

CHAPTER 11

Histamine in Normal and Malignant Cell Proliferation

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Abstract

Histamine is a biogenic amine widely distributed throughout the body. Given the observations that histamine can be induced and made available in an unstored diffusible form in tissues undergoing rapid growth (such as tumors and regenerating liver), it could have a role beyond inflammatory and allergic responses.

Histamine and Cell Proliferation

It is an old clinical/pathological observation that the risk of the development of cancerous processes is increased in tissue adjacent to areas of long-standing inflammation. Intuitively researchers and clinicians have long ago deduced that abnormal inflammatory responses and in particular those that are persistent, may promote the development of certain tumors. Recently, researchers have generated a more detailed picture about the molecular background of this empirical observation. It has been demonstrated that inflammatory mediators, which under normal circumstances are activated only for a short time and then are rapidly down-regulated, can, when improperly regulated, support the development, invasivity or angiogenic activity of some tumors. Convincing evidence is available showing that if production of inflammatory mediators is prolonged or their normal functions become modified, they can provide support for both tumor formation and progression. In accordance with these observations an attempt to redefine the paradigm of solid tumors has taken place, with new the interpretation of tumors as “wounds that never heal”—referring to an abnormally long and drawn-out regeneration-like process that is frequently present around progressing tumors. Histamine may have a role in this process since overexpression of histidine decarboxylase (HDC) has been detected in a wide range of tumors, including colon, breast, stomach, lung cancer and leukemia. On the other hand neoangiogenesis and antitumor immune responses are also clearly influenced by histamine and can modify local tumor growth. In this chapter we attempt to summarize the most well known effects of histamine on normal and tumor cell growth.

Histamine in Normal Cell Proliferation

The hypothesis that histamine could be involved in cell differentiation and proliferation was proposed in the 1960s and still remains controversial. In this section the discussion will be confined to “normal proliferation”, that is proliferation where the normal highly sophisticated systems for controlling proliferation are functionally intact. Situations where proliferation control is corrupted, damaged or even completely abolished will be dealt with in the section on malignant proliferation.

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In the following section an attempt will be made to overview the large amount of available data regarding the effects of histamine on cell proliferation. It is a widely accepted fact that proliferation—being one of the most common phenomena in living organisms—represents the very fundament of a great number of vital processes such as reproduction, growth, differentiation, functional and structural repair, regeneration, hematopoiesis and the immune response. Furthermore, as a consequence of its vast impact on virtually all physiological processes, proliferation stands under the strict control of probably the most secured regulative systems that evolution has equipped the species with. Obviously, proliferation cannot be interpreted within narrow borders as in most cases it means far more than simply cell reproduction. Proliferation often represents only an initiation step and is part of more complicated processes such as wound healing and immune responses.

Gastric Mucosa

Histamine is involved in the regulation of diverse physiological and pathological processes in the gastric mucosa. It is generally accepted that histamine plays a central role in mediating gastrin-stimulated gastric acid secretion of the stomach. Gastrin acts indirectly, as it induces HDC-expression, enhances HDC activity and forces histamine release from ECL (enterochromaffin-like) cells in the mucosa that in turn stimulates acid secretion in an H_2R dependent manner. In addition, gastrin is able to induce massive proliferation of several cell types within the mucosa. It has been proposed that gastrin-induced mucosal proliferation could in fact be a histamine/ECL cell-elicited response as well. The first known targets of the proliferation-supporting effects of gastrin were the mucus secreting cells of the mucosa. In a recent study, however, somewhat unexpected results were reported regarding the induction of gastrin-mediated mucosal proliferation.² In this work the impact of treatments with histamine H_1 receptor (H_1R), histamine H_2 receptor (H_2R) and histamine H_3 receptor (H_3R) antagonists (mepyramine, famotidine and clobenpropit, respectively) was investigated. In consensus with an earlier study¹ it was reported, that although signals coming through H_2R or H_1R are probably irrelevant, inhibition of H_3R expressed mostly on neurons blocked proliferation and emigration of stem cells of the fundic mucosa. In complete agreement with this, experimental H_3R activation via its specific agonist, (R)-alpha-methylhistamine, resulted in increased number, volume and secretory activity of differentiated mucus-secreting cells on the mucosal surface.²

In addition to mucus-secreting cells it is possible that gastrin-induced ECL cells could be targets of their own histamine secretion as well. The observation that ECL cells—being highly sensitive to gastrin induced proliferation—express considerable amounts of H_1R and H_2R support this possibility and it was suggested that H_1R acts as a proliferation promoting-factor in emerging ECLomas. Finally, some light was shed in this area owing to the work of two independent groups studying H_2R antagonist-mediated suppression of acid secretion.^{3,4} Sustained blockade of acid secretion increases stomach pH, which evokes gastrin production as compensation. However, the prolongation of this hypergastrinaemia aberrantly increases tissue histamine content and overall mucosal thickness due to gastric cell and ECL-cell hyperplasia. The two groups independently concluded that although H_1R -coupled signals are unable to influence gastrin levels, gastric cell proliferation and, under normal physiological circumstances, ECL cell proliferation, this situation is changed during sustained suppression of acid secretion. In such cases, H_1R mediated signals support the proliferation of ECL cells.^{3,4}

The third possible question is the putative connection between histamine and regenerative proliferation during the removal of mucosal damage associated with massive stress or ulcers. Ulcer healing can be accelerated by careful H_2R antagonist treatment owing to its moderating impact on acid secretion. Interestingly, in an in vitro experimental setting where the deleterious effect of gastric acid secretion was excluded, H_2R antagonist treatment remained effective by enhancing regeneration-like processes within a stimulated ulcer. It was observed that ulcer-like “wounds” scratched into confluent monolayers of MKN 28 gastric adenocarcinoma cells “healed” faster in H_2R -antagonist treated cultures than in untreated control ones. Accelerated healing was a result of a faster proliferation of cells neighboring the damaged areas, rather than enhanced migration

to the "wounds".⁵ Whether H₂R blockade could foster ulcer healing in this way in vivo remains to be elucidated. The already mentioned data suggesting that H₂R antagonists in healthy animals fail to influence mucosal proliferation may be insufficient to clearly rule out this possibility. As we have seen for examples with H₁R and ECL cells, the proliferation-inducing efficiency of histamine through the same receptor can be very different under different physiological situations. While H₁R remained irrelevant regarding proliferation of ECL-cells under normal physiological circumstances, they gained relevance in acid suppression. It is possible that similar differences can be observed with the roles played by H₂R in a healthy stomach versus an ulcer-bearing one.

Hematopoietic Proliferation

After initial work in the late 1970s showing that histamine was able to induce hematopoietic stem cell proliferation by promoting resting bone marrow cell progression from the G0 to the S phase via H₂R,⁶ a real rush broke out in searching for further effects of histamine on hematopoiesis. At first it was suggested that histamine-mediated signals through H₂R may induce proliferation of certain precursor cell types within the myeloid lineage. At low concentrations (10⁻⁸ M) histamine was able to enhance granulocyte precursor proliferation and colony-forming unit activity (CFU-C) resulting in an increased number of differentiated neutrophils. The effect described, however, was limited to granulocytes, as the monocyte-macrophage lineage remained unaffected.⁷

The possible existence of such a differentiated effect of histamine on distinct hematopoietic precursors was again suggested by a report investigating LPS-provoked induction of HDC-expression in several tissues. It was found that G-CSF and GM-CSF could specifically evoke rapid HDC-activation in the bone marrow in contrast to other cytokines strongly coupled with inflammatory responses and characterized by broad HDC-activating properties like TNF- α , TNF- β , IL-1 α and IL-1 β . However, M-CSF does not transmit such signals, emphasizing the proposed differences between the sensitivity of granulocyte and macrophage precursor proliferation to histamine.⁸ Later Dy and coworkers suggested that instead of exogenous histamine signals it might be advisable to consider nascent (i.e., newly synthesized) histamine from the hematopoietic bone marrow cell itself.⁹ After stimulation with IL-3, a cytokine known to promote hematopoiesis, bone marrow derived colony-forming units in the spleen (CFU-S) strongly up-regulated histamine production and this was apparently coupled with their entry in the cell cycle. This remarkable temporal association was proven to be functional as well, as inhibition of histamine synthesis with α -fluoromethylhistidine (α FMH) or blocking histamine signaling via H₂R strongly impeded IL-3 induced proliferation.⁹ Further research by this group provided evidence for a similar requirement of nascent histamine synthesis for hematopoietic proliferation initiated by a combined treatment with IL-1 and GM-CSF.¹⁰ Interestingly, neither IL-1 nor GM-CSF could evoke proliferation alone, although both supported survival of CFU-S cells under some circumstances. Regarding GM-CSF, this result was far more surprising: how is it possible to stimulate histamine synthesis in bone marrow cells on the one hand (as noted above), but not to induce proliferation on the other?

Although the exact background of these phenomena was not fully clarified, a theory was proposed that GM-CSF acts as a factor modulating not only histamine synthesis, but also diminishes the H₂R/H₁R ratio on the surface of the precursor cells. This reduces the proliferation-promoting capacity of histamine since H₂R and H₁R have opposite influences on the proliferation of stem cells. This proliferation-blocking regulatory effect of GM-CSF on histamine receptors was suggested to be alleviated by simultaneous IL-1 signals thereby rendering the cells sensitive to H₂R-mediated mitogenic signals rather than to an H₁R-mediated inhibition. This theory was supported to some extent by similar observations indicating that IL-1 combined with other mitogenic cytokine signals was able to enhance bone marrow proliferation, although alone it fails to induce hematopoiesis.¹⁰ Interpretation of this data and other available reports regarding histamine-induced hematopoietic proliferation has led to the notion that it was heavily questionable whether histamine should be considered as a common general regulator of bone marrow proliferation. Histamine-provoked proliferation of hematopoietic stem cells is apparently a rather

exceptional, intermittent phenomenon limited to periods characterized by an activated immune system, as almost all of the cytokine signals that induce histamine synthesis in the bone marrow are more or less coupled with ongoing immune responses.

Fibroblasts and Fibrosis

Enhanced proliferation, migratory activity, altered production of and interactions with extracellular matrix components (matrix remodeling) are characteristic features of fibroblasts participating in fibrosis. There is a clear and accepted connection between chronic inflammation and fibrotic aberration of connective tissues (e.g., *Mycobacteria*-infected tissues show heavy granulomatous fibrosis because of permanent inflammation due to unsuccessful immunological clearance of the bacteria), however the fact that mast cell activation could also result in similar consequences is not widely recognized. Since the late 1970s, experimental models have provided strong evidence for abnormal accumulation and enhanced degranulation of mast cells in lung fibrosis¹¹ and, furthermore, for increased histamine content in the bronchoalveolar lavage of patients suffering from these disorders.¹² As mast cell over-activation appeared in response to many structurally unrelated fibrosis-inducing agents in several experimental settings and the exhibited mitogenic effect of mast cell mediators was not limited to the lung,¹³ it was proposed that histamine might be a general inductor of fibrosis.

In their pioneer work Jordana et al¹⁴ first demonstrated in a pure *in vitro* setting that histamine was in fact able to enhance fibroblast proliferation, an effect that could be abrogated by H₂R but not by H₁R antagonist treatment.¹⁴ More recently a significant advance was made in this area as it was reported that histamine induced both proliferation (via both H₁R and H₂R) and migration of conjunctival fibroblasts (via H₂R dependent signaling pathways).¹⁵ Histamine seemed also to be capable of stimulating procollagen I production in these cells, however this effect remained unaffected by H₁R or H₂R antagonists¹⁵ suggesting involvement of another type of histamine receptor. Finally, similar results were obtained in a study conducted with human fibroblasts treated with sonicated human mast cells, as it was again shown that mast cell components such as histamine and tryptase support fibroblast proliferation and collagen synthesis.¹⁶

Mammary Gland and Uterus

In the murine uterus rapidly dividing epithelial cells of the endometrium are major sources of histamine. In these cells the level of HDC-expression is controlled mainly by progesterone-mediated signals, which, interestingly, induce maximal level of HDC-expression on the day of implantation (day four of pregnancy). Epithelial cells from the mammary glands of mice, rats, pigs, guinea pigs, cows and humans express HDC at high levels leading to a local histamine concentration that is one of the highest among mammalian tissues.¹⁷ In the mammary glands activity of the HDC gene is under the control of estradiol. Estradiol signal transduction appears to influence HDC expression at the transcriptional level. Estradiol induces HDC expression resulting in a progressively increasing rate of histamine synthesis during the estrus cycle and, in mice and rats, a significant increase in the histamine content of the mammary gland can be observed during the late, proestrus-estrus phase of the cycle.

Moreover, during the development of the mammary glands in young females there is an elevated histamine level along with rapid cell proliferation.¹⁷ Mammary glands are able to synthesize and inactivate histamine, since the activity of both histidine decarboxylase and at least one of the histamine-catabolizing enzymes has been demonstrated in these tissues. Furthermore, expression of both H₁R and H₂R has been detected in the mammary gland.¹⁸ These data suggest that histamine fulfills the basic criteria for involvement in the physiological regulation of mammary tissue. Interestingly, during the development of the mammary glands H₁R and H₂R change the coupling to their respective signal transductional pathways.¹⁹ Between 30 and 60 days of age, as a consequence of progressive branching, the gland of young virgin rats exhibits a profuse mitotic and DNA-synthesizing activity, which declines progressively with age. During this period histamine H₁R and H₂R are coupled to their second messenger systems in a rather uncommon way initially described in mammary adenocarcinoma cells.²⁰ Consequentially, expression of a high affinity H₂R

that activates phospholipase C (PLC) instead of adenylyl cyclase makes it possible for histamine to modulate cell growth. Later in the adult female tissue, the coupling of the high affinity H₂R changes to adenylyl cyclase, thus playing a role in differentiation. All these data support the hypothesis that histamine is a mediator of hormonal actions regulating proliferation in tissues such as mammary glands and the uterus.

Skin

The ability of keratinocytes to synthesize, store and release histamine has been proposed to be related to the physiological functions of histamine in the skin.²¹ Initially these functions were thought to be related to inflammation and itching, however, more recently it was suggested that they might also be coupled to keratinocyte proliferation, differentiation and function.²² Histamine is released in the skin from both mast cells and keratinocytes; both cell types contain considerable amounts of HDC. The effects of histamine in the skin are mainly mediated by the activation of H₁R.²³ The expression of H₂R on keratinocytes was also reported, but its physiological importance is less clear. Recent observations have suggested that the activation of this receptor may have a role beyond the usually described response to inflammation. Accumulating evidence indicates that the activation of the H₂R may not always increase cAMP production in keratinocytes, but under some circumstances can be connected to the PLC signaling pathway. Interestingly, histamine metabolism is reduced during keratinocyte differentiation and is associated with a significant reduction in HDC mRNA levels, intracellular histamine content and histamine release. This reduction is followed by a substantial down-regulation in the expression of H₂R that influences the functional coupling to the PLC signaling pathway, suggesting that histamine may have a paracrine/autocrine role on the regulation of keratinocyte growth.²⁴ Histamine could also stimulate the production of IL-6 and other cytokines by keratinocytes, thereby enhancing cell proliferation.²³ The regulation of H₂R expression has been demonstrated in other cell lines during cellular differentiation. Furthermore, strong evidence suggests that histamine could participate in epithelial cell differentiation in an autocrine manner. Consequently, the presence of HDC and the accumulation of histamine in the undifferentiated phenotype, point to a broader function for histamine and for the H₂R as mediators of keratinocyte growth.

Tumor Formation—Principles

The development of malignant tumors is a long process lasting years or decades and recent progress has led to a more detailed picture as to the molecular mechanisms involved. Recent information suggests that there are two main phases in the development of clinically manifested tumors—that is the malignant transformation of normal cells and the subsequent tumorous progression of the transformed clones that results in a gradually independence from the mechanisms controlling cellular growth, tissue integrity and homeostasis. We also know that one major driving forces of this process is the random mutations that cells accumulate during their individual life. This effect modifies their genome and can transform healthy cells as well as constantly leading to the formation of newer mutant variants among the already cancerous cells. The other driving force is continuous clone selection, which sorts out the most resistant clones from the numerous competing tumor cell variants. These cells are then able escape from the grab of the anti-tumor mechanisms activated against them. In the long run this process is the microscopic analogue of the gradual adaptation process of different species evolving in their natural environments, i.e., evolutionary development. This has led to the view that the development of tumors is a type of microevolution. One of the capital conclusions of this concept is that in the body among the permanently appearing precancerous cells (cells that have just started transformation) only an insignificantly small proportion can reach a degree of development where they can form clinically relevant tumors. However, the other message of this theory is that cells found in such tumors have come down a long evolutionary road and are well adapted to the environment surrounding them and to its defensive reactions. In other words, cells of clinically manifested tumors can be considered as a peak in tumor microevolution.

It is well known that there are several intrinsic reasons for initiating and stimulating tumor formation and malignant progression. Such intrinsic reasons are the limited chemical stability of DNA, faulty DNA replication in dividing cells, errors of genomic repair and imprinting systems and the DNA damaging effects of reactive free radicals. Furthermore, there are external transforming effects as well. For instance, physical mutagens like ionizing radiation that cause chain breaks in DNA or ultraviolet radiation-induced dimerizing of adjacent pyrimidine bases. There are also chemical mutagens such as alkylating agents, other agents that intercalate into the DNA double chain, various nucleotide-base analogues and so on. Finally, besides the physical and chemical effects, certain biological factors also belong to the group of external carcinogenic factors. For instance, some pathogens, like the retroviruses, infiltrate randomly into the genome and may inactivate crucial genes or transactivate adjacent genes through insertion of aggressive retroviral promoters. In addition, there are certain DNA-viruses that are not built into the genome, but can produce proteins with transforming effects. Other biological factors are genomic parasites that are located at the border of endogenous and exogenous tumorigenic effects, for instance the various transposons that are moving continuously in the human genome as well as other, similar transposable elements.

To counter these effects numerous regulating, correcting, cellular distress and immunological defensive systems are mobilized to maintain the organism's operability. In the majority of cases these systems are able to keep the process of malignant transformation and cancerous progression in check. These systems include the DNA repair systems mentioned above that protect the integrity of the information coded in the genome and the automatically activated "built-in" cell cycle controlling points and tumor suppressors in dividing cells that stop the further division of the cells, if necessary. These can also start the process of programmed cell death, thereby destroying both recently transformed and, though less frequently, progressing cancer cells. There are also regulating systems at the organism level that inhibit the further spread of precancerous cells by controlling the accessibility of growth factors, cytokines and other different regulating molecules. Beyond the direct obstructive effects on the division and survival of transforming cells, these systems can efficiently impede the oxygen and nutriment supply of the given cancerous cells, their invasion into the adjacent tissues and their emigration into the surrounding blood and lymph circulation. Last, but not least, the organism also directs an aggressive machinery, the immune system, against developing tumors. The immune system deploys its commandingly ample weapon arsenal and presents a waxworks of various sorts of cellular death when tracing and destroying cancer cells.

Histamine in Benign and Malignant Tumors

The first evidence reported on the relevance of histamine in tumor development came when increases in histamine content, urinary excretion and HDC activity was observed in tumor bearing mice.²⁵ Since 1960 many authors have demonstrated that histamine synthesis is significantly increased in tumoral tissues like breast cancer, colon carcinoma, melanoma, lymphomas and leukemia, compared to surrounding normal tissues.^{26,27} In experimental tumor models the role of histamine has been more clearly established. In N-nitroso-N-methylurea (NMU)-induced mammary adenocarcinomas in rats histamine was demonstrated as an autocrine growth factor.²⁸ In vitro studies employing cell lines have demonstrated the expression of H₁R and H₂R and the associated signaling pathways through which histamine may modulate cell proliferation. Direct effects of histamine on tumor cells were found to be primarily autocrine, although paracrine effects of histamine released by tumor cells influencing immune responses or stimulation of angiogenesis has to also be considered.

Proliferation of Malignant Cell Lines

Several recent literature reports have demonstrated the effect of histamine on the proliferation of different cell lines, but the data remain controversial. The decrease in proliferation caused by HDC antisense oligonucleotides indicates considerable functional relevance of histamine synthesis in melanoma growth.³¹ The diverse effects of histamine can be explained by the relative abundance of the different receptors and differences in their affinity for histamine. Histamine receptors are

Table 1. Histamine synthesis and the presence of H_1R , H_2R , in different cell lines derived from human neoplasias

Cell Line/References	Histamine Receptors	Effects on Cell Proliferation
Parietal cell ²⁹ HEK-293	H_2R	Histamine stimulates cell growth
Colon carcinoma. ³⁰ C170, LIM2412	H_2R	Histamine stimulates cell proliferation in C170, but neither histamine nor H_2R antagonist affected basal growth of LIM2412
CT-26. ⁴⁵	H_2R	Histamine does not effect proliferation
Melanoma ^{27,31,44,45} A875, Js, DU, BH, NEW WM-35,983, HT-168, M1	H_1R and H_2R	Different effects depending on histamine concentration and cell line
Pancreatic carcinoma. ^{33,34} PANC-1	H_1R and H_2R	At low concentration histamine increases proliferation while at high doses histamine inhibits cell growth, producing a G1/G0 cell cycle arrest
Promonocytic cell line. ^{35,36} U937	H_1R and H_2R	Differentiation induced by histamine via H_2R
Human epidermal carcinoma cells A431 and HeLa. ³⁷	H_1R	Stimulating proliferation of cells that express functional H_1R
Astrocytoma. ³⁸ U373 MG cells	H_1R	H_1R activation stimulates the proliferation
Prostate cancer cell line. ³⁹ DU-145	H_1R	Histamine inhibits the proliferation by H_1R

expressed in multiple malignant cell types, however the effect of histamine depends on the type of the cell, the balance between different receptor subtypes and the downstream effectors that are subsequently activated. For example, histamine influences the growth of human melanoma cells depending on the actual receptor balance, i.e., it increases cell proliferation through H_2R , but inhibits it through H_1R .²⁷ In addition H_2R obtain functional heterogeneity by activating adenylate cyclase or phospholipase C by either different subclasses of H_2R or by coupling to two different effector G proteins^{29,32} (Table 1). Interestingly, most cell lines express HDC and contain high amount of histamine in a diffusible, unstored form. The histamine released to the extracellular medium is in the nanomolar concentration range, thus clearly indicating that this endogenously synthesized histamine can modulate diverse biological responses through the activation of high affinity histamine receptors in an autocrine way.

In-Vivo Experimental Models

Histamine has proven to be crucial for tumor growth and development in various experimental models. If we consider that histamine is a mediator of keratinocyte growth and hormonal action in the mammary gland, it could then be assumed that it plays a role as a promoter in skin and mammary gland carcinogenesis. In the development of different animal tumors such as EMT6 sarcoma in mice, Lewis Lung carcinoma in mice and HTC hepatoma in rats, a parallel increase in ornithine decarboxylase and HDC activities occurs during early stages. The induction of HDC is

followed by a rapid increase in tumor histamine content and can lead to increases in tissues distant from the tumor such as spleen or lymphoid nodes.²⁵ The specific HDC inhibitor, α FMH, reduces histamine levels in some tissues and produces a marked inhibition of tumor growth in different animal models.^{40,41} The multistage model of mouse skin carcinogenesis is a useful system to study the sequential changes that normal skin undergoes during its transformation into neoplastic tissue. Studies of histamine receptors in initiated skin of Sencar mice during the promotion-progression period showed a sequential change in the coupling of both H_1R and H_2R to signal transduction pathways.⁴² In uninvolved skin H_1R were coupled to inositol phosphate production and H_2R to cAMP production as normal. However, in tumors this was reversed. A simultaneous increase in mast cell numbers, with a homogeneous subepithelial distribution and marked phenotypic changes was observed suggesting that such cells may play a role in the process of carcinogenesis. These findings indicate an atypical association of histamine receptors to second messengers that could enable histamine to behave as a growth factor through H_2R . This alteration seems to be a significant feature for the postulated action of histamine in tumor growth. Strengthening this hypothesis, PDV-C57 cells, a cultured cell line derived from DMBA-transformed mouse keratinocytes and different mice epidermal tumor cell lines exhibit a similar atypical signal transduction linkage of histamine receptors.⁴³

In another study our group previously showed that transgenic enhancement of histamine production in B16-F10 melanomas strongly supports tumor growth in C57BL/6 mice.⁴⁴ Gene expression profiles (validated by real-time PCR and immunohistochemistry) of transgenic mouse melanomas secreting different amounts of histamine suggested that H_1R activation suppressed RNA-level expression of the tumor suppressor insulin-like growth factor II receptor (IGF-IIR) and the antiangiogenic matrix protein fibulin-5 (FBLN5). Pathway analysis suggested that since plasma membrane-bound IGF-IIR is required to activate matrix-bound, latent transforming growth factor-B1, a factor suggested to sustain FBLN5 expression, the effect of H_1R activation can be explained by the suppression of a known antineoplastic regulatory pathway. Surprisingly, these data show that in melanoma H_2R are rather irrelevant compared with H_1R .⁴⁵

A critical role has been described for histamine in the development of an experimental mammary adenocarcinoma induced in rats with NMU.⁴⁶ In these tumors histamine exerts a regulatory function on cell growth by acting directly through H_1R and H_2R , which exhibit an atypical coupling to intracellular signaling systems. In these tumors histamine acts as an autocrine growth factor and stimulates cell proliferation. Interestingly, in the NMU-induced tumors, HDC loses its normal response to estrogen. Furthermore, HDC mRNA abundance and enzyme activity are regulated by histamine itself acting upon its specific membrane receptors. Therefore, the escape of HDC from the characteristic estrogen control present in the normal mammary gland is a common feature of all NMU-induced tumors and it may be one the first and most significant alterations in the development of the malignant phenotype. The oral administration of ranitidine at 50 mg/kg to rats bearing mammary adenocarcinomas resulted in the complete remission in 55% of tumors, partial remission in 35% while 10% remained without changes. The survival of treated animals was significantly higher than control groups. On the contrary, the treatment with an H_1R antagonist augmented tumor growth rates in all cases and animal survival was significantly decreased. The daily administration of α FMH, 5 mg/kg, produced the remission of 100% of the tumors.⁴⁶

In an experimental syngenic tumor model using a colon adenocarcinoma cell line, CT-26, in Balb/c mice, daily administration of cimetidine significantly suppressed the increase in tumor volume and weight observed on day 6 after inoculation. Cimetidine also reversed the suppression of the expression of tissue cytokines such as lymphotoxin- β , TNF- α , IFN- γ , IL-10 and IL-15. The effects of cimetidine on tumor growth in this model might be mediated by the restoration of local cytokine expression and thereby exert antitumor effects.⁴⁷ In human melanoma-grafted mice the combined treatment of cimetidine and DPPE reduced tumor growth and increased survival. These changes were accompanied by enhanced infiltration of IFN γ producing mouse macrophages into the tumor tissue.⁴⁸

Experimental results obtained working with a model of human bronchogenic carcinomas propagated as subcutaneous xenografts in immunosuppressed mice, indicated that the treatment with the H₂R antagonists cimetidine and ranitidine increased the tumor mass doubling time. The co-administration of the dual H₂R/histamine H₄ receptor (H₄R) agonist 4-methyl histamine abolished the effects of cimetidine, thus indicating that in these tumors histamine may stimulate growth through the H₂R.

Human Tumors

In addition to the data available from studies in tumor cell lines derived from human neoplasias and in xenotransplanted models in nude mice, a number of investigations have also been carried out in biopsies of tumoral tissues. Most reports are coincident in showing an increase in histamine synthesis and content in tumors and the presence of histamine receptors.

Breast and Colorectal Cancer

Tumor and adjacent normal breast content of histamine was measured in 29 patients having surgery for breast cancer.⁵⁰ The median content of histamine in breast cancer tissue was 5.4 (range 0.9-27.3) µg/g and was significantly greater than that in adjacent breast tissue. The authors postulated that the concentration of histamine in breast cancer was sufficient to inhibit lymphocyte function suggesting that it could be locally immunosuppressive.⁵⁰ In agreement with this result, Garcia-Caballero et al reported that the HDC activity of breast cancer is significantly higher than that of the healthy mammary gland tissue of the same patient.²⁶ It is interesting that the activity of HDC was the highest in benign tumor tissue. It was also found that the histamine content in muscle tissue was significantly higher in cancer patients than in noncancer patients. These findings suggest that high histamine synthesis by malignant tumors can affect other host tissues.²⁶

A study with tissue samples obtained by surgery from 25 patients indicated that both H₁R and H₂R are present in human mammary glands, in benign lesion and in breast carcinomas.⁵¹ In benign lesions H₂R produced increases in cAMP levels, while H₁R were coupled to PLC activation. On the other hand, the response observed in carcinomas was different: H₁R were invariably linked to the PLC pathway, but H₂R stimulated both signal transduction pathways. In agreement with a previous report, approximately 25% of breast carcinomas were negative for H₂R. In all cases the lack of expression of H₂R in tumors corresponded to patients with poor prognosis and progression.⁵¹

Histamine has been found to stimulate growth of colorectal cancer in vitro and in vivo. Similarly to the studies carried out in breast carcinomas, the histamine content was measured in 31 colorectal cancer specimens using a radioenzymatic assay.⁵² The median histamine concentration in colorectal cancer tissue was 8.4 µg/g, ranging from 0.3 µg/g to 20.6 µg/g. Again the high concentration of histamine in colon cancer seems high enough to be locally immunosuppressive.⁵² Another study was designed to determine the activity of HDC in normal and tumor tissues in a series of ten surgical patients with colorectal carcinoma. A significantly increased HDC activity, almost double that of normal tissues, was found in specimens of human tumors, consistent with numerous reports of high HDC activity in tumor-bearing animals.⁵³

In humans, several clinical trials have been carried out with H₂R antagonists as an adjunct to surgical resection, with conflicting results. While the H₂R antagonist cimetidine has been shown to reduce the number of tumor infiltrating lymphocytes in colorectal cancer this was not found to be the case in breast cancer.⁵⁴ A comparison of breast cancer with colorectal cancer showed no relationship between preoperative cimetidine administration and tumor cell proliferation. Furthermore, cimetidine did not have any influence on tissue histamine content and mast cell numbers. The presence of mast cells around tumor tissue raises questions concerning the source of histamine in breast tumor tissue. Tumor cell proliferation correlated well with other prognostic indicators such as grade and differentiation.⁵⁴

The beneficial effect of cimetidine on survival in colorectal cancer patients has been demonstrated in several cases, but the mode of action has not been elucidated. In one animal study cimetidine was demonstrated to block the adhesion of colorectal tumor cells and metastasis of the tumor cell in a nude mouse model.⁵⁵

A recent study suggested that in human colorectal cancer tumors both H₁R and H₄R expression was markedly decreased ($p < 0.001$) both at the mRNA and protein levels compared to those of normal colonic mucosa, without significant change in H₂R.⁵⁶

The up-regulation of HDC protein expression and activity in colorectal tumor specimens has been detected and shown to be higher in metastatic tumors than in nonmetastatic ones. These variables significantly correlated with tumor PGE₂ production. These data showed that histamine exerts both a proliferative and a proangiogenic effect via H₂R/H₄R activation. These effects are likely to be mediated by increasing COX-2-related PGE₂ production in colon cancer cells that express COX-2.⁵⁷

Melanoma

Analysis of HDC expression in melanoma showed that in primary melanomas and cutaneous metastases HDC is present at significantly higher levels than in benign nevi and the surrounding nontumoral skin. Parallel expression of HDC and synthesis of histamine has also been demonstrated in melanoma. Moreover, HDC and the released histamine both have been shown to be related to the malignant phenotype and it is also likely that the presence of these markers may have a prognostic value.³¹

It has been demonstrated that melanomas not only have a histamine-producing capacity, but also perform continuous histamine secretion into the environment as well.²⁷ In addition, melanoma cells are also able to detect the presence of histamine since surface expression of H₁R and H₂R has been demonstrated. Moreover they most likely also display H₃R, which is in line with the fact that melanocytes originate from the neuronal crest during embryonic development. However, in spite of the above data, the many *in vitro* observations and the data derived from mouse tumor models, there is no clear evidence that histamine-mediated autocrine signaling has an actual role in the *in vivo* progression of human melanomas and if it does, which aspects of malignant development are affected. Although definite *in vivo* evidence for this concept is not yet available, it has been shown that histamine-mediated signals may support the proliferation of melanoma cells in culture.³¹ In addition to this it is notable that histamine can efficiently influence the immune system in the local milieu of the tumor and it may also be able to do the same at the antigen-presenting level in draining lymph nodes. Furthermore, it seems that histamine primarily mediates Th2-type effects and, hence, can inhibit anti-tumor Th1 responses. It is also known that in dermal mast cells UVB-radiation, one of the most widely suspected causative agents of melanoma, evokes a robust histamine release that has significant immune-modulating effects frequently even leading to systematic immune-suppression. Observations suggesting that in the stroma of certain tumors, including melanoma, a robust mast cells inflow is perceptible make an interesting parallel with these thoughts and emphasize the possible existence of significant external histamine-release that can also assist melanoma growth. Notably, it has recently become evident that in addition to histamine, several other mediators and enzymes released from mast cells can stimulate invasivity and angiogenesis by increasing capillary permeability and inducing remodeling of the adjacent stroma.^{27,31}

Lung Cancer

It was recently reported that human small cell lung carcinomas (SCLCs) express vesicular monoamine transporters in addition to other neuroendocrine markers indicating that SCLCs are histaminergic. The biosynthetic enzyme HDC was detected by immunohistochemistry in paraffin sections of 12 biopsies of SCLC tumors. This finding was supported by immunoblotting and RT-PCR using established SCLC cell lines, as well as, frozen and paraffin-embedded SCLC tumors. Moreover, it was found that histamine is synthesized, stored and released by cultured SCLC cells. These observations may be useful for developing new diagnostic tools for this frequent and highly malignant tumor.⁵⁸ There are also data about human lung H₁R and H₂R in cancer and chronic inflammatory processes. It has been found that the number of H₁R significantly increases both in cancer and chronic pneumonia, although it does not change in tuberculosis lung parenchyma. In contrast, the binding parameters of H₂R both in cancer and inflammatory processes were similar to those obtained for the normal tissue. The authors proposed an important role of parenchymal H₁R in the neuromodulation of airways in human lung adenocarcinoma.⁵⁹

Lymphomas and Leukemia

The median levels of histamine were determined in lymph nodes of patients with malignant lymphomas, Hodgkin's disease (HD) or non-Hodgkin's lymphomas (NHL) and in all cases the values were higher than in controls. In patients with NHL, the levels of histamine showed a dependence on the grade of malignancy, as they were significantly higher in those classified as high-grade malignant.⁶⁰ Immunostaining and ELISA also confirmed the presence of histamine in the cytoplasm of acute lymphocytic leukemia (ALL) cells. Primary leukemia cells had detectable levels of histamine ranging from 12.5 pg/10⁶ cells to 1235.4 pg/10⁶ cells. ALL cells can therefore produce histamine and H₁R antihistamines can inhibit their clonogenic growth. However, there was no correlation between the clonogenic growth of ALL cells and their histamine content suggesting that, while histamine may be important for the clonogenic growth of ALL cells, other factors also affect their clonogenicity.⁶¹

Histamine Blood Levels in Cancer Patients

A number of different authors have demonstrated that histamine serum levels are significantly decreased in cancer patients, suggesting that decreased levels may be a good marker for the onset and progression of solid malignant tumors. In patients with gastrointestinal tumors, blood histamine levels provided information additional to that derived from serum carcinoembryonic antigen (CEA) determination. In patients with nongastrointestinal tumors, the blood histamine level may be of more value than CEA as a marker of disease progression.⁶³ In a similar study, the concentration of histamine in blood was determined in 22 patients with solid malignant tumors, 16 hospitalized noncancer patients and 9 healthy subjects. Patients with cancer (mainly carcinomas of the breast and gastrointestinal tract) were divided into two groups: patients with resected primary tumor without known metastases (group I) and patients with present primary tumor with or without metastases (group II). In comparison to healthy subjects (histamine concentration 69.0 ± 6.0 ng/ml), cancer patients in both groups had significantly decreased levels of histamine in blood. Also, the concentration of histamine in patients with present tumor (group II; 40.1 ± 3.48 ng/ml) was significantly lower than in patients with resected primary tumor (49.9 ± 3.14 ng/ml). Furthermore, hospitalized noncancer patients had slightly lower (not significant) concentrations of histamine (59.7 ± 6.13 ng/ml) compared to healthy subjects.⁶³ Blood histamine levels were reported to be significantly decreased in patients with active phase Hodgkin's lymphoma and returned to normal values after treatment or during remission. A recent work investigated the utility of a histamine assay for detecting the presence of primary cancers. In order to assess the usefulness of this assay in primary tumor monitoring, two groups of individuals, 29 controls and 29 colon cancer patients were selected and serum levels of histamine, CEA and tumor staging were determined. A significant reduction in histamine levels was found between controls and patients. No correlation was found, however, between tumor node metastasis staging and histamine levels, indicating that this marker is not related to the tumor mass and that it could be a potentially interesting nonspecific tumor marker in colon cancer monitoring.⁶⁴

Angiogenesis

Clinically tumor progression, invasion and metastasis are more relevant than tumor induction. It is well known that the outcome of tumor invasion and metastasis is closely dependent on the capability to induce angiogenesis. Angiogenesis is tightly regulated by pro- and anti-angiogenic factors. Activated mast cells are able to induce and enhance angiogenesis via multiple interacting pathways. In tumor models, mast cells have been shown to play a decisive role in inducing the angiogenic switch, which precedes malignant transformation. In fact, it is well documented that heparin, combined with a range of heparin-binding factors such as bFGF (basic fibroblast growth factor) or TGFβ (transforming growth factor) is able to promote neovascularisation and that mast cell proteases cause cell structural alterations by destroying extracellular matrix integrity. Moreover, there is strong evidence that mast cells significantly influence angiogenesis and thus growth and progression in human cancers.⁶⁵ The role of histamine secreted by mast cells is less

clear. It seems that histamine can behave as a pro- or an anti-angiogenic modulator, depending on which histamine receptor is bound.^{66,67}

Many years ago it has been reported that histamine increases endothelial cell proliferation via both H₁R and H₂R. Histamine is able to induce VEGF production in the granulation tissue via the H₂R-cyclic AMP-protein kinase A pathway and augments angiogenesis in the granulation tissue.⁶⁸ Recently it has been demonstrated that HDC-deficient (HDC-KO) mice show lower VEGF levels in the granulation tissue and that there is notably less angiogenesis and granulation tissue formation than in the wild-type mice. The topical injection of histamine or the H₂R agonist dimaprit rescued the defective angiogenesis and granulation tissue formation in HDC-KO mice. This effect is not observed in mast cell deficient mice. In addition, macrophages in the granulation tissue were found to express HDC. These findings indicate that histamine derived from cells other than mast cells play a significant role in the angiogenesis of inflammatory granulation tissue.⁶⁹ IP-10, (interferon-induced protein of 10 kDa) induces antitumor immune responses in synergy with IL-12 via activated Th1 cells. In addition, IP-10 inhibits tumor angiogenesis and abrogates a route for nutrition and metastasis. Tumor cells can produce IP-10 in response to IFN γ and histamine inhibits this effect.⁷⁰ In different melanoma and squamous carcinoma cell lines, it was observed that histamine suppresses IP-10 expression and secretion via H₂R and the cAMP-protein kinase A signaling pathway.⁷⁰ By this mechanism histamine released from tumor cells or peritumoral mast cells may increase angiogenesis and sustain the growth and survival of the tumor.⁷⁰

Effect of Histamine on Immune Regulation

Histamine strongly affects the balance of cytokines from T helper type 1 (Th1) cells and T helper type 2 (Th2) cells by shifting cytokine production from a Th1 to a Th2 pattern. Stress mediators, as well as histamine and adenosine, are increased in certain circumstances and thus upregulate Th2 cytokines and may play a role in the induction and progression of certain allergic/atopic reactions and tumor growth.^{27,71} Using a CT-26 colon adenocarcinoma-based syngenic mouse experimental tumor model, endogenous tumor histamine synthesis was shown to enhance tumor growth by suppressing local expression of LT- β (lymphotoxin), TNF- α (tumor necrosis factor alpha) and IFN- γ (interferon gamma) in an H₂R-dependent manner.⁷³

Conclusion

Convincing evidence is available that if production of inflammatory mediators is prolonged or their normal functions become modified, they can provide support for both tumor formation and progression. Histamine seems to be one of the modulators in normal cell proliferation in many tissues, including skin, gastric mucosa, bone marrow and fibroblasts. Moreover, there is an increase in histamine synthesis and content in tumors and in most cases the expression levels of histamine receptors are also increased. Histamine serum levels are significantly decreased in cancer patients, suggesting that decreased levels may be a good marker for the onset and progression of solid malignant tumors. Histamine regulates angiogenesis, as well, and it seems that it can behave as a pro- or an anti-angiogenic modulator, depending on which histamine receptor is bound.

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