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Antihistamines as promising drugs in cancer therapy

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Abstract

Histamine is a biogenic amine, synthesized and released by mast cells, which acts as a vasodilator in several pathologic processes, namely in allergies and conjunctivitis. Its role on cancer is not fully understood. High levels of histamine have been associated with a bivalent behavior in regulation of several tumors (i.e. cervical, ovarian, vaginal, uterine, vulvar, colorectal cancer, and melanoma), promoting or inhibiting their growth. Histamine receptors (H1, H2, H3 and H4) are present in a vast group of cells, including tumor cells, making them sensitive to histamine variations. In this work, we review the role of mast cells and histamine on cancer development and the possibility of use antihistamines in the clinical management of this disease.

Keywords: cancer therapy, histamine, histamine receptors, mast cell, microenvironment, tumor

Cancer

Cancer is one of the most important public health problems in many countries around the world. Despite all advances in the diagnosis and treatment of this disease, it is still one of the principal causes of death globally [1]. According to the World Health Organization (WHO) [2], approximately 14 million new cases and 8.2 million deaths from cancer were recorded in 2012. Moreover, disappointing projections are being pointed for the next years, with an increase in the number of new cancer cases *per year* to 22 million over the next two decades [3]. Cancer is a multistage process that arises from genetic and epigenetic alterations responsible for the transformation of normal cells into neoplastic cells [4–6] (Figure 1). Cancers are not only masses of malignant cells but complex “rogue” organs, to which many other cells are recruited and may be changed by the transformed cells. The interactions between the malignant and non-transformed cells constitute the tumor microenvironment [7]. Lymphatic and vascular endothelial cells, pericytes, adipocytes, mesenchymal stem cells, smooth muscle cells, fibroblasts, myofibroblasts, myeloid cells and inflammatory cells (B and T lymphocytes, neutrophils, dendritic cells, eosinophils, basophils, natural killer cells, macrophages and mast cells) are among the non-malignant cells of tumor microenvironment [6,8]. These cells may be identified in the tumor microenvironment by their specific cell surface molecules and may act as tumor-promoting at all stages of

carcinogenesis [9]. Each of them have the capacity to synthesize cytokines, reactive oxygen species (ROS), serine and cysteine proteases, metalloproteinases, growth and pro-angiogenic factors, inflammatory and matrix remodelling enzymes, chemokines, and adhesion molecules that interact among them and with tumor cells promoting tumor growth, invasion and dissemination to other organs (metastization) [10–13]. The evolution, structure and activities of cells in tumor microenvironment have many parallels with the processes of wound healing and inflammation; however, cells such as macrophages may be found in cancers that have no known association with chronic inflammatory conditions [14–16]. Now, it is known that targeting the non-malignant cells of tumor microenvironment or mediators of communication among them could complement other cancer therapeutic approaches, such as chemotherapy and radiotherapy. However, questions about the similarity of tumor microenvironment among different types of cancer, and between primary cancers and metastasis remain unclear.

Mast cells

Mast cells are bone-marrow derived leukocytes that were first described by Paul Ehrlich more than 130 years ago in his PhD thesis [17]. Mast cells were identified in all vertebrates [18] and some authors consider that they may be primitive cells, maybe the surviving remnant of an ancient model of the immune system [19]. Actually, mast cells are strategically placed at the host/environment interfaces. They may be found in proximity to surfaces that are common portals of infection, namely in mucosa of the respiratory, digestive and urogenital tracts, and in the dermis of the skin. Mast cells may also be found in the connective tissue near vessels and nerves, making them key elements in processes of tissue remodeling, wound healing, fibrosis and angiogenesis, and in the central nervous system where the histamine acts as a neurotransmitter [20,21]. Mast cells are not found in avascular tissues, namely mineralized bone, cartilage and cornea [22]. At histological analysis, mast cells appear as round or elongated cells with a diameter ranging from 8 to 20 μm . They have a non-segmented monolobed nucleus with peripherally condensed chromatin [18] and may be easily recognized by their toluidine blue positive granules that fill the cytoplasm. The fully granulated mast cells contain up to 1000 secretory granules (also known as secretory lysosomes) of 60-80 nm that occupy more than 40% of cytoplasm volume [23]. These

granules are the functional cell organelles and they are composed by several substances, namely histamine, serotonin, proteases, cytokines and growth factors [24]. Beyond the secretory granules, in the mast cells' cytoplasm there are also lipid bodies that are a source of triglyceride-derived arachidonic acid [25]. At electron microscopy, it was observed that mast cells' cytoplasm also contains some mitochondria and rough endoplasmic reticulum, and several free ribosomes [18].

Mast cells' maturation

Enerback *et al.* [26] verified that mast cells have a long half-life, they observed that rodent intestinal mast cells have a half-life of at least 40 days. In another study, Ekoff *et al.* [27] concluded that mast cells normally survive within tissues for several months and their number kept relatively constant. Unlike other cells that leave the bone marrow as fully matured cells, mast cells stem from immature precursors (non-granulated cells) that leave the bone marrow to circulate in the blood [28–30]. Then these precursors migrate into different tissues and under the influence of the microenvironmental growth factors such as the stem cell factor (SCF) that is synthesized by fibroblasts, stromal cells and endothelial cells of each tissue, they proliferate and differentiate into fully mature granulated cells (granulated mast cells) [31,32] (Figure 2). Once the progression of mast cells' precursors to fully mature mast cells depends on *c-kit* activation that occurs as a consequence of *c-kit* dimerization and auto-phosphorylation by the SCF, the SCF is also known as *c-kit* ligand. The SCF also regulates mast cells' survival by inhibiting FOXO3a and down regulating the pro-apoptotic BH3 protein [27]. It was observed that mice with a defective surface expression or catalytic activity of *c-kit* have lower number of mast cells in tissues when compared with animals without any alteration [33]. It was also observed that the inhibition of kit catalytic activity by specific tyrosine kinase inhibitor such as imatinib induced human mast cell apoptosis [27]. Although the SCF and its receptor (*c-kit*) are essential for the differentiation, proliferation and survival of mast cells, there are other factors, namely, cytokines and growth factors such as immunoglobulin E (IgE) that are involved in the differentiation, proliferation and survival of mast cells [34] (Figure 2). The IgE acts on mast cells progenitors to induce differentiation into mature mast cells. The linkage of different IgE subtypes to the surface mast cells tetrameric $\alpha\beta\gamma_2$ form of the high-affinity receptor for IgE (Fc ϵ RI) in early stages of mast cells differentiation change the expression of various genes, mainly

those essential to the differentiation, and contributes to the mast cells heterogeneity [34]. Activated mast cells have also the ability to release mediators that induce activation of themselves and their neighboring mast cells. Additionally, the IgE in absence of antigen promote mast cells survival as mentioned above (the IgE reduced the mast cells apoptosis in the absence of growth factor and promote their survival by FcεRI stimulation) and amplify the inflammatory response in allergic tissues (the accumulation of mast cells FcεRI may amplify the inflammatory reactions via molecules such as histamine, leukotrienes, chemokines and cytokines released during their degranulation). These molecules will recruit other immune cells, such as T cells, eosinophils, monocytes and neutrophils, and induce the synthesis of other pro-inflammatory effector molecules [34].

Granules' content and release

Mast cells have the ability to produce, store and release immune-modulatory molecules upon activation. Depending on the agent responsible for the infection (bacteria, virus or parasite), the mediators released by mast cells are different. They produce three main classes of mediators: **1)** granule associated substances: histamine, serotonin, heparin, chondroitin sulphate peptidoglycans, tryptase, chymase, carboxypeptidase, tumor-necrosis factor (TNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), **2)** newly generated lipid-derived substances: leukotriene (LT) C₄, LTB₄, prostaglandin D₂, prostaglandin E₂ and platelet-activating factor, and **3)** a wide variety of cytokines [TNF, interleukin (IL)-1 α , IL-1 β , IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-15, IL-16, IL-18, interferon (IFN)- α , IFN- β , IFN- γ , leukemia inhibitory factor (LIF), granulocyte/macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF)- β and VEGF], chemokines [CC-chemokine ligand (CCL) 2, CCL3, CCL4, CCL5, CCL11, CCL20, CXC-chemokine ligand (CXCL) 1, CXCL 2, CXCL 8, CXCL 9, CXCL 10, CXCL 11], nitric oxide, oxide radicals and antimicrobial peptides [35,36]. The granules' content is extruded to the cell exterior upon cell activation under the form of massive (exocytosis or anaphylactic degranulation) or limited degranulation (piecemeal degranulation) [25] (Figure 2). The first one is characterized by a quick and generalized release of the granules content and occurs during type I allergic reactions. Conversely, the piecemeal degranulation is a selective process (the mast cells may release subtle amounts of granule-stored

mediators) and occurs for a long period of time, namely in chronic inflammatory processes, such as cancer [24]. The regeneration of a granular compartment may take up to 72 hours [23].

Mast cells' responses are governed by their wide range of cell surface receptors which regulate the selective release of mediators. On their surface, they express the FcεRI that is crucial to the activation of their anaphylactic degranulation [37]. For a long period of time, it was thought that two steps were necessary for the mast cells' activation. In the first one, denominated sensitization, the monomeric IgE binds to FcεRI on the mast cells' surface. In the second one, the antigen binds to the IgE that had previously bound with mast cells receptors. However, recent findings verified that the monomeric IgE has the ability to activate mast cells in the absence of antigen, for this the IgE concentrations should be 2-3 log higher when compared with the situation where the antigen is present (Figure 2). In this way, the allergic symptoms may also occur in patients not exposed to allergens [34]. Upon activation via cross-linking of FcεRI, phosphorylation cascades are activated, leading to calcium influx, nuclear importation of transcriptase factors and the mast cells may release all pre-formed granule-associated mediators (degranulation), and they also produce de novo synthesized lipid mediators (namely prostaglandins and leukotriens) within minutes after activation, and a wide range of growth factors (such as cytokines and chemokines) over a more sustained time period [38]. Mast cells may also be activated by other pathways, such as aggregation of FcγRIII by IgG/antigen complexes, *c-kit* and toll-like receptor (TLR) mechanisms, exposure to chemokines, anaphylatoxins C3a and C5a, fragments of fibrinogen and fibronectin, via hypoxia-inducible factor 1α [36,39,40].

Mast cells' classes

In spite of common characteristics, mast cells phenotype differs among species and anatomical locations, being this phenomenon known as "mast cells heterogeneity" [41,42]. Depending on what tissue and species they are derived from, the mast cells may exhibit differences in lifespan, morphology, development, expression of proteases and proteoglycans, and sensitivity to immunologic and non-immunologic stimuli [34]. Rodent mast cells may be classified into two main groups according to their placement: connective tissue mast cells (CTMC) and mucosal mast cells (MMC). The CTMCs only require SCF for their persistence, while MMCs, additionally to the SCF, also require the

T-cell derived cytokines [34]. Accordingly, a reduced number of MMCs was observed in a T-cells deficient mice model, while the number of CTMCs remained normal. Human mast cells are classified according to their granules' proteases content into three different classes. Mast cells that only contain tryptase are denominated as mast cells T (MC_T) and can be found in respiratory and intestinal tracts. Mast cells that contain both tryptase and chymase (MC_{TC}) mainly reside in connective tissues in the stomach, in the intestine mucosa, in the skin, in the parenchyma of the mammary gland, in the myocardium, in the cornea and in the lymph nodes. Comparing humans and rodents, in terms of localization in tissues, the human MC_T correspond to rodent MMC that are mainly found in mucosal tissues, and the MC_{TC} correspond to rodent CTMC that are mainly located in connective tissues. Similarly to that was observed in the T-cells deficient mice model, the humans with a T-cells immunodeficiency lack MC_T, while the MC_{TC} appeared at normal numbers [27].

Mast cells and disease

Historically, the role of mast cells has been focused on atopic disorders, pathogenesis of allergic reactions, response to parasites and bacteria, and anaphylaxis [43,44]. Mast cells are among the first inflammatory cells that interact with invading pathogenic agents, acting as important sentinels of the immune system [43,45]. They have the ability to recognize, attach to, phagocyte and kill Gram-negative and Gram-positive bacteria (innate immunity). By the interaction with B and T cells, and interference in the migration, maturation and function of dendritic cells, mast cells contribute to the initiation of acquired immune response [35,36]. The initiation of innate and adaptive immune response during an infection depends on a rapid burst of pro-inflammatory mediators at the site of infection. Previous studies suggested that the mast cells may be involved in the creation of this pro-inflammatory environment [46]. The mast cells location, expression of diverse receptors that facilitate the pathogens recognition and the pro-inflammatory mediators (cytokines and chemokines) released by them support this hypothesis [46].

The knowledge about mast cells was changing over the years, and nowadays they appear as highly versatile tissue elements that play an important role in several biological settings, namely autoimmune diseases (multiple sclerosis and rheumatoid arthritis), angiogenesis, immune modulation, tissue repair and remodelling, and cancer

[47,48]. However, their role in these diseases and mainly in cancer is not fully understood [49,50]. Although the dense infiltration of mast cells at the periphery of carcinomatous tumors had been described in 1891 by Westphal, the studies about the role of these cells in tumor immunity are very limited [51,52]. Previous studies concluded that mast cells number increase in inflammatory conditions, such as allergy, asthma, skin and autoimmune diseases, and cancer, and they accumulate inside the tissues and orchestrate the inflammatory response [27]. This increased number of mast cells may occur not only due to the increase in the migration of mast cells precursors from the blood, but also due to the *in situ* division of few mature mast cells. Indeed, mast cells and their precursors express several chemokine and growth factors that in response to chemotactic stimuli lead to their migration to inflamed or damaged tissues [53]. It was observed that SCF overexpression in mammary tumors increases mast cells accumulation at sites of tumor growth, while the inhibition of SCF expression results in decreased mast cells accumulation and angiogenesis [54]. A correlation between mast cells number and severity of these diseases was previously reported [33]. The ability of mast cells to synthesize and release potent angiogenic compounds, such as FGF, VEGF, tryptase and chymase is the major point that links them to cancer [55]. Actually, mast cells are among the first immune cells recruited to solid tumors. In the context of tumor environment, several stimuli such as anti-tumor antibodies, hypoxia, alarmins, cytokines and chemokine may activate mast cells' degranulation [56]. The role of mast cells on tumor development is yet contradictory, mast cells and their mediators may exerts both pro-tumor (angiogenesis, extracellular matrix degradation and immune suppression) and anti-tumorigenic effects (cytotoxic activity, immune cell recruitment and activation) [56] (Figure 3). Although the overall impact in tumor microenvironment is contradictory, the mast cells density was described as an indicator of poor prognosis in Hodgkin's lymphoma, melanoma, endometrial, cervical, esophagal, lung, gastric, colorectal and prostate carcinomas. Since the mast cells are involved in several diseases, their use as a target for new therapeutic approaches seems very attractive. Their control may be done by the regulation of their number or activity (inhibiting the release of substances or inhibiting their linkage with respective receptors, such as inhibition of histamine linkage to their receptors). The mast cells' activity may be directly suppressed by the use of mast cell stabilizing agents or indirectly targeting mast cells mediators. As example, the tumor necrosis factor (TNF) may be targeted by anti-TNF monoclonal antibody and antihistaminic drugs may be inhibited the histamine action [57].

Cancer and inflammation

Since 1863, when Virchow hypothesized that cancer arises from sites of chronic inflammation, a possible link between chronic inflammation and cancer has been recognized. Inflammation is defined as a physiological process in response to tissue damage by microbial pathogen infection (virus, bacteria or parasite), chemical irritation or wounding [58]. Since chronic inflammation is characterized by several processes that have been implicated in cancer initiation and progression, such as infiltration of mononuclear immune cells (macrophages, lymphocytes), up-regulation of pro-inflammatory molecules (cytokines, reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS) and NF- κ B), tissue destruction, fibrosis, increased angiogenesis and promotion of invasion, increased genomic damage and DNA synthesis, increased cellular proliferation, disruption of DNA repair pathways and inhibition of apoptosis, it is reasonable to consider that inflammation provides the key mutations and a favorable microenvironment for cancer development [59,60]. Indeed, most tumors are infiltrated by several inflammatory cells [8,58,61–63]. Chronic inflammation induces both proliferation of resident mast cells and recruitment of mast cells and their precursors [64] and they have been associated with angiogenesis, and tumor growth and metastasis [34]. These facts suggest that mast cells may participate in tumorigenesis rather than providing a defense against the tumors [34]. Numerous epidemiologic, research and clinical studies verified that an association exists between chronic inflammation and cancer development in several organs, namely breast, urinary bladder, ovary, liver, stomach, intestine, prostate and skin [51,52,65–68]. According to some authors, tumor cells express phenotypes similar to inflammatory cells, expressing cytokines, chemokines and their receptors that have an important role on cancer angiogenesis, migration and metastasis. Some authors also verified that the expression of referred mediators is higher in high-grade mammary tumors when compared with low-grade mammary tumors [8,69,70].

The gastric infection by *Helicobacter pylori* is the leading cause of gastric adenocarcinoma [8,62]. The chronic inflammation of biliary tract by *Clonorchis sinensis* is associated with the development of cholangiocarcinoma [8]. The chronic hepatitis by hepatitis B and C viruses predisposes to the development of hepatocellular carcinoma [71]. Infection by human papillomavirus is the main cause of penile and anogenital (anal and cervical) cancers in humans [58,72]. *Schistosoma haematobium*'s

chronic infection is a factor that contributes to increase the incidence of urinary bladder cancer [73] and the infection by this agent represents the main risk factor for the development of urinary bladder squamous cell carcinoma in several schistosomal endemic countries in Africa [74]. Human herpesvirus 8 is associated with high risk to develop Kaposi's sarcoma [58,72]. The risk of colorectal cancer was higher in people with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis [75,76]. A higher risk of esophageal and pancreatic cancer was also observed in people with esophagitis and Barrett's metaplasia, and chronic pancreatitis, respectively [62,77]. An association between Marjolin's ulcer and skin carcinoma was also observed [62], asbestos exposure and mesothelioma [62], chronic asthma and lung cancer [78,79], silica exposure and bronchial cancer [62], sarcoidosis and lung, skin and liver cancer [80], ulcerative lichen planus and verrucous carcinoma [81,82], foreskin inflammation and penile cancer [83], pelvic inflammatory disease or ovarian epithelial inflammation and ovarian cancer [62,84], chronic prostatitis and prostate cancer [85]. Allergies are also responsible by chronic inflammation. Although several researchers have studied the association between cancer risk and allergies, this association remains unclear and contradictory [86,87]. As mentioned above, some investigators have reported that the development of cancer in several organs is positively influenced by the inflammation [88–90]; according to the other authors the inflammation does not exert any kind of influence [91,92]; and for other investigators the inflammation associated with allergies seems to have a negative influence on cancer development [93–95]. According to some authors, allergy may confer protective effects to cancer development due to the hyperstimulation of the immune system [93,96,97], with a consequent better response of a stimulated immune system to an initiated cell when compared with a non-stimulated immune system. Inversely, other investigators suggest that allergies are permanent state of inflammation associated with the release of several inflammation mediators, such as cytokines that increase the risk of cancer development [90]. Over the last years, researchers have focused their attention on the development of new drugs for cancer therapy, however poor response and severe toxicity of these drugs remain as a main problem in the treatment of oncologic patients. Besides to the development of new drugs, it is important to improve the cancer therapeutic strategies with the existing ones [98]. One of therapeutic approaches used in oncology that has been used from several years in the treatment of allergic diseases is immunotherapy; through the stimulation of the immune system, it intends that inflammatory cells phagocyte neoplastic cells [99–

102]. Due to their abundance at tumor periphery, their proximity to blood vessel, their radiation resistance and ability to change tumor microenvironment, mast cells represent an important target for tumor immunotherapy [98].

Histamine

Histamine, also known as 2-(4-imidazolyl)ethylamine or 5b-amino-ethylimidazole, is an endogenous physiological active substance that was discovered and chemically classified as a biogenic amine in 1910 by Henry Dale and Patrick Laidlaw [103–106]. They observed that histamine promoted the contraction of smooth muscle from the gut and respiratory tract, vasodilation, increased vasopermeabilization, increased mucous production, stimulated cardiac contraction and induced shock-like syndrome when injected in animals [104,107]. Some years later, in 1920, histamine was recognized as a stimulator of the acid secretion in the stomach and proposed as mediator of anaphylactic and allergic reactions [108–110]. Histamine is synthesized by the enzyme L-histidine decarboxylase from the amino acid histidine [109]. It is synthesized and stored within cytoplasmic granules or vesicles of several cells, namely mast cells (they are the main source of histamine), basophilic mediate, lymphocytes, platelets, enterochromaffin cells and histaminergic neurons, acting as a neurotransmitter in the central nervous system [19,111]. Histamine is the major and the most important bioactive amine released by degranulation of mast cells. Upon release into the extracellular microenvironment, it has a half-life of around one minute in the extracellular fluid and it is degraded by the enzymes *N*-methyltransferase and diamine oxidase [18]. Serum and tissue histamine levels may be measured by fluorometric and radio-enzymatic techniques [112]. Histamine is present in all tissues of mammals, ranging from less than 1 µg/g to higher than 100 µg/g. The histamine is present in higher concentration in skin, connective tissue, lung and gastrointestinal tract [112].

Histamine has a crucial role in several physiological and pathophysiological processes, namely conjunctivitis, allergic rhinitis, urticaria, atopic dermatitis, anaphylaxis, bronchoconstriction, mucus secretion, asthma and gastric acid secretion [113–116]. *In vivo* and *in vitro* studies with human cell lines of breast cancer, lymphoma, leukemia, cervical, ovarian, vaginal, uterine, vulvar and colorectal cancer, and melanoma showed the positive involvement of histamine in cancer cell proliferation, migration and invasion [98].

Histamine receptors

Histamine exerts its effects by binding to and activating histamine receptors [113,117]. Up to now, four different types of histamine receptors have been identified: H1, H2, H3 and H4 [118]. All of these receptors belong to the family of heptahelical G protein-coupled receptors family [98,118] and are expressed by several cells and tissues (Table 1). These histamine receptors were also identified by genomics-based approaches (reverse transcription polymerase chain reaction) in several human tumors, namely breast cancer, lymphoma, leukemia, cervical, ovarian, vaginal, uterine, vulvar, and colorectal cancer and melanoma [98].

Depending on the binding of histamine to each receptor, the induced physiological response will be different. The activation of H1-receptors is responsible by the activation of pathways that trigger many symptoms of allergy, namely vasodilatation, bronchoconstriction, pruritus, rhinorrhea, oedema and smooth muscle contraction [112,119]. H2-receptors are the main responsible by the regulation of gastric secretion and in low grade by the control of arterial blood pressure and bronchoconstriction, when these receptors are activated they stimulate gastric acid secretion and promote vasodilation [98,120]. H3-receptors inhibit excessive bronchoconstriction and regulate pruritus. They also act as presynaptic autoreceptors in central and peripheral nervous system, controlling release and synthesis of histamine and other neurotransmitters, such as dopamine, serotonin, noradrenaline, γ -aminobutyric acid and acetylcholine [112,121–124]. H4-receptors show significant homology with H3-receptors [112]. They regulate the differentiation of myeloblasts and promyelocytes, induce chemotaxis and have an important role in chronic inflammatory skin diseases [112,125–127].

Histamine and allergic diseases

Although it is not the purpose of this work, the role of histamine in allergic reactions is essential to understand its role in cancer. During the acute phase of allergic reactions, histamine is released in high quantities by mast cells [113–116,128]. Activation of histamine receptors promotes smooth muscle constriction, vasodilation, endothelial permeability, and stimulates sensory nerves. These alterations promote clinical manifestations that are characteristic signs or symptoms of allergic diseases [117]. In the nose, histamine stimulates the sensory nerve endings and increases vascular permeability and glandular secretions, causing itching, sneezing, oedema, obstruction,

rhinitis and rhinorrhoea [113–117]. Similar to that occurs in the nose, the histamine also increases vascular permeability in the skin, promotes vasodilation and stimulates sensory nerve endings causing erythema, pruritis, urticaria, oedema and itching. In chronic allergic inflammation, histamine released by mast cells is responsible for the activation of inflammatory cells, such as basophils and eosinophils and the release of proinflammatory mediators, such as leukotriens and cytokines [113].

Mast cells and histamine in cancer

During the tumor development, mast cells precursors migrate into the tumor and constitute one of the major stromal cell populations [64]. Some studies suggest that the mediators released by mast cells have both detrimental (promote tumor growth, neovascularization, immunosuppression and tumor invasion) and beneficial effects for the host (inhibit the tumor, induce apoptosis, stimulate inflammation, inhibit metastasis) [19]. So, the involvement of mast cells in tumor onset and progression is far from being fully understood [19] (Figure 3). If in one hand, some authors observed a correlation between the progressive increase in mast cells number and poor prognosis in human melanoma, oral squamous carcinoma and prostate cancer; in the other hand, other studies observed a positive correlation between mast cells infiltration and prognosis in women with breast cancer [64]. A positive correlation between mast cells density and microvessel density was also observed in esophageal squamous cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, renal cell carcinoma, melanoma and oral squamous cell carcinoma [129]. If proved the positive role of mast cells on cancer progression, they may be a new target for the adjuvant treatment of tumors by inhibiting angiogenesis, tissue remodeling and tumor promoting molecules [64].

Despite firstly hypothesized in 1960's that histamine may be involved in carcinogenesis process, nowadays this issue still remains in discussion [130]. Some researchers observed high activity of the enzyme L-histidine decarboxylase by immunohistochemistry and reverse transcription-polymerase chain reaction, and high levels of histamine by radioimmunoassay in some tumors, namely colon, breast and endometrial cancers, melanoma and small cell lung carcinoma [131–138]. It was also observed that blood levels of histamine in human patients with breast, prostate and lung malignant tumors were two or three times higher when compared with healthy ones and

they remained high for two months after surgery and dropped close to normal levels three months after surgery [139]. Histamine content was unequivocally increased in ovarian, cervical and endometrial cancer when compared with adjacent normal tissues, suggesting the participation of histamine in carcinogenesis [134]. According to some authors, the effects of histamine on tumor growth depends on histamine concentration, the tumor cell type and the receptor subtype to which it binds [140,141]. Rivera and colleagues [142] studied the mammary adenocarcinoma chemically-induced by the carcinogen agent *N*-methyl-*N*-nitrosourea (MNU) in female rats and observed that the activation of histamine receptors with concentrations of histamine up to 50 nM increased tumor cells proliferation while the use of higher concentrations inhibited tumor cells growth. Likewise, the stimulation of human pancreatic carcinoma PANC-1 cells with low levels of histamine (0.01 μ M) increased tumor cells proliferation and the stimulation with higher concentrations (10 μ M) decreased tumor cells proliferation [143]. According to an *in vivo* study performed on a melanoma xenograft model and an *in vitro* study using cells from mice spleen, histamine promotes cancer growth by stimulating cell division and activating suppressor T-cells that are responsible by the down regulation of immune system [144,145]. Lawson *et al.* [146] observed a high number of mast cells in colorectal cancer tissue. They also observed that cancer cells that are near to the histamine-producing cells are highly proliferative, affecting negatively the prognosis. Our research team also identified a mixed inflammatory infiltrate composed of numerous mast cells and less abundant lymphocytes in mammary tumors and urinary bladder tumors chemically-induced by carcinogen agents MNU and *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in a rodent model, respectively [147,148].

Several reports also demonstrated that histamine may be a promising pharmacological agent for the protection of radio-sensitive healthy tissues against ionizing radiation-induced adverse effects. The administration of histamine preserved the morphological and functional characteristics of small intestine, salivary glands and bone marrow in rodents [149–151]. Additionally to this, it was also described that histamine potentiates radiation-induced anti-neoplastic effects in human breast cancer cells. The combination of histamine and gamma radiation enhanced the apoptosis and DNA damage in triple-negative breast tumor cell line (MDA-MB-231 cells) implanted in nude mice [152]. Damodar *et al.* [153] and Martinel Lamas *et al.* [154] also demonstrated the cytoprotective effects of histamine against the doxorubicin-induced toxicity in heart and liver, without compromising the anti-tumor activity of doxorubicin.

As mentioned above, histamine acts by binding with different receptors [140,155]. Histamine may exert angiogenic effects through the interaction with H1 and H2 receptors [64]. It may also induce tumor cell proliferation through H1 receptors and the suppression of immune system through H2 receptors [64]. Different histamine receptors were found in several cancer cell lines and human neoplastic lesions. H1 and H2 receptors were identified in breast cancer [142,156,157], lymphoma, leukemia [158], melanoma [159], cervical, ovarian, vaginal, vulvar [160] and colorectal cancer [161]. H3 receptors were identified in breast cancer [162] and melanoma [159]. H4 receptors were identified in breast [162], cervical, ovarian, vaginal, vulvar [163] and colorectal cancer by genomics-based approaches [161]. H3 and H4-receptors are the main receptors in human neoplasias, controlling the metabolic pathways responsible by the tumor growth and progression [98].

Antihistamines

The term antihistamine is frequently used to define only substances that act as inverse agonists of H1-receptors [113,164], however the other substances that act as inverse agonists of H2, H3 and H4-receptors are also considered antihistamines. The first antihistamine was synthesized by Staub and Bovet in 1937 [165]. Antihistamines have a molecular structure similar to the histamine with which they compete [166]. The first antihistamine applied in humans was phenbenzamine in 1942 to treat allergies and skin conditions, such as pruritus and irritation [112]. Since then, the antihistamines have been used for many years as the main treatment for the relief of allergic signs or symptoms caused by histamine release [113,167,168]. They are frequently used in several clinical conditions, including allergic conditions (rhinitis, dermatoses, atopic dermatitis, contact dermatitis, allergic conjunctivitis, hypersensitivity reactions to drugs, mild transfusion reactions and urticaria), motion sickness, vertigo and insomnia [111]. According to their chemical structure, H1-antihistamines may be classified into six groups: alkylamines, ethanolamines, ethylenediamines, phenotiazines, piperazines and piperidines [111,117,169–171] (Table 2). Based on antihistamines pharmacological and toxic properties and their side-effects in central nervous system, these H1 antihistamines may also be divided into two distinct groups: the first-generation and the second-generation antihistamines [113,172] (Table 2). The first-generation antihistamines, also called classic antihistamines, have a low molecular weight, are highly liposoluble, easily cross the blood-brain barrier and show high affinity to the H1-receptors of the

brain, causing sedation, incoordination, vertigo, lack of concentration and in some cases, agitation and excitability [113,170]. The sedative effects reflect not only in sleepiness, they also affect the cognitive performance that can prejudice several daytime activities that require high concentration [113]. These first-generation antihistamines have short half-life, being necessary multiple daily doses [170,171]. They are less expensive when compared with the second-generation ones [173]. Beyond their inhibition of central and peripheral H₁-receptors, H₁ antihistamines also inhibit muscarinic and adrenergic receptors, causing drying of nasal secretions and mouth, urinary retention, tachycardia, blurred vision and hypotension [113,126].

The second-generation antihistamines, also called newer antihistamines, were developed in the early 1980's to minimize the adverse effects of first-generation antihistamines mentioned above [170]. They have high specificity to H₁-receptors and low affinity to non-histamine receptors, namely to the muscarinic and adrenergic receptors [113,170,174,175]. Contrary to the first-generation antihistamines, the second-generation antihistamines have high molecular weight, are low liposoluble and have low affinity to the cerebral H₁ receptors, being unprovided of effects on central nervous system when administered at therapeutic doses [113]. These antihistamines have longer half-life, allowing the administration of only one or two doses *per day* [170,174,175]. Although the second generation antihistamines were designed to overcome the sedative effects of the first generation antihistamines, some of them show sedative effects when used in high doses [113]. In the last years emerged a new class of antihistamines, the third-generation antihistamines. Third generation antihistamines are active metabolites of first-generation antihistamines that were developed with the aim of improving clinical efficacy and minimizing adverse effects [169]. The definition of this class is not consensual among the scientific community. So, the Consensus Group on New generation antihistamines concluded that a new class of antihistamines must demonstrate clinical advantages over present compounds and must be free of cardiotoxicity, drug interactions and central nervous system effects [113]. The cardiotoxic effects of antihistamines, namely arrhythmia and prolongation of the QT interval, are associated with the use of excessive doses or when they are simultaneously administered with other drugs [113].

The most frequently used H₃ and H₄ antihistamines may be consulted in Table 2. H₂ antihistamines or H₂ blocker drugs are frequently used in the treatment of duodenal ulcers, gastroesophageal reflux disease and in the prophylaxis of conditions where there

is high gastric acidity [155]. Due to their interaction with H₂-receptors, these drugs may also have a modulatory effect on immune system [155]. The effects of antihistamines vary from patient to patient [113]. It is necessary to adjust the dose of antihistamines in patients with renal or hepatic insufficiency [172]. Similar to that occurs in all medicines, the knowledge of pharmacodynamics and pharmacokinetics is essential to the correct use of these drugs [113,172,173]. Although the antihistamines' safety and appropriate use is not fully clarified, they are among the most frequently prescribed drugs in both children and adults [113,172,173]. Even though the role of mast cells is not fully understood, they have been generally considered protumorigenic cells; their inhibition by the use of frequently used and well-known antihistamine drugs, namely the ketotifen that not only acts as antihistamine drug but also stabilizes mast cells' membranes inhibiting their degranulation, would be a promisor therapeutic approach.

Pharmacodynamics

Antihistamines are a class of pharmacological agents that may inhibit the action of histamine by different ways: blocking histamine receptors (acting as inverse agonists) or inhibiting the activity of the enzyme L-histidine decarboxylase [176]. Besides their capacity to interact with histamine receptors and enzyme L-histidine decarboxylase, some antihistamines, namely ketotifen and desloratadine, have the capacity to inhibit the release of histamine by mast cells and consequently the mast cell activity. They inhibit mast cells degranulation by stabilizing their membranes, presenting antiallergic and anti-inflammatory effects [113,177–180]. Antihistamines also exerts an anti-inflammatory activity by inhibiting the accumulation of inflammatory cells and their activation, probably by the suppression of nuclear transcription factor kappa B (NF- κ B) [181].

Pharmacokinetics

Nowadays, antihistamines are available as both prescription and non-prescription drugs [167]. Antihistamines may be administered by different routes, namely orally and topically [167,182]. When administered by oral route, antihistamines show a good absorption and reach the plasma concentration within three hours after administration [126]. The simultaneous administration of antihistamines and some food, namely grapefruit juice, change plasmatic concentration of antihistamines due to the blockage of action of cytochrome P450 (CYP) 3A4. This may also occur due to the interaction

between antihistamines and some drugs [126,174]. Although the biotransformation of antihistamines is not clearly understood, it is known that they are predominantly biotransformed in the liver by the CYP enzyme system, mainly by CYP3A4 isoenzyme. Other isoenzymes, namely CYP1A2 and CYP2D6 may be involved in antihistamines metabolism [174,183–186]. The metabolic breakdown products, mainly inactivated, are excreted by the kidneys and eliminated in the urine [113,172]. Some antihistamines are eliminated in the feces after biliary excretion, without metabolic alterations [172].

Antihistamines and cancer risk

Several investigators have studied the relationship between cancer risk development and the use of antihistamines in humans. The results of the studies are complex and contradictory [140]. Nadalin and collaborators [167] performed a study where they evaluated the relationship between antihistamines use and development of breast cancer. In this study, they enquired a total of 3,133 women with breast cancer and 3,062 without the disease with age ranging from 25 to 74 years-old, about the regular use of antihistamines at any time of their lives; they found no association between antihistamines use and the risk of breast cancer development. In another study, Kelly and colleagues [187] studied the association between antihistamines use and breast cancer risk in 5,814 women with invasive breast cancer and in 5,095 healthy women between 18 and 69 years of age; similarly to that was observed by Nadalin and collaborators, their findings did not support any association between the antihistamines use and breast cancer development. Some studies suggest that the use of antihistamines is not associated with a risk for cancer development, cancer recurrence or occurrence of metastases [167,187–189]. The opinions regarding to the association between the exposition of antihistamines for a long period of time (ten years or more) and the development of glioma are also divergent. According to some investigators, the exposition to these compounds is favorable [97,190–193]; based in epidemiological studies, Scheurer and colleagues [194] verified that the risk of glioma development is reduced with the exposition of antihistamines. It was also observed that antihistamines inhibit the growth of human melanoma [195], colorectal [196] and leukemic [197] cell lines. Several researchers observed that the aminoethyl ether group of antihistamines is structurally similar to N,N-diethyl-2-(4-(phenylmethyl)phenoxy) ethanamine HCl (DPPE) that is a tamoxifen derivative known to inhibit the *in vitro* growth of MCF-7 breast cancer cells by binding with intracellular histamine receptors [167,198,199].

Brandes and collaborators [199] observed that B16F10 melanoma and C-3 fibrosarcoma cell lines injected in a syngeneic mice model grown quickly after the administration of human equivalent doses of the H1 antihistamines loratadine and astemizole (for both tumors) and hydroxyzine (for melanoma only), they also verified that doxylamine and cetirizine did not change the growth of any cell lines. In an *in vitro* study performed by Brandes and co-workers [198] in MCF-7 and EVSA-T human breast cancer cell lines, it was observed that hydroxyzine was cytotoxic against these human breast cancer cells. Hadzijusufovic and colleagues [200] reported that H1 antihistamines terfenadine and loratadine inhibited the *in vitro* growth of HMC-1 human leukemia cell line, C2 and NI-1 canine mastocytoma cell lines. Since the growth of stomach cancer is promoted by the histamine [201], it was hypothesized that the inhibition of histamine receptors may be an effective strategy for blocking the growth of stomach cancer cells [202,203].

The H2 antihistamine cimetidine remains as one of the most commonly prescribed medicines around the world [204]. It was first proposed as an anti-cancer drug in 1979 [205], but its effects are not consensual. It was observed that cimetidine has positive effects in patients with renal cell carcinoma [206], malignant melanoma [207] and glioblastoma [208]. Jiang and collaborators [203] performed a study where they evaluated the *in vitro* and *in vivo* effects of the H2 antihistamine cimetidine. By 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltrazolium bromide (MTT) assay, they evaluated the growth inhibitory effects of different concentrations of cimetidine after 24 and 48 hours of exposition in SGC-7901 human gastric carcinoma metastatic lymph node cell line, in MGC-803 human gastric mucinous adenocarcinoma cell line and in GES-1 normal human gastric epithelial cell line. They verified that cimetidine induced apoptosis in neoplastic cells and had almost no effect in the normal gastric cells. In the same work, they performed a xenograft model by subcutaneous injection of SGC-7901 cell line in the dorsal region of three groups of BALB/c nude female mice; when tumors reached 100 mm³, tumors from group one were injected with cimetidine at a concentration of 100 mg/kg, tumors from group two were injected with cimetidine at a concentration of 200 mg/kg, and tumors from group three did not receive any treatment. The treatment was performed two times a week, during four consecutive weeks. At the end of the experiment, they observed that tumor volume and weight were lower in cimetidine treated animals when compared with non-treated animals, being this reduction higher in the group that received the highest concentration of cimetidine. However, Brandes and collaborators [199] observed that the daily intraperitoneal injection of the well-known

H2 antihistamine cimetidine for 18 days did not have any effect in B16F10 melanoma and C-3 fibrosarcoma cell lines subcutaneously injected in C57BL and C3H female mice. Takahashi and colleagues [209] evaluated the effects of cimetidine in a syngeneic model. CT-26 mouse colon adenocarcinoma cell line was intradermally (i.d.) injected in the lumbar region of BALB/c female mice. Rats were daily treated with a subcutaneous (s.c.) injection of cimetidine at a concentration of 0.12 mg/kg or with saline during consecutive 14 days. During the experiment they observed that the tumor volume and weight were lower in treated animals when compared with non-treated animals. Bowrey *et al.* [210] performed a clinical trial, where they evaluated the effects of a short-term preoperative course of cimetidine (400 mg twice a day for five days prior surgery) in breast cancer patients and no relationship between preoperative cimetidine administration and tumor cell proliferation was observed.

Cimetidine inhibits tumor growth and metastasis by different ways. It inhibits cell adhesion of tumor cells, exerts antiangiogenic effects by the inhibition of VEGF that has been recognized as an important angiogenic factor, induces apoptosis, activates macrophages, activates the immune system through the increase of interleukin levels, increases infiltration of tumors by immune cells and inhibits immunosuppression [155]. Several *in vitro* studies with cell lines of different types of cancer, namely mammary, colon, prostate, ovarian, liver and Ehrlich ascites cancer, melanoma, glioblastoma, leukemia, mastocytosis and lymphoma have been employed to evaluate the effects of several antihistamines in cancer development. Furthermore, *in vivo* studies in humans, in syngeneic, xenograft and chemically-induced animal models of cancer have been also employed to assess the influence of antihistamines in carcinogenesis. These studies may be consulted in Table 3.

In a study performed by our research team, where the role of mast cells was evaluated in the initiation and progression of mammary tumors chemically-induced by the carcinogen agent MNU in Sprague-Dawley female rats, through the inhibition of mast cell degranulation by the administration of ketotifen, we observed that animals from ketotifen-treated groups developed less number of mammary tumors (palpable masses) but higher number of mammary lesions when compared with non-treated animals. A lower proliferation (Ki-67 immunoexpression) and apoptotic index (caspase-3 and -9 immunoexpression) in ketotifen-exposed animals was also observed. The main positive effect of mast cell inhibition seemed to be the reduction of tumor proliferation when the

mast cell degranulation was inhibited before tumor development (submitted for publication).

Conclusion

Histamine receptors were identified in several cancers, namely in mammary, cervical, ovarian, vaginal, uterine, vulvar, colorectal cancer, and melanoma. The results of some studies that evaluated the effects of mast cells mediators on cancer development suggest that they may be potential targets in new cancer therapies, since the inhibition of their degranulation avoid the release of pro-tumor mediators. Since monotherapy is typically insufficient to completely eradicate cancer, combination therapy is generally administered. Given that antihistamines toxicity is lower when compared with conventional chemotherapeutic agents used in cancer, the study of their use as adjuvants for conventional therapy is warranted. However, before recommending the use of antihistamines as new cancer agents, it is necessary to clarify the exact level of histamine receptors in different types of tumors and the effects of the activation of each one on cancer growth, evaluating them *in vitro* and *in vivo*.

Conflict of interests: None to declare.

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Figures' legends:

Figure 1. Schematic representation of carcinogenesis stages and tumor microenvironment. Cancer begins with the mutation of one cell (Initiation), then this cell divides itself originating other mutated cells (Promotion). During this process, tumor is reached by several inflammatory and non-inflammatory cells that constitute tumor microenvironment. As last step, tumor cells go to other tissues, originating a new tumor in distant organs (Progression).

Figure 2. Schematic representation of mast cells' maturation and activation. Mast cells derived from non-granulated immature precursors (hematopoietic stem cells) that originate in bone marrow. These stem cells give rise to mast cell progenitors that circulate in the blood and migrate into different tissues. In tissues, under the influence of several factors, namely stem cell factor (SCF) that links with c-kit receptor and immunoglobulin (Ig) E that links with FcεRI high-affinity Fc receptor for IgE (FcεRI), they undergo differentiation and maturation becoming mature granulated mast cells. After a contact with an antigen, mast cells degranulation is promoted and the substances contained in the cytoplasmic granules are released.

Figure 3. Bivalent role of mast cells on tumors' progression. Mast cells may promote or inhibit tumor growth by the synthesis and release of several granule compound. FGF-2 -

fibroblast growth factor-2; IL - interleukin; INF- α - interferon; LTB₄ - leukotriene B₄; MCP - monocyte chemoattractant protein; MMP - matrix metalloproteinases; NGF - nerve growth factor ; PDGF - platelet-derived growth factor; TGF- β - transforming growth factor β ; TNF- α - tumor necrosis factor- α .

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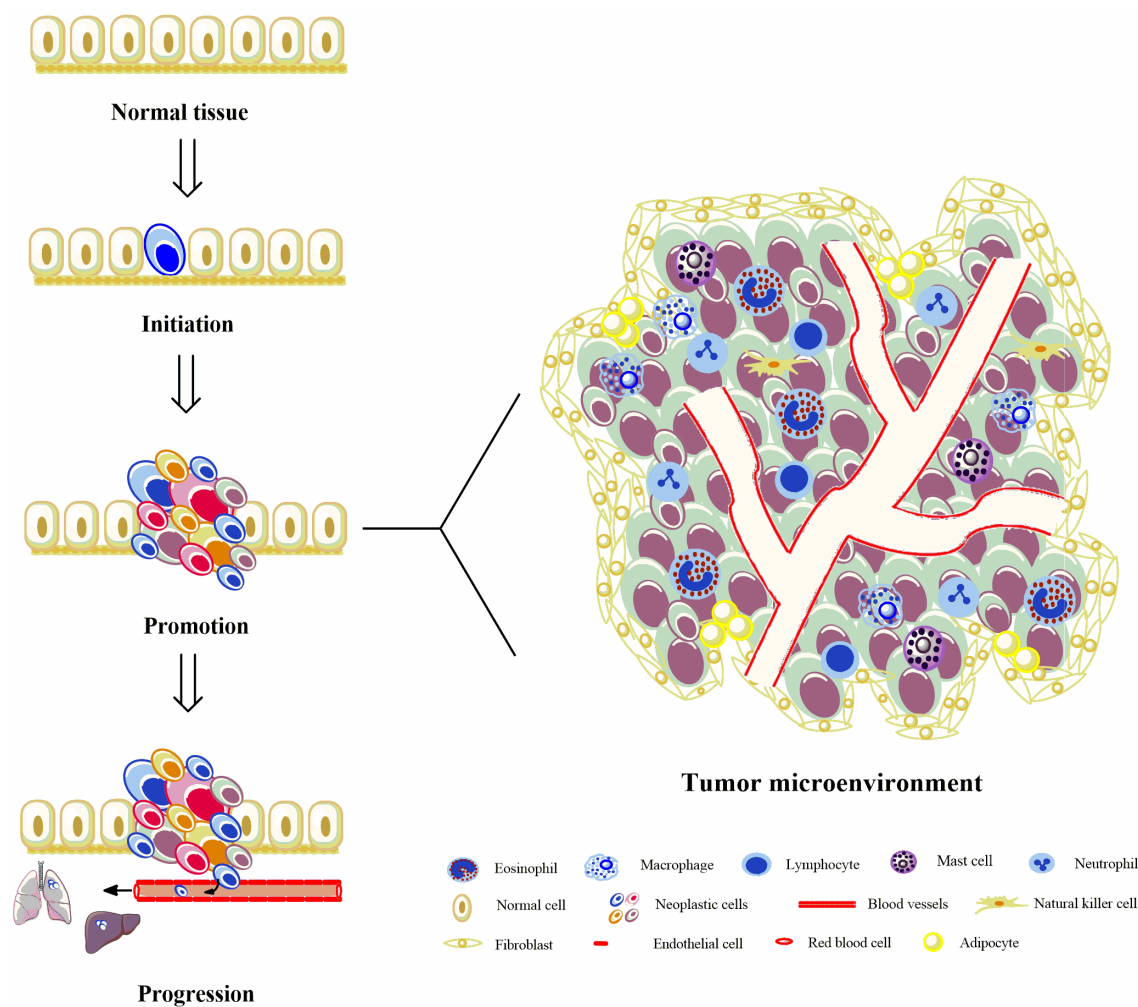


Figure 1

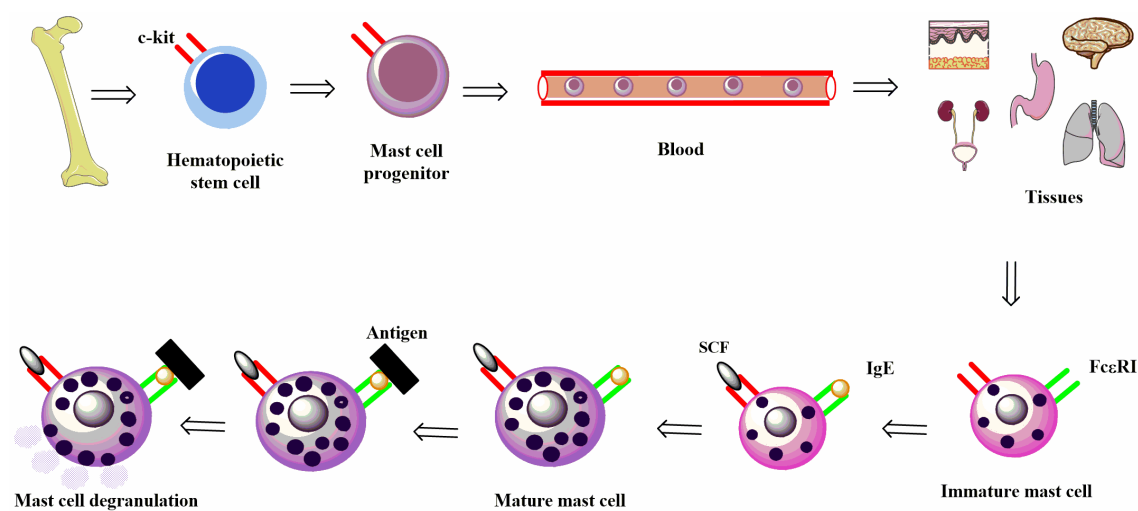


Figure 2

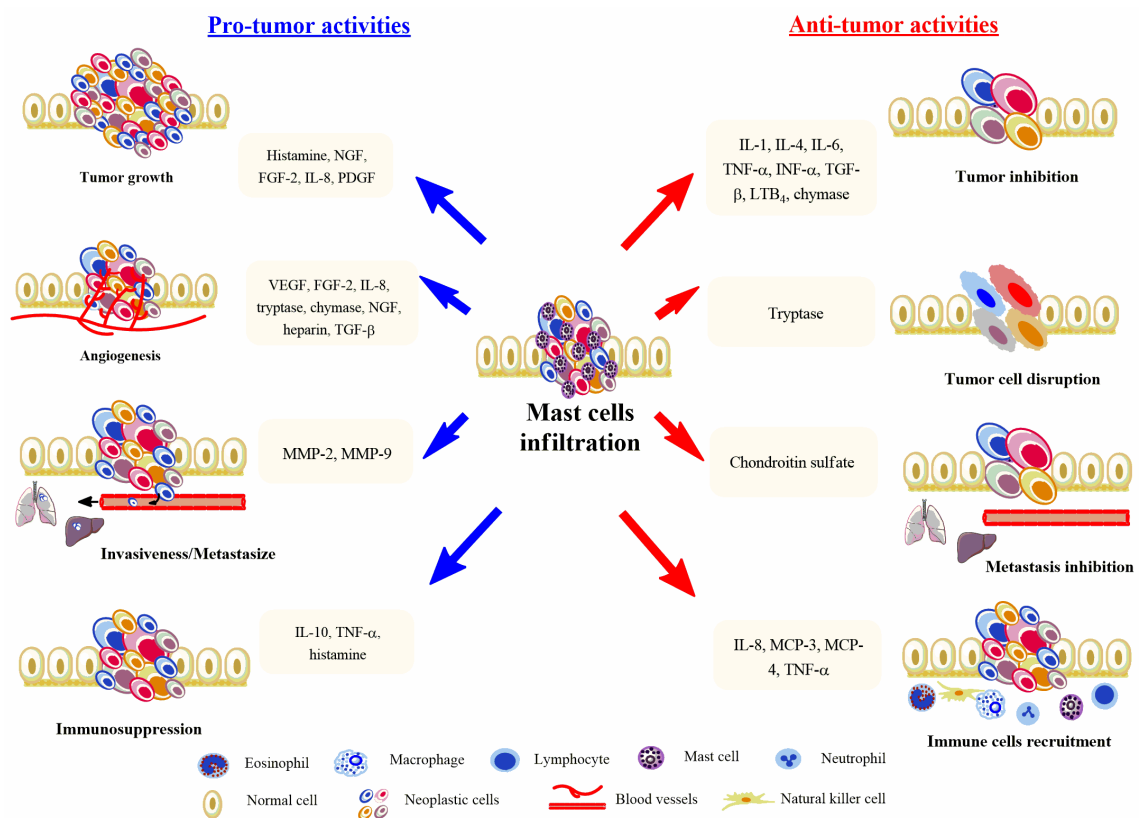
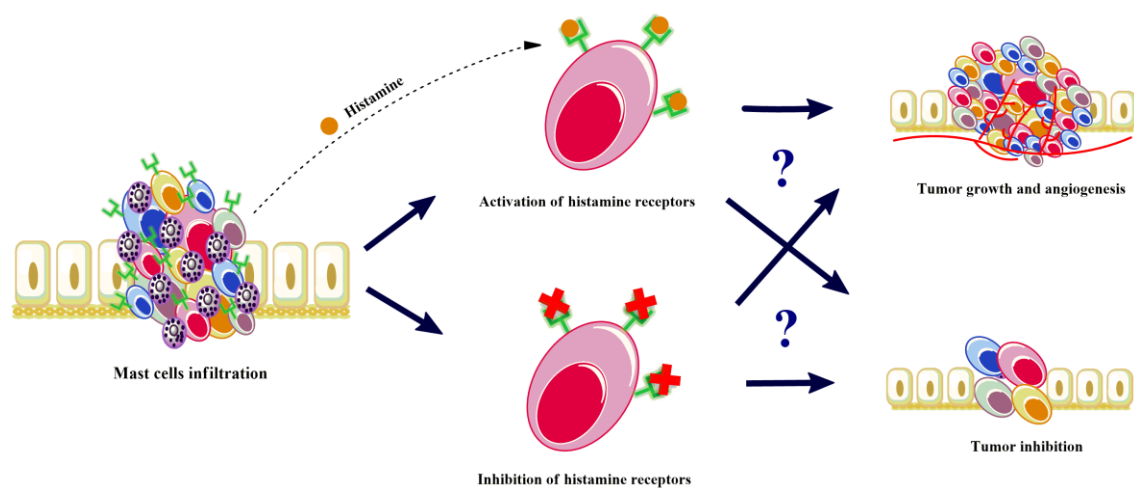


Figure 3



Graphical abstract

Table 1. Distribution of histamine receptors in all cells and tissues [98,105,112,125,126,211–221].

H1	H2	H3	H4
Adrenal medulla	Chondrocytes	Eosinophils	Basophils
Cardiovascular system	Dendritic cells	Histaminergic neurons	Bone marrow
Chondrocytes	Endothelial cells	Monocytes	Colon
Dendritic cells	Eosinophils		Dendritic cells
Endothelial cells	Epithelial cells		Eosinophils
Eosinophils	Gastric parietal cells		Heart
Epithelial cells	Heart		Hematopoietic cells
Gastrointestinal tract	Hepatocytes		Hepatocytes
Genitourinary system	Monocytes		Lung
Hepatocytes	Nerve cells		Mast cells
Monocytes	Neutrophils		Monocytes
Nerve cells	Smooth muscle		Nerve cells
Neutrophils	T and B cells		Neutrophils
Smooth muscle			Small intestine
T and B cells			Spleen
			Stomach
			T cells
			Thymus

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Table 2. Most frequently used H1, H2, H3 and H4 antihistamines [111,113,117,120,126,169–172,222].

H1 antihistamines	First generation	Alkylamines	Brompheniramine; Chlorpheniramine; Dexbrompheniramine; Dexchlorpheniramine; Dimethindene; Pheniramine; Triprolidine
		Ethanolamines	Bromazine; Carbinoxamine; Clemastine; Dimenhydrinate; Diphenhydramine; Doxylamine; Ophenadrine; Phenyltoloxamine
		Ethylenediamines	Antazoline; Mepyramine; Pyrilamine; Tripeleennamine
		Phenothiazins	Methdilazine; Promethazine; Trimeprazine
		Piperazines	Buclicine; Chlorcyclizine; Cyclizine; Hydroxyzine; Mebhydrolin; Meclizine; Oxatomide
		Piperidines	Azatadine; Cyproheptadine; Diphenylpyraline
	Second generation	Alkylamines	Acrivastine
		Piperazines	Cetirizine; Levocetirizine
		Piperidines	Astemizole; Bilastine; Desloratadine; Ebastine; Fexofenadine; Ketotifen; Levocabastine; Loratadine; Mizolastine; Olopatadine; Terfenadine; Rupatadine
	H2 antihistamines	Burimamide; Cimetidine; Dimaprid; Famotidine; Lafutidine; Nizatidine; Pibutidine; Ranitidine; Zolantidine	

H3 antihistamines	Ciproxifan; Imoproxifan; Impromidine
H4 antihistamines	Alobenpropit; Clobenpropit; Thioperamide

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Table 3. In vitro and in vivo studies to assess the efficacy of antihistamines in cancer therapy.

Model		Drug	Dose	Effects	Reference
<i>In vitro</i>	Tumors N-methyl-N-nitrosourea induced in ♀ Sprague-Dawley rats	Ranitidine	Concentration of 10µM	Inhibited tumor cells proliferation	[156]
	HT29 (human colon carcinoma); DU145 (human prostate carcinoma); SF295 (human glioblastoma)	Loratadine followed by radiation treatment	Concentration of 75µM	Pre-treatment with loratadine increased radiation induced cytotoxicity	[223]
	SUM-229PE and T-47D (human invasive ductal carcinoma cell lines)	Astemizole	Concentration of 0.5-4.5 µM, for 6 days	Inhibited tumor cells proliferation	[224]
	A375, HT144, HSs294T and MJOI (human melanoma cell lines)	Terfenadine, astemizole, diphenhydramine, tripolidine	Concentration of 0.1-1mM for diphenhydramine and tripolidine;	All drugs induced apoptotic cell death in all cell lines	[195]

		1-10 μ M for terfenadine and astemizole, for 6 to 24 hours		
HMC-1 (human mast cells leukemic cell line)	Terfenadine, loratadine	Concentratio n of 10 μ M, for 6, 12, 24, 48 or 72 hours	Both drugs induced apoptosis in neoplastic mast cells	[200]
HT29 and COLO 205 (human colon adenocarcinom a cell lines)	Meclizine	Concentratio n of 10- 100 μ M, for 24 hours	Induced a dose- dependent decrease in cell number	[225]
MDA-MB231 and MCF-7 (human breast cancer cells)	Chlorphenira mine	Concentratio n of 250 μ M, for 48 hours	Induced a dose- dependent decrease in cell number	[226]
A375, HT144, Hs294T (human melanoma cell lines)	Terfenadine	Concentratio n of 0-20 μ M; for 24 hours	Induced apoptosis	[227]
A375 (human melanoma cell lines)	Cimetidine, Terfenadine	Concentratio n of 0-10 μ M; for 2-10 hours	Cimetidine did not show effects on cells;	[228]

				terfenadine induced a dose and time- dependent cytotoxicit y	
	HBL-2, Granta-519 and Leko-1 (human lymphoma cell lines)	Cyproheptadi ne	Concentratio n of 25µmol/L, 30 µmol/L and 40 µmol/L	Decreased mitochondr ial membrane potential at high concentrati ons; induced apoptosis	[229]
	Mz-ChA-1; SG-231; HuCCT-1; CCLP-1; HuH- 28; TFK-1 (human cholangiocarci noma cell lines)	Clobenpropit	Concentratio n from 1- 50µM; for 48 hours	Inhibited cells proliferatio n in a dose- dependent manner	[230]
Human	Colorectal cancer	Cimetidine	(1) p.o.; 400mg/Kg; for 2 years after surgery. (2) p.o.;	(1) Increased patients surveillanc e in 40 months (1)	[231,23 2]

		400mg/Kg; for 5 days before surgery.	or 14 months (2 and 3)	
		(3) p.o.; 800mg/Kg; for 5 years before surgery.		
	Ranitidine	i.v.; 100mg intra- operatively followed by 150mg/Kg p.o. for 5 years	Increased patients surveillanc e in 80 months	[233]
Mastocytosis	Cyproheptadi ne	0.38mg/Kg/d ay; for 33 months	Reduced degree of blistering; child grown and developed normally without sign of disease	[234]
	Ruptadine	Concentratio n of 20mg/day; for 28 days	Controlled symptoms and improved quality of life	[235]

50 Grey horses	Melanoma	Cimetidine	p.o.; 3.5mg/Kg/2 times days or 7.5mg/Kg/day; for 60 days	It was not effective in the treatment of horses melanoma	[236]
Sprague-Dawley rats	Colonic tumors chemically- induced by 1,2- dimethylhydrazine	Cimetidine; Diphenhydramine	p.o. in drinking water; 100mg/Kg/day; for 26 weeks	Cimetidine did not reduce the incidence of colon tumors; both drugs did not affect the staging and degree of differentiation of tumor	[237]
		Cyproheptadine	i.p.; 1mg/Kg; single doses	Reduced number of tumors; increased necrosis in neoplastic cells	[238]
♀ C57BL mice/ ♀ C3H mice	<i>Syngeneic</i> ; B16F10 melanoma cells and C-3 fibrosarcoma cells;	Loratadine, astemizole, cetirizine, hydroxyzine	i.p. administration; human-equivalent dose; once a day; for 18-	Loratadine and astemizole promoted the growth of both	[199]

	subcutaneous injection		21 days	tumors	
				Hydroxyzi ne promoted the growth of melanoma. Cetirizine did not have any effects	
BALB/c nude mice	♀ <i>Xenograft</i> ; SGC-7901 (human gastric carcinoma metastatic lymph node cells)	Cimetidine	Intratumoral injection; 100mg/Kg for 2 days; 200mg/Kg for 2 days; for 4 weeks	Decreased tumors volume and weight	[203]
	♂ <i>Xenograft</i> ; C170 and LIM2412 (human colon adenocarcinom a cell lines)		Subcutaneou sly implanted; 100mg/Kg/d ay; for 21 or 28 days	Inhibited tumor growth (lower number and volume of tumors)	[131]
	<i>Xenograft</i> ; KK (ovarian carcinoma cell lines)		p.o. in drinking water; 25, 50 or 100mg/Kg/d ay; for 20 days	Decreased tumor growth	[239]

C57BL mice	♀ LL57B004 (mice Lewis lung carcinoma); subcutaneous or intramuscular injection	Cimetidine	p.o. in drinking water; 100mg/Kg/day; for 20 days	Decreased cell growth	[132]
	♂ <i>Syngeneic</i> ; McB6-1 (mice fibrosarcoma cell line); subcutaneous injection	Mepyramine	i.p.; 0.2mg; 7days/week; for 35 days	Induced a slight increase in tumor growth; decreases animals' survival	[240]
Immunodeficient nude mice	<i>Xenograft</i> ; Mz-ChA-1 (human cholangiocarcinoma cell lines); subcutaneous injection	Clobenpropit	i.p.; 20mmol/Kg/day; for 39 days	Inhibited tumor progression and decreased tumor volume	[230]
Immunodeficient SCID mice	<i>Xenograft</i> ; HT168 (human melanoma cell line); intradermal injection	Ranitidine, cimetidine	p.o. in drinking water; 50mg/Kg/day	Both drugs inhibited tumor growth	[241]
♂ nude mice	<i>Xenograft</i> ; C170 and LIM2412	Ranitidine	p.o. in drinking water; 25, 50	Ranitidine had no effect in	[146]

	(human colonic adenocarcinoma cell lines)		or 100mg/Kg/day (C170); 10, 25 or 50mg/Kg/day (LIM2412); for 28 days	C170 cell line. Ranitidine stimulated tumor growth in LIM2412 cell line	
	<i>Xenograft</i> ; MKN45G (gastric adenocarcinoma cell line); subcutaneous injection	Cimetidine	p.o. in drinking water; 100mg/Kg/day; for 20 days	Inhibited proliferation of tumor cells	[242]
DBA2 mice	<i>Syngeneic</i> ; MDAY-D2 (mouse leukemic cells); subcutaneous injection	Cyproheptadine	i.p.; 10mg/Kg/day; for 5 or 10 days	Abolished formation of malignant ascites; inhibited tumor growth; induced apoptosis of tumor cells	[243]
Sublethally irradiated NOD/SCID mice	<i>Xenograft</i> ; LP-1(human multiple myeloma line); subcutaneous			Delayed tumor growth; lower tumor	[243]

	injection			volume; induced apoptosis of tumor cells	
Mice	<i>Syngeneic</i> ; Ehrlich carcinoma cells were inoculated	Chlorphenira mine	i.p.; 0.2mL/day of 6.4mM chlorphenira mine solution; for 7 or 11 days	Decreased tumor growth	[244]

i.p. intraperitoneal injection, **i.v.** intravenous administration, **p.o.** oral administration