

Tumor formation and antitumor immunity; the overlooked significance of histamine

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ABSTRACT

HA is a biogenic amine, widely distributed throughout the body. Given the observations that HA, the decarboxylated amino acid histidine, can be induced and made available in an unstored, diffusible form in tissues undergoing rapid growth (such as tumors and regenerating tissues), it could have a role in antitumor response beyond the well-studied inflammatory and allergic responses. *J. Leukoc. Biol.* **96**: 000–000; 2014.

HA AND CELL PROLIFERATION

It is an early clinical/pathological observation that the risk of the development of cancerous processes is increased in tissue adjacent to areas of long-standing inflammation. 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 down-regulated rapidly, can, when improperly regulated, support the development, invasivity, or angiogenic activity of some tumors. Convincing evidence is available that if production of inflammatory mediators is prolonged or their normal functions become modified, then they can provide support for tumor formation and progression. In accordance with these observations, an attempt to redefine the paradigm of solid tumors has taken place, with a new 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.

Abbreviations: ALL=acute lymphocytic leukemia, CEA=carcinoembryonic antigen, COX-2=cyclooxygenase-2, CT-26=colon adenocarcinoma cell line, DMBA=2,4-dimethoxybenzaldehyde, EMT6=epithelial-to-mesenchymal transition 6, FBLN5=fibulin-5, H₁₋₄R=histamine receptors 1–4, HA=histamine, HD=Hodgkin's disease, HDC=histidine decarboxylase, IGF-1IR=insulin-like growth factor 1R, IP-10=IFN-induced protein of 10 kDa, KO=knockout, LT- α =lymphotoxin- α , NHL=non-Hodgkin lymphoma, PKA=protein kinase A, PLC=phospholipase C, SCLC=small cell lung carcinoma, T_{reg}=regulatory T cell, VEGF=vascular endothelial growth factor

HA and mast cells seem to have a considerable role in this process, as in addition to local accumulation of mast cells in a tumor environment, overexpression of 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 local enrichment of mast cells [1] and HA and can modify local tumor growth. In this chapter, we attempt to summarize the most well-known effects of HA on normal and tumor cell growth.

HA IN NORMAL CELL PROLIFERATION

The hypothesis that HA could be involved in cell differentiation and proliferation was proposed in the 1960s and still remains controversial. Situations where proliferation control is corrupted, damaged, or even completely demolished will be dealt with in the following section on malignant 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 with which evolution has equipped the species. Obviously, proliferation cannot be interpreted within narrow borders, as it, in most cases, 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, immune responses, and others.

The role of the physiological proliferation in many tissues, such as gastric mucosa [2–6], hematopoietic tissue [7–11], fibroblasts [12–17], mammary gland, uterus [18–21], and skin [22–25], has already been studied intensively. The main interest of these studies (not given in details in this article) was focused on HA receptor distribution and tissue-specific cytokine regulation.

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HA IN BENIGN AND MALIGNANT TUMORS

The first evidence reported on the relevance of HA in tumor development came [26] when increases in HA content, urinary excretion, and HDC activity were observed in tumor-bearing mice. Since 1960, many authors have demonstrated that HA synthesis is increased significantly in tumor tissues, such as breast cancer [27], colon carcinoma, melanoma [28], lymphomas, and leukemia, compared with surrounding, normal tissues. In experimental tumor models, the role of HA has been established more clearly. In N-nitroso-N-methylurea-induced mammary adenocarcinomas in rats, HA was demonstrated as an autocrine growth factor [29]. Direct effects of HA on tumor cells were found to be primarily autocrine, although paracrine effects of HA released by tumor cells influencing immune responses or stimulation of angiogenesis have to be considered also.

Proliferation of malignant cell lines

Several literature reports have demonstrated the effect of HA on the proliferation of different cell lines, but the data remain controversial. HA receptors are expressed in multiple malignant cell types. However, the effect of HA depends on the type of the cell, the balance between different receptor subtypes, and the downstream effectors that are subsequently activated. For example, HA influences the growth of human melanoma cells depending on the actual receptor balance; i.e., it increases cell proliferation through H₂R but inhibits it through H₁R [28–30]. Moreover, the decrease in proliferation caused by HDC antisense oligonucleotides indicates considerable, functional relevance of HA synthesis in melanoma growth [31]. The diverse effects of HA can be explained by the relative abundance of the different receptors and differences in their affinity for the HA receptor. In addition H₂R obtain functional heterogeneity by activating adenylate cyclase or PLC by different subclasses of H₂R or by coupling to two different effector GTP-binding proteins [29, 32]. However, the exact outcome of various HA receptors is far to be clear. Based on data of Blaya et al. [33], in spite of exogenous HA-stimulated human melanoma cell proliferation, clonogenic ability, and migration activity in a dose-dependent manner, the melanoma tumor growth was not modulated by *in vivo* HA treatment. On the contrary, terfenadine treatment *in vitro* induced melanoma cell death by apoptosis, and *in vivo* terfenadine treatment inhibited tumor growth significantly in murine models.

Interestingly, most melanoma cell lines express HDC and contain a high amount of HA in a diffusible, unstored form. The HA released to the extracellular medium is in the nanomolar concentration range, thus clearly indicating that this endogenously synthesized HA can modulate diverse biological responses through the activation of high-affinity HA receptors in an autocrine way. Similar data were obtained on pancreatic, monocytic, and astrocytoma cell lines [34–39].

In vivo experimental models

HA has proven to be crucial for tumor growth and development in various experimental models. If we consider that HA 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 hepatoma tissue culture 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 HA content and can also take place in tissues distant from the tumor, such as spleen or lymphoid nodes [26]. The specific HDC inhibitor α -fluoromethyl histidine reduces HA 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 HA receptors in initiated skin of Sencar mice during the promotion-progression period showed a sequential increase in the coupling of H₁R and H₂R to signal transduction pathways.

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 HA receptors to second messengers that could enable HA to behave as a growth factor through H₂R. This alteration seems to be a significant feature for the postulated action of HA in tumor growth. Nontumor skin cells in close vicinity to tumor cells exhibited the same coupling of HA receptors as nontreated skin [42]. With the strengthening of this hypothesis, C57 derivative of epidermal cell line transformed *in vitro* by DMBA 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 HA receptors [42, 43].

In another study, our group showed previously that transgenic enhancement of HA 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 HA suggested that H₁R activation suppressed RNA-level expression of the tumor suppressor IGF-IIR and the antiangiogenic matrix protein FBLN5. Pathway analysis suggested that as plasma membrane-bound IGF-IIR is required to activate matrix-bound, latent TGF- β 1, a factor suggested sustaining FBLN5 expression, the effect of H₁R activation can be explained by the suppression of a known antineoplastic regulatory pathway. These data show that surprisingly, in melanoma, H₂R are rather irrelevant compared with H₁R [45] (Table 1).

In an experimental syngenic tumor model, using 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 LT- α ,

TABLE 1. HA Synthesis and the Presence of H₁R and H₂R in Different Cell Lines Derived from Human Neoplasias

Cell line/references	HA receptors	Effects on cell proliferation
Parietal cell [29]	H ₂ R	HA stimulates cell growth.
HEK-293		
Colon carcinoma [30]	H ₂ R	HA stimulates cell proliferation in C170, but neither HA nor H ₂ antagonist affected basal growth of LIM2412.
C170, LIM2412		HA does not affect proliferation.
CT-26 [45]	H ₂ R	
Melanoma [27, 31, 44, 45]	H ₁ R and H ₂ R	Different effects depending on HA concentration and cell line
A875, Js, DU, BH, NEW, WM-35,983, HT-168, M1		
Pancreatic carcinoma [33, 34]	H ₁ R and H ₂ R	At low concentration, HA increases proliferation, whereas at high doses, HA inhibits cell growth, producing a G1/G0 cell-cycle arrest.
PANC-1		
Promonocytic cell line [35, 36]	H ₁ R and H ₂ R	Differentiation induced by HA via H ₂ Rs
U937		
Human epidermal carcinoma cells A431 and HeLa [37]	H ₁ R	Stimulating proliferation of cells that express functional H ₁ Rs
Astrocytoma [38]	H ₁ R	H ₁ R activation stimulates the proliferation.
U373 MG cells		
Prostate cancer cell line [39]	H ₁ R	HA inhibits the proliferation by H ₁ R.
DU-145		

Cell lines: HEK-293, C170, LIM2412, CT-26, A875, Js, DU, BH, NEW, WM-35,983, HT-168, M1, PANC-1, U937, A431, HeLa, U373 MG, DU-145.

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 the local cytokine expression and thereby exert antitumor effects [46]. In human melanoma-grafted mice, the combined treatment of cimetidine and *N,N*-diethyl-2-(4-(phenylmethyl)phenoxy) ethanamine HCl, reduced tumor growth and increased survival [47].

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 tumor tissues. Most reports are coincident in showing an increase in HA synthesis and content in tumors and the presence of HA receptors.

Breast and colorectal cancer

Tumor and adjacent normal breast content of HA, as well as mast cell number, were measured in 29 patients having surgery for breast cancer [48]. The median content of HA in breast cancer tissue was 5.4 $\mu\text{g/g}$ (range 0.9–27.3) and was significantly greater than that in adjacent breast tissue. The authors postulated that the high local concentration of HA in bronchogenic carcinomas and breast cancer was sufficient to inhibit lymphocyte function, suggesting that it could be locally immunosuppressive [49, 50]. Moreover, mast cells mobilize T cells and antigen-presenting dendritic cells. They function as intermediaries in T_{reg}-induced tolerance but can also modify or reverse T_{reg}-suppressive properties [48, 51]. The central role of mast cells and their products (such as HA) is the control of innate and adaptive immunity which endows them with

the ability to tune the nature of host responses to cancer and ultimately, to influence the outcome of disease and fate of the cancer patient. A study with tissue samples, obtained by surgery from 25 patients, indicated that H₁R and H₂R are present in human mammary glands, in benign lesion, and in breast carcinomas [52]. In benign lesions, H₂R produced increases in camp levels, whereas 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, ~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 [52]. The role of HA in regulation of metalloproteinase expression and adherence of breast cancer cells seems to be a relevant factor too [53]. Clobenpropit, a potent H₄R agonist, inhibits mammary adenocarcinoma growth [54]. Clobenpropit significantly decreased bile duct cancer (cholangiocarcinoma) proliferation by way of a Ca²⁺-dependent pathway and altered morphological development and invasion. Loss of H₃R expression or overexpression of H₄R significantly decreased cholangiocarcinoma proliferation. In vivo, clobenpropit inhibited xenograft tumor growth compared with controls [54].

HA has been found to stimulate growth of colorectal cancer in vitro and in vivo. Similarly to the studies carried out in breast carcinomas, the HA content was measured in 31 colorectal cancer specimens using a radioenzymatic assay. The median HA concentration in colorectal cancer tissue was 8.4 $\mu\text{g/g}$, ranging from 0.3 to 20.6 $\mu\text{g/g}$. Again, the high concentration of HA in colon cancer seems high enough to be locally immunosuppressive [55, 56]. Another study was designed to

determine the activity of HDC in normal and tumor tissues in a series of 10 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 [56].

In humans, several clinical trials have been carried out with H_2R antagonists as an adjunct to surgical resection, with conflicting results. Whereas the H_2R antagonist cimetidine has been shown to reduce the number of tumor-infiltrating lymphocytes in colorectal cancer, that was not found to be the case in breast cancer [56]. 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 HA content and mast cell numbers. The presence of mast cells around tumor tissue raises questions concerning the source of HA in breast tumor tissue. Tumor cell proliferation correlated well with other prognostic indicators, such as grade and differentiation [55–57].

A study suggested that in human colorectal cancer tumors, H_1R and H_4R expression was decreased markedly ($P < 0.001$), both at the mRNA and protein levels, compared with those of normal colonic mucosa, without significant change in H_2R [58].

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 [59].

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 correlated significantly with tumor PGE_2 production. These data showed that HA exerts a proproliferative and a proangiogenic effect via H_2R/H_4R activation. These effects are likely to be mediated by increasing COX-2-related PGE_2 production in COX-2-expressing colon cancer cells [59–61]. The role that HA, HDC, HA receptors, and mast cells play during pancreatitis and pancreatic cancer has also been suggested recently [62].

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 nontumor skin. Parallel expression of HDC and synthesis of HA have also been demonstrated in melanoma. Moreover, HDC and the released HA 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 HA-producing capacity but also perform continuous HA secretion into the environment as well [31]. In addition, melanoma cells are able to detect the presence of HA, as surface expression of H_1R and H_2R has been demonstrated. Moreover, they

most likely also display H_3R , 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 HA-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 HA-mediated signals may support the proliferation of melanoma cells in culture [31]. In addition to this, it is notable that HA 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 HA 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 HA 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 cell in-flow is perceptible make an interesting parallel with these thoughts and emphasize the possible existence of significant external HA release that can also assist melanoma growth. Notably, it has become evident that in addition to HA, 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 [28, 29, 31].

Lung cancer

It was reported that human 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 HA 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 [63]. There are also data about human lung HA H_1R and H_2R in cancer and chronic inflammatory processes. It has been found that the number of HA H_1R significantly increases in cancer and chronic pneumonia, although it does not change in tuberculosis lung parenchyma. In contrast, the binding parameters of H_2R in cancer and inflammatory processes were similar to those obtained for the normal tissue. The authors proposed an important role of parenchymal HA H_1R in the neuromodulation of airways in human lung adenocarcinoma [64]. As found recently [65], activation through HA H_4Rs prevents EMT6 transition, an important character of non-SCLC, suggesting a potential therapeutical application of H_4 activation.

Lymphomas and leukemia

The median levels of HA were determined in lymph nodes of patients with malignant lymphomas, HD, or NHL, and in all

cases, the values were higher than in controls. In patients with NHL, the levels of HA showed a dependence on the grade of malignancy, as they were significantly higher in those classified as high-grade-malignant [66]. Immunostaining and ELISA also confirmed the presence of HA in the cytoplasm of ALL cells. Primary leukemia cells had detectable levels of HA ranging from 12.5 pg/10⁶ to 1235.4 pg/10⁶ cells. ALL cells can therefore produce HA, and H₁R anti-HAs can inhibit their clonogenic growth. However, there was no correlation between the clonogenic growth of ALL cells and their HA content, suggesting that whereas HA may be important for the clonogenic growth of ALL cells, other factors also affect their clonogenicity [67].

HA BLOOD LEVELS IN CANCER PATIENTS

In patients with gastrointestinal tumors, blood HA levels provided information additional to that derived from serum CEA determination. In patients with nongastrointestinal tumors, the blood HA level may be of more value than CEA as a marker of disease progression [68]. In a similar study, the concentration of HA in blood was determined in 22 patients with solid malignant tumors, 16 hospitalized noncancer patients, and nine 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). Compared with healthy subjects (HA concentration 69.0±6.0 ng/ml), cancer patients in both groups had significantly decreased levels of HA in blood. Also, the concentration of HA 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 HA (59.7±6.13 ng/ml) compared with those of healthy subjects [69]. Blood HA levels were reported to be decreased significantly in patients with active-phase HD and returned to normal values after treatment or during remission. In a study to assess the usefulness of a HA assay in primary tumor monitoring, two groups of individuals (29 controls and 29 colon cancer patients) were selected, and serum levels of HA, CEA, and tumor staging were determined. A significant reduction in HA levels was found between controls and patients. No correlation was found, however, between tumor-node metastasis staging and HA levels, indicating that this marker is not related to the tumor mass and that it could be a potentially interesting, non-specific tumor marker in colon cancer monitoring [70].

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, which is tightly regulated by pro- and antiangiogenic 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 basic fibroblast growth factor or TGF- β , is able to promote neovascularization 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 [71]. The role of HA secreted by mast cells is less clear. It seems that HA can behave as a pro- or an antiangiogenic modulator, depending on which HA receptor is bound [72, 73].

Thirteen years ago, it was reported that HA increases endothelial cell proliferation via H₁R and H₂R. HA is able to induce VEGF production in the granulation tissue via the H₂R-cAMP-PKA pathway and augments angiogenesis in the granulation tissue [74]. It has also 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 HA 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 HA derived from cells other than mast cells plays a significant role in the angiogenesis of inflammatory granulation tissue [74]. IP-10 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 HA inhibits this effect [72]. In different melanoma and squamous carcinoma cell lines, it was observed that HA suppresses IP-10 secretion and mRNA expression via H₂R and the cAMP-PKA signaling pathway. By this mechanism, HA released from tumor cells or peritumoral mast cells may increase angiogenesis and sustain the growth and survival of the tumor [75, 76].

EFFECT OF HA ON IMMUNE REGULATION

HA strongly affects the balance of cytokines from Th1 and Th2 cells by shifting cytokine production from a Th1 to a Th2 pattern, regulated, in part, by polarized dendritic cells [77]. Stress mediators, as well as HA and adenosine, are increased in certain circumstances and thus, up-regulate Th2 cytokines and may play a role in the induction and progression of certain allergic/atopic reactions and tumor growth [28, 73].

With the use of a CT-26 colon adenocarcinoma-based, syngenic mouse experimental tumor model, endogenous tumor HA synthesis was shown to enhance tumor growth by suppressing local expression of LT- α , TNF- α , and IFN- γ via an H₂R-dependent manner [78].

CONCLUSION

Convincing evidence is available that if production of inflammatory mediators is prolonged or their normal functions become modified, then they can provide support for tumor formation and progression. HA seems to be one of the modulators in normal cell proliferation in many tissues, including skin, gastric mucosa, bone marrow, and fibroblasts. Moreover, the literature claims that there is an increase in HA synthesis and content in a series of tumors, and in most cases, it is the same with the expression of HA receptors. HA serum levels are decreased significantly in cancer patients, suggesting that decreased levels may be a good marker for the onset and progression of solid malignant tumors. HA regulates angiogenesis as well; it seems that it can behave as a pro- or an antiangiogenic modulator, depending on which HA receptor is bound. One cannot exclude that activation of HA receptors may be an active component in multiple rare diseases [79].

AUTHORSHIP

A.F. was the principal investigator of the HA-tumor studies. A.G. performed experimental work and made a significant contribution to the article.

DISCLOSURES

Both authors disclose any arrangements that could be considered to pose a conflict of interest regarding the submitted manuscript.

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KEY WORDS:

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