

Commentary

Histamine in cancer

The dual faces of the coin

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Although the hypothesis that histamine might be involved in carcinogenesis was proposed in the 1960s,¹ it still remains under discussion today. Clarification of the molecular structure of histidine decarboxylase (HDC), i.e., the only enzyme responsible for the generation of histamine from L-histidine, has improved our knowledge of the connections between histamine and cancer. Accumulated evidence points to a direct relationship between upregulation of HDC activity and growth of several types of human tumors. Overexpression of HDC at both the mRNA and protein levels and increased levels of histamine have been shown in melanoma,² small cell lung carcinoma,³ breast carcinoma,⁴ endometrial cancer⁵ and colorectal carcinoma.⁶ Nevertheless, evidence for the direct involvement of histamine in cancer progression remains to be obtained. This is mainly due to the different and, sometimes, contradictory effects that histamine can produce on tumor cell growth through activation of its four membrane-specific receptors, H₁, H₂, H₃ and H₄. Moreover, most of the physiological and pathological actions of histamine have been shown to strictly depend on both its endogenous/exogenous concentration and the tumor cell type under study. H₁ and H₂ receptors were the first two histamine receptor subtypes described and thus, the most frequently investigated in tumor cells and tissues. Selective activation of the H₁ or H₂ receptor has been shown to produce, respectively, inhibition or stimulation of tumor growth in a dose-dependent manner.^{7,8} Relative abundance and differences in the affinity of the histamine receptor subtypes may explain these diverse effects of histamine. For example, in *N*-nitroso-*N*-methylurea (NMU)-induced mammary adenocarcinoma, the activation of the receptor with histamine concentrations up to 50 nM increases tumor cell proliferation whereas higher histamine levels inhibit cell growth via receptor activation.⁹ Similarly, in the human pancreatic carcinoma PANC-1 cells, histamine at low concentration

(0.01 μ M) increases tumor cell proliferation whereas at high concentration (10 μ M) decreases cell proliferation via receptor activation thereby inducing a G₀/G₁ cell cycle arrest associated with partial stimulation of cell differentiation.¹⁰

The results reported by Medina et al.¹¹ in their article published in this issue of *Cancer Biology & Therapy*, well illustrate this bivalent behaviour of histamine in regulating tumor cell growth. The authors investigate, for the first time, the expression of the H₃ and H₄ receptors in human benign and malignant mammary lesions. Although previous work demonstrated that the H₃ receptor is expressed primarily in the central nervous system, Medina and colleagues have demonstrated the upregulation of H₃ in breast carcinomas and its significant association with proliferating cell nuclear antigen expression and elevated HDC expression and histamine levels in the same samples. Moreover, they found that histamine at low concentration (0.01 nM) can increase breast cancer cell proliferation and this effect is mediated by receptor activation. On the other hand, histamine at 10 μ M decreases cell growth through activation of the H₁, H₂ and H₄ receptors. H₄ receptor activation can also induce apoptosis and decrease migration of the MDA-MB-231 cells. Taken together, these results clearly demonstrate that histamine can behave as a pro- or an anti-proliferative factor within the same tumor type cells, depending on its concentration and the receptor subtype to which it binds. Similar results have been recently reported for hepatocellular carcinoma cells.¹² Indeed, both exogenous and mast cell-related histamine has been shown to either inhibit or promote cell growth through H₁ and H₂ receptor activation, respectively.

This scenario is complicated by the opposite effects induced by activation of the same histamine receptor in different cancer cells. Whereas the H₄ receptor seems to mediate inhibition of cell proliferation and apoptosis in breast cancer cells¹¹, we have recently demonstrated that H₄ receptor activation in colon cancer cells can produce both a proliferative and a pro-angiogenic effect through an increase in cyclooxygenase-2 expression and thus, prostaglandin production.¹³ As regards H₂ receptor, the majority of the published studies have demonstrated the correlation between the activation of this receptor and stimulation of tumor cell growth and invasiveness, in particular in melanoma, colorectal cancer and glioma cells.^{7,8} According to these data, H₂ selective antagonism by cimetidine or ranitidine has been shown to significantly reduce cell proliferation in vitro and to delay tumor growth or improve survival in experimental tumor models.¹⁴ Nevertheless, the administration of H₂ agonists in

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pancreatic and breast cancer cells mimic the anti-proliferative action induced by histamine in these cell lines.^{15,16} With respect to the H₁ receptor, its activation has been correlated with inhibition of cell growth in a number of experimental tumor models.^{7,8} It has been reported recently that selective H₁ blockage can induce apoptosis through caspase-2 activation in human melanoma cells.¹⁷

In addition to the actions directly exerted by histamine on tumor cells, it has to be taken into account that histamine can positively influence the immune response against cancer by augmenting the antitumoral properties of IL-2 and thus the antineoplastic capabilities of natural killer cells and T-cells.¹⁸ This effect is presumably due to the histamine-induced decrease in the local production of reactive oxygen species by tumor-infiltrating monocytes. On this basis, the combined administration of IL-2 and histamine has been proposed for treatment of patients with metastatic melanoma or acute myelogenous leukaemia.¹⁸

In conclusion, the current state-of-the art on the role of histamine in carcinogenesis is complex and somehow confusing. The endogenous activity of HDC in tumor cells and tumor-infiltrating mast cells is likely to establish an autocrine loop in which histamine acts as a growth factor. Paradoxically, the exogenous administration of histamine at higher concentration seems to exert anti-tumoral properties through both direct and indirect effects on tumor cells. However, the exact level of expression of the four histamine receptors in the different tumor tissues and the regulatory pathways induced by their activation have to be better elucidated before histamine or its receptor agonists/antagonists can be proposed as new anticancer agents.

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