocytes.[190,191] Although oral ranitidine, another H_2 receptor antagonist (8 mg/kg added to drinking water 1 day prior to tumor cell injection, refreshed every other day), did not affect tumor growth in the B16-F10 melanoma, LLC1 lung cancer, and EL4 thymoma experimental models, it consistently reduced primary tumor growth and metastasis in the breast cancer models E0771 and 4T1, respectively. Ranitidine affects monocyte populations in breast cancer, providing a reduction of tumor-associated immune suppression.[192] In addition, the simultaneous inhibition of the H_1 receptor (mepyramine, 50 μM oral administration during treatment with dextran sulfate sodium, DSS) and the stimulation of the H_2 receptor (cimetidine, 100 μM oral administration during DSS treatment) signaling pathways were described to effectively suppress the pro-inflammatory signaling in macrophages, reducing the inflammation-associated colonic tumorigenesis.[11] In this response, the described mechanisms of H_1 and H_2 receptors' cross-regulation should be considered, including the cross-desentization and cross-internalization, which could have potential therapeutic implications in combined treatments.[38]

3.5 | Effect of histamine on myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are one of the major components of the TME and are characterized by their potent immunosuppressive activity. MDSCs are immature myeloid cells that are precursors of DCs, macrophages, and granulocytes. They are generated in the bone marrow and migrate to tumors and peripheral lymphoid organs to contribute to the formation of the TME, being the main contributors to immune dysfunction observed in cancer patients (Table 1).[193–195] The accumulation of immature myeloid cells and the deficit of mature DCs is associated with increased tumor growth and poor prognosis in human and murine cancers.[173,196–198]

Histamine can regulate myeloid cell differentiation[199] (Figure 1). Increased inflammation-associated carcinogenesis was observed in histamine-deficient mice, which were associated with decreased myeloid cell differentiation and accumulation of $CD11b^{+}Gr1^{+}$ immature myeloid cells. The treatment with exogenous histamine (0.8 mg/kg i.p. per day for 20 days) induced their terminal differentiation into monocytes and neutrophils, acting through H_1 receptor and H_2 receptor, and suppressed their ability to support the growth of tumor allografts.[200] Adoptive transplant of histidine decarboxylase-deficient bone marrow to WT mice reproduced the cancer phenotype of histidine decarboxylase-KO mice, associated with an increase in $CD11b^{+}Ly6G^{+}$ cell mobilization.[200]

Accordingly, Grauers Wiktorin et al showed in vivo that the treatment with histamine (75 µg/mouse i.p. three times a week starting 1 day before tumor inoculation) diminished tumor growth and the accumulation and immunosuppressive features of MDSCs in EL4 lymphoma. Histamine also improved the anti-tumor efficacy of immune checkpoint blockade with anti-PD-1/anti-PD-L1 (100–240 µg/mouse of each antibody, i.p. starting 3, 6, and 10 days after tumor inoculation) in the murine EL4 lymphoma and MC-38 colon carcinoma.[201] The counts of MDSCs in blood samples from patients with AML significantly predicted leukemia-free survival (LFS). Interestingly, their frequency and absolute counts were significantly reduced during treatment with histamine and IL-2.[201]

In this line, Gao et al reported that the administration of *L. reuteri*, a histamine-producing member of the gut microbiota, protects histidine decarboxylase-deficient mice from colon carcinogenesis induced with azoxymethane/DSS, by reducing the recruitment of MDSCs and the production of inflammatory cytokines.[202] Another lactobacilli, *L. rhamnosus*, is a source of histamine that promotes a Tregs response profile in intestinal Peyer patches.[141,203] The microbial community in the intestine is indeed an important determinant of the gut pathophysiology and its unbalance may produce other consequences outside the gastrointestinal tract. Histamine-secreting microbes are present within the human gut microbiota and they may modulate host immunological responses.[203,204] The microbiome, which not only includes gut bacteria but also skin bacteria, and other resident microorganisms is an emerging area of research. Studies suggest that microbiome impacts both the development and progression of cancer as well as patient responses to cancer treatments, including immunotherapy.[205,206] Recent data show that each tumor type has a distinct microbiome composition and intratumor bacteria are present mostly intracellularly in both cancer and immune cells.[206] Further studies are needed to unravel whether the tumor microbiome could be another source of histamine involved in tumor and TME interaction.

4 | HISTAMINE AS AN ADJUVANT TO CANCER IMMUNOTHERAPY

Immunotherapy comprises a series of agents designed to stimulate the immune system in order to develop a tumor-specific immune response to eradicate cancer. Cutting-edge immunotherapies include immune checkpoints blockade, adoptive T cellular therapies, chimeric antigen receptor T-cell immunotherapy, oncolytic viruses, and cancer vaccines. In particular, immunotherapy with immune checkpoint inhibitors using CTLA-4, PD-1, and PD-L1 neutralizing or blocking antibodies is a promising and rapidly growing field of interest with impressive success in many solid tumors.[207–210] It seeks to unleash anti-tumor T-cell responses by avoiding host immunotolerance, and results in durable clinical responses but only in a fraction of patients.[211,212]

Immunotherapeutics such as IL-2, and interferons (IFN), among others, have been used as options for the treatment of certain cancers such as metastatic malignant melanoma, AML, and renal cell carcinoma.[213,214] The basis for the anti-tumor effects of these cytokines is correlated with their ability to activate elements of the immune system that recognize and destroy tumor cells. NK cells and a subset of T lymphocytes are among the principally activated cells. However, these agents show not sufficiently optimal results in terms of effectiveness and the development of adverse effects.[215,216] When administered in addition to IL-2, histamine dihydrochloride improves the activation of T cells and NK cells, controlling tumor growth of various cancers. This combination therapy appears to be a useful maintenance therapy alternative for patients with AML in remission. Table 2 summarizes the most important clinical trials.

The pharmacokinetic properties of subcutaneous histamine administration (1 mg) as well as the drug–drug interactions with subcutaneously administrated IL-2 (1.1 mg) were evaluated in a clinical study with healthy volunteers and cancer patients. Pharmacokinetic parameters showed a high inter-individual variability. In healthy subjects, the administration of histamine for more than 10 min revealed a maximum plasma concentration peak at 18 min (C_{max}, 38 nmol/L), a distribution volume of 59 L and an elimination rate of 6%/min. Similar results were observed in a 20-min infusion in melanoma patients. There was no effect on histamine kinetics when IL-2 was injected either 10 min prior to or 10 min following histamine administration.[217–219] A phase I study showed no severe adverse events upon a single dose of histamine (0.5 or 1.0 mg) subcutaneous injection in healthy volunteers. The administration of a histamine dose of 0.5 and 1 mg showed a time to C_{max} (T_{max}) of 0.15 and 0.14 h, a mean C_{max} of 26.59 and 71.01 nmol/L, area under the plasma concentration–time curve from time zero to the last sampling (AUC 0–∞) of 9.61 and 22.69 nmol/h/L, maximum urine excretion rates of 21.85 and 38.94 nmol/h, respectively.[220]

In this section, we highlight the current progress and foundational developments in the field of cancer immunotherapy in combination with histamine and pharmacological compounds targeting histamine receptors.

4.1 | Leukemia and lymphoma

The initial treatment for leukemia comprises the induction and consolidation chemotherapy aimed at inducing and sustaining the disappearance of leukemic cells (complete remission, CR). Several immunotherapies have been developed to prevent relapse, including the administration of a low-dose of IL-2 in combination with histamine dihydrochloride (HDC/IL-2) for the treatment of AML.[220-225]

As compared to IL-2 as a single agent, the use of histamine, acting specifically through the H_2 receptor, restored the IL-2-induced destruction of AML blasts by preventing the inhibition of the cytotoxic lymphocytes induced by monocyte-derived ROS, and enhancing the accumulation of $CD25^+$ T cells in peripheral blood. In five patients with early relapse, the remission duration after the treatment with HDC/IL-2 (0.9 MIU IL-2 s.c. twice daily, and 0.4–0.7 mg HDC s.c. twice daily, in cycles of 21 days and separated by 6-week intervals) has in each case exceeded that of previous remissions.[225] The effect of famotidine was also investigated on the cytotoxic activity of peripheral blood mononuclear cells and TILs. Both the cytotoxic activity and DNA synthesis of activated TILs were increased by the combination of IL-2 and famotidine, effects that were independent of a decrease in the suppressor T-cell population.[226]

Patients with AML receiving post consolidation immunotherapy with HDC/IL-2 displayed enhanced efficacy in terms of relapse prevention and overall survival (OS) in patients with CR.[227-233] Nevertheless, the treatment did not affect LFS or OS in patients who required more than one cycle of induction to attain CR and was not significantly beneficial in older patients (>60 years old). Statistical analyses confirmed the consistency of the HDC/IL-2 effects compared with untreated patients (Table 2).[232]

Treatment with HDC/IL-2 aims at targeting the formation of immunosuppressive ROS produced by the NOX2 enzyme of myeloid cells (HDC component), while concomitantly activating and expanding populations of NK cells and T cells (IL-2 component) (Table 2).[214] These components act in synergy to promote the NK- and T-cell function and viability demonstrated in vitro, and also synergize to inhibit tumor growth in animal models. Some studies suggest that the combined treatment activates a pool of otherwise hyporesponsive, unlicensed NK cells to exert anti-leukemic activity and reduces MDSCs in blood of AML patients in CR (Table 2).[151,201] Furthermore, Tregs, eosinophil, and NK cell counts were markedly increased in the blood of patients, whereas the absolute counts of $CD8^+$ T cells were not altered (Table 2).[214,225,234,235] In particular, a threefold increase in $CD56^{bright}$ NK cells was observed upon combined treatment in AML patients after chemotherapy.[183] In another clinical trial, treatment with HDC/IL-2 resulted in a blood expansion of $CD56^{bright}$ and $CD16^+$ NK cells, together with an increase in the expression of the natural cytotoxicity receptors (NCR) NKp30 and NKp46 in NK cells, mainly in older patients, being a predictor of LFS and OS (Table 2).[214,236,237] In contrast, the counts of DCs, neutrophils, and monocytes, principally the two major monocyte populations in blood $CD14^{++}CD16^-$ ($CD14^+$) and $CD14^+CD16^+$ ($CD16^+$), were reduced during the first treatment's cycle.[238] This combined treatment also induced a significant increase in the frequency of T effector cells, only in older patients (Table 2).[235] Additionally, it significantly improved LFS and OS of younger AML patients (<60 years) with normal karyotype versus control. These results imply that the clinical benefit of HDC/IL-2 in AML is pronounced in patients harboring leukemic cells of normal karyotype, especially in NPM1-mutated AML patients (Table 2).[230]

Post hoc analyses of efficacy in morphological subtypes of AML among patients participating in the HDC/IL-2 phase III trial, showed a nonsignificant trend toward improvement of LFS in those patients with M0/M1 (undifferentiated/minimal maturation) AML versus controls. No benefit for the treatment was observed in M2 (myeloblastic) AML, whereas HDC/IL-2 significantly improved LFS among patients with M4/M5 (myelomonocytic/monocytic) AML (Table 2). Interestingly, M4/M5 cells, but not M2 cells, expressed H_2 receptors and produced ROS that induced apoptosis in adjacent NK cells, effects that were inhibited by HDC. Therefore, the expression of the H_2 receptor could determine the effectiveness of histamine-based immunotherapy.[231,239] The expression of H_2 receptor was significantly enhanced in $CD14^{++}$ monocytes during and between treatment cycles, as well as in $CD16^+$ monocytes during the first HDC/IL-2 treatment cycle. A high H_2 receptor expression in both monocyte types could better predict LFS and OS (Table 2).[238,239]

On the basis of the results of three completed clinical trials, the treatment of immunotherapy with low-dose IL-2 and histamine dihydrochloride was approved for relapse prevention in AML patients within the European Union.[201,231,234,239]

The development of immunotherapies for lymphoma has undergone a revolutionary evolution over the past decades. Since the first successful immunotherapy with rituximab (monoclonal antibody) for the treatment of B-cell non-Hodgkin lymphoma, a plethora of new immunotherapeutic approaches has ensued.[240,241]

Preclinical studies show that histamine administration (1500 µg/mouse i.p. injection three times a week starting 1 day before tumor inoculation) enhanced the efficacy of anti-PD-1/anti-PD-L1 (100–240 µg/mouse of each antibody, 3, 6 and 10 days after tumor inoculation) in reducing EL4 tumor growth developed in C57BL/6J mice. Although the treatment did not affect the intra-tumoral proportion of MDSCs, or T and NK cells, it slightly increased the fraction of $CD8^+$ T cells displaying an effector phenotype. Treatment of EL4 tumor-bearing mice with histamine did not alter the expression of PD-L1 on MDSCs or PD-1 on $CD8^+$ T cells.[201] A clinical trial was carried out in patients with high-grade non-Hodgkin lymphoma who received repeated cycles of IFNα, IL-2, and histamine [3 million international units (MIU) IFNα, 1.5 mg/kg IL-2, and 0.5 mg histamine, s.c. 1–2 times daily administration, 5 days a week] following relapse and high-dose chemotherapy with stem cells demonstrate that combined immunotherapy induced significant increases in the frequency of cytokine-producing T cells and in NK-cell-mediated cytotoxicity, as well as a reduction in the count of $CD8^+$ T cells that remained low during the posttreatment observation period.[242]

A switch of histamine receptor expression from H_2 to H_1 during the differentiation of monocytes into macrophages is observed in the promonocytic U-937 cell line (derived from a histiocytic lymphoma).[181] The role of cAMP pathways has been well established in hematological malignancies. Elevation of intracellular cAMP using cAMP analogs induces cell cycle arrest, cell differentiation, or apoptosis in leukemia and lymphoma cell lines.[243,244] Although histamine or H_2 receptor agonists increased cAMP levels, they failed to promote U-937 cells' differentiation due to rapid homologous and GRK2 dependent desensitization of H_2 receptors.[245] To further complicate the scene, the H_2 receptor agonist, amthamine, increased intracellular cAMP levels while concomitantly augmented cAMP efflux regulated by multidrug resistance-associated proteins (MRPs), particularly MRP4 in U-937 and other AML cell lines.[246,247]

Therefore, the beneficial anti-tumor effects of histamine in hematological malignancies could not only involve the H_2-receptor-mediated counteraction of the ROS-induced immunosuppressive signals from monocytes/macrophages but also a direct anti-proliferative action via the H_2 receptor expressed in tumor cells, which might further contribute to reach tumor control.

4.2 | Kidney cancer

The most common subtype of kidney cancer arises from the renal epithelium and is called renal cell carcinoma (RCC). Histamine and its receptor ligands have been tested in several clinical trials, although many of the results have been inconclusive and controversial. Donskov et al, have studied the effectiveness and safety of histamine dihydrochloride in combination with low-dose IL-2 and IFNα (1 mg HDC s.c., b.i.d. days 1–5, weeks 1–4, and 3 MIU IFNα s.c., once daily for 1 week, followed by up to nine 4-week cycles of 3 MIU IFNα s.c., days 1–7, weeks 1–4, and IL-2, 2.4 MIU/m^2 s.c., b.i.d., days 1–5, weeks 1 and 2) in patients with metastatic RCC. Although histamine was well tolerated, it does not seem to add efficacy in the scheduled regimen.[248] Using a similar treatment scheme, the same authors found positive correlations between the absolute number of peripheral blood lymphocytes and objective response.[249] However, histamine did not influence TILs, blood leukocyte count, f-chain expression, or cytotoxicity.[250] Regardless of the histamine treatment (1.0 mg HDC, slow 20 min s.c. injection twice daily, concomitantly with 18 MIU IL-2 s.c. once daily, 5 days per week for 3 weeks followed by 2 weeks' rest), patients with high counts of monocytes and neutrophils in peripheral blood had a poor survival.[94,251] The combined treatment of IFNα and cimetidine (5 MIU IFNα per day, five times a week or 5 MIU IFNα intramuscular plus 2400 mg cimetidine oral daily administration), did not result in a significant improvement in the response rates compared with the IFNα monotherapy in a prospective randomized phase III trial conducted in patients with advanced RCC and pulmonary metastases.[252]

The combination of immunotherapies with H_2 receptor antagonists, such as famotidine and cimetidine, have been further investigated. A phase II study showed that combined treatment of IFNα with cimetidine, cyclooxygenase 2 inhibitor meloxicam, and renin–angiotensin system inhibitor candesartan or perindopril (3–6 MIU s.c. thrice/week IFNα, 800 mg cimetidine, 10 mg meloxicam, and 4 mg candesartan or perindopril oral administration), provides favorable responses and low toxicological profiles in patients with advanced RCC.[253] Combined treatment with IL-2 and famotidine (9–21.6 MIU/m^2 IL-2 i.v. and 20 mg famotidine i.v. twice a day) in patients with metastatic RCC suggests some benefit of the combination but the results are not conclusive or significant, probably due to the small number of patients recruited.[254–258]

4.3 | Melanoma

Advanced melanoma is a disease with a very poor prognosis. Dacarbazine and IL-2 have been approved by the FDA for a long time to treat patients with metastatic melanoma. However, overall response rates are very low (16%).[216] Recent studies have shown a significantly higher success rate with the combination of immunotherapy with chemotherapy or targeted molecular therapies. Treatment with nivolumab (anti-PD-1) in combination with ipilimumab (anti-CTL-4) was approved by FDA for melanoma patients with lymph node involvement.[209,259]

Several clinical trials have been performed adding histamine or H_2 receptor antagonists as an adjuvant to IL-2 therapy for patients with metastatic melanoma.[219] Quan et al reported clinical trials conducted from 2004 to 2012, in patients with metastatic melanoma who were treated with famotidine combined with IL-2 in different treatment regimens (9–21.6 MIU/m^2 IL-2 i.v. and 20 mg famotidine i.v. twice a day). Even though the results of one study show that 25% of the patients (4) treated with the combination survived at least 20 months,[260,261] the mean survival of this and other regimens was 7–13 months.[262–265] Another study performed with 241 patients shows that the treatment with HDC/IL-2/IFNα was safely administered on an outpatient basis (3 MIU IFNα s.c., once daily for 7 days, 2.4 MIU/m^2 IL-2 s.c., twice a day for 5 days, and 1 mg HDC s.c., twice a day for 5 days or dacarbazine 850 mg/m i.v. every 3 weeks), but this immunotherapeutic regimen did not improve the response rate or OS compared with dacarbazine.[266]

A significant increase in the production of IFNγ-producing T lymphocytes was observed in patients with melanoma and liver metastases treated with HDC/IL-2 (HDC 1 mg s.c. daily, b.i.d., IL-2 9 MIU/m s.c., daily week 1, 3, and 7, IL-2 2 MIU/m^2 s.c., daily week 2 and 4) compared with those who received IL-2 alone.[267] Other clinical trials investigated the tolerance and response of the combination of IL-2 and IFNα with different concentrations of HDC or cimetidine in patients with melanoma. Treatment regimens were safe and well tolerated. Most of them did not improve the results obtained with IL-2 or IFNα as a single agent.[268–274] However, in three of them, a longer survival was observed in patients with melanoma with liver metastases when using IL-2/HDC and IL-2/IFNα/HDC (2–18 MIU/m^2 IL-2 s.c., 1 mg HDC by slow s.c. injection, and eventually plus 3 MU IFNα s.c. daily administration).[92,275,276]

Other studies in patients with metastatic melanoma treated with protocols comprising histamine, IFNα, and low-dose IL-2 (3 MIU

IFNα s.c. daily, 1 mg HDC s.c., b.i.d., and 2.4 MIU/m^2 IL-2 s.c., b.i.d. for 1–2 weeks) demonstrated a trend toward a gradual increase in the absolute number of circulating $CD56^+$ $CD3^+$ NK cells in patients maintaining stable disease during therapy, and additional tumor infiltration of NK cells ($CD56^+$) and monocytes during treatment was only seen in responding patients.[277]

In addition, preclinical studies showed that the combined treatment with IL-2 and histamine receptor ligands (25 mg/kg histamine, 50 mg/kg ranitidine, 6000 U/kg IL-2; all compounds were administered i.v. as a single dose 24 h before i.v. melanoma cells' inoculation) completely blocked the development of metastasis in Swiss albino, C57BL/6 and BALB/c mice inoculated with B16 murine melanoma cells (F1 and F10 strains). On the other hand, concomitant treatment with ranitidine nullified the anti-metastatic effects of IL-2.[278]

4.4 | Colorectal cancer

In colorectal cancer (CRC), immunotherapy has become an attractive option compared with conventional chemotherapy. Treatment efficiency of three FDA-approved immune checkpoint inhibitors targeting PD-1 and CTLA-4 is influenced by the microsatellite instability status in each CRC patient. Multiple studies are using combination modalities to enhance immune response.[279,280]

MC-38 tumor growth was strongly reduced by the treatment with histamine (1500 µg/mouse i.p. injection 3 times a week starting 1 day before tumor inoculation) and anti-PD-1/anti-PD-L1 (100–240 µg/mouse of each antibody, 3, 6, and 10 days after tumor inoculation), tending to increase the fraction of intra-tumoral $CD8^+$ T cells and raised significantly the fraction of $CD8^+$ T cells with an effector phenotype. In addition, the percentage of intra-tumoral $CD4^+$ T cells was not altered, and NK cells were decreased.[201]

IL-2 was used alone (200 units/ml) or in combination with ranitidine (0.02 mg/ml) to improve in vitro NK cell activity in peripheral blood of CRC patients with liver metastases. Ranitidine synergizes the IL-2-induced NK cell activity.[281]

In addition to the histamine-induced modulation of the anti-tumor immunity, it produces numerous effects on both gastrointestinal epithelium and CRC, considering that H_1, H_2, and H_4 receptors are expressed in both healthy tissues and CRC samples. H_2 receptor signaling suppressed tumor growth in inflammation-associated CRC. On the other hand, H_1 and H_4 receptors, both suppressed in CRC, may have a protective effect against CRC growth. Until now, the use of antihistamines has been used exclusively in CRC to prevent chemotherapy-induced adverse events.[7,282-284]

4.5 | Prostate cancer and other cancers

In prostate cancer, immunotherapy has not yet reached a therapeutic breakthrough as compared to several other solid tumors. Sipuleucel-T and pembrolizumab are the only registered immune-oncology drugs to treat this malignancy.[285]

A study was conducted to determine whether IL-2 and histamine alone, or in combination could modulate the effects of irradiation on Dunning (R3327) rat prostatic adenocarcinoma at the cellular level. It was demonstrated that IL-2, especially in combination with histamine, alters the response to radiation, increasing the number of apoptotic cells, and significantly reducing tumor cells compared to irradiation alone.[286,287]

Immunotherapy for sarcoma (Coley's toxins, IL-2, adoptive T-cell transfer, and immune checkpoint blockade) showed limited success. Ongoing research is studying the combined use of immune checkpoint blockade with other immune modulators, surgery, or radiation.[288] In a rat experimental model bearing BN-175 tumors the association of histamine and IL-2 in the melphalan-based isolated limb perfusion setting showed no improved response (40 µg melphalan, 1 mg histamine, and 50 µg IL-2 in 5 ml total volume perfusate).[289]

On the other hand, glioblastoma is the deadliest form of brain cancer. Some interesting, though controversial, results have been obtained with immunotherapy including IL-2 in various experimental models, as well as in the clinical setting. Combination immunotherapies or treatment regimens involving both standard therapies and immunotherapies show promising results as powerful anti-cancer therapies in glioblastoma.[290] The combination of HDC/IL-2 (HDC 4 mg/kg s.c. as daily injections from day 6 after intracranial tumor implantation, and 1.8 MIU/ml s.c. on day 6 after tumor implantation) significantly reduced tumor growth and the microvessel density in the syngeneic BT4C rat malignant glioma model.[291]

5 | CONCLUSIONS AND FUTURE PERSPECTIVE

Histamine produces a complex and fine-tuned regulation of the phenotype and functions of the different immune cells, producing distinct effects depending on the activated receptor subtype and its signaling. This biogenic amine is able to promote inflammatory and immunoregulatory responses that contribute to pathological conditions, as well as homeostatic function, balancing the inflammatory reactions.

The fate of tumors depends on the levels of pro- versus anti-tumorigenic signals that are provided by the tumor cells and the TME, as well as their specific interactions. Although there are numerous well-known described effects of histamine on the immune system, the number of studies that identify its effects on anti-tumor immunity is still poor. Experimental and clinical findings show that histamine is a crucial mediator of immune cell responses, participating in the anti-tumor immunity in different types of cancer. On the one side, some studies support the pro-tumorigenic effects of histamine through enhancing tumor immune escape via the generation of an immunosuppressive TME. On the other side, a vast majority of the reports demonstrated potent anti-tumorigenic properties, shaping innate and adaptive immune responses to control tumor growth. Not only immune cells but also cancer cells can produce and respond to histamine in a paracrine or autocrine way, which denotes the complexity of the histamine/histamine receptor axis modulation of the anti-tumor immunity. Differences in the levels of histamine, the composition of TME, or histamine receptor subtypes present in tumor cells and immune cells could ultimately determine the biological effects of histamine and pharmacological agents targeting histamine receptors. Therefore, these facts help to understand the controversial studies in cancer research.

In the modern era of cancer immunotherapy, the immuno-oncology field is continuously expanding, with more immunotherapeutic drugs and trials that are transforming the care of cancer patients. In this scenario, the histaminergic system provides a promising strategy for the potential therapeutic exploitation of new immunomodulatory drug targets.

The potential role of histamine in cancer immunotherapy has been investigated for more than a decade. Histamine dihydrochloride is being used in numerous clinical trials as an adjuvant to IL-2 immunotherapy based on its ability to preserve the function of T lymphocytes and NK cells by reducing the monocyte- and macrophage-induced formation and release of ROS. Several studies proved the clinical benefit of the combination, especially in AML. It is important to highlight that histamine was generally well tolerated and no unexpected or irreversible adverse effects were observed, demonstrating that it can be safely administered.

Immunotherapy is now a mainstay of cancer treatment. The success in targeting immunologic checkpoints, including the PD-1/PD-L1 blockade in different solid tumors, has revived the interest in immunotherapies and in combinatorial strategies to achieve additive or synergistic clinical benefits.

One obstacle in the effectiveness of immunotherapy is the complexity and the dynamic nature of immune-related responses. In this line, novel immunotherapy combinations seek immunomodulatory agents capable of manipulating the signals in the TME to boost the immune system against cancer, targeting T cells and other components including myeloid cells. Considering the promising preclinical and clinical data using the combination of histamine with immunotherapies, future clinical trials should be developed to evaluate the efficacy and safety of the combined therapy of immune checkpoint inhibitors and histamine receptor ligands. Taking into consideration the pleiotropic nature of histamine, we hypothesize that histamine could produce nonredundant and complementary anti-tumor effects through modulation of the anti-tumor immunity and induction of direct anti-proliferative actions via histamine receptors expressed in tumor cells. This could further contribute to reach tumor control and gain clinical response, especially for hard-to-treat cancers (e.g., triple-negative breast cancer).

One of the challenges in research on cancer immunotherapy is the lack of appropriate laboratory models to study the immune response and the TME. Several preclinical data that study the tumor response and help to drive clinical actions, are originated in xenograft models developed in immunodeficient hosts, in which the role of the immune system in the response to therapeutics could not be evaluated. One of the major limitations in clinical translation is the use of trustful mouse models that recapitulate the complexity of human cancer and immune populations within the TME. Considering the key role of the histaminergic system in immunomodulation, it is necessary to evaluate the potential therapeutic efficacy of histamine receptor ligands globally, in immunocompetent experimental models. Another challenge in cancer immunotherapy is the discovery and validation of new biomarkers to predict which patients will respond to a determined combination strategy. Further research is needed to evaluate whether any member of the family of histamine receptors could be a molecular marker to guide treatment.

Finally, a completely unexplored topic is the role of histamine-producing bacteria in the response to cancer immunotherapy. The dynamic relationship between the microbiome, the immune system, and cancer is a topic of recent exploration. Microbiota has a key role in how the immune response develops and has a potential impact on the response to immunotherapy. Future studies should have this topic into consideration.

As immunotherapy comes to the forefront of cancer treatments, a better understanding of how histamine regulates immune cells within the TME and how this can influence anti-tumor immunity and patient prognosis is needed and is an interesting avenue for future research.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[384] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[385]

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DISCLOSURE

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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