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Modulation of hematopoiesis through histamine receptor signaling

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1. ABSTRACT

Histamine is one of the most versatile biogenic amines targeting a variety of cells through extra- and intracellular binding sites and specific receptors, which trigger different signal transduction pathways. It has been associated with cell growth ever since G. Kahlson demonstrated that its synthesis was increased in rapidly growing tissues of plants and animals. He proposed that the newly formed amine, as opposed to its stored counterpart, might play a major role in growth processes. Later on, a number of investigators provided evidence for the contribution of histamine to the expansion of normal and malignant cells, whether of hematopoietic origin or not. These studies have generated conflicting results, revealing growth-promoting as well as inhibitory effects, most likely because the final outcome of exposure to histamine depends on the signaling pathways triggered by distinct receptors and their differential distribution among the target population. The purpose of the present review is to outline our current understanding of the regulatory functions of histamine during growth and differentiation of hematopoietic progenitors, focusing on those mediated through its H_4 receptor.

2. INTRODUCTION

The term hematopoiesis designates a complex process of proliferation and/or differentiation leading from stem cells to the formation of all mature blood cells through a series of lineage commitment stages controlled by specific transcription and growth factors as well as stimulatory or inhibitory signals from the stroma (1). Recent studies have established that molecules of the neural-immunological axis, such as biogenic amines, can also take part in this complex network (2,3). Indeed, the bone marrow is not only highly innervated with both nonmyelinated and myelinated fibers (4), but also expresses a number of neurotransmitter G-protein-coupled receptors (5) through which hematopoietic progenitor cells can be targeted. In support of a regulatory function, it has been reported that catecholaminergic neurotransmitters regulate migration and repopulation of human hematopoietic progenitor cells (6) and that serotonin is able to stimulate their expansion (7).

It has been known for a long time that increased histamine formation is associated with growth processes in

plants (8) and animals (9). Furthermore, the histamine-forming enzyme histidine decarboxylase (HDC) is expressed at high levels in fetal liver (10, 11), which together with the concomitant expression of specific receptors supports a potential contribution of histamine to the modulation of hematopoiesis. Such a function has been repeatedly assigned to H_1 (H1R) and H_2 (H2R) histamine receptor subtypes during early steps of inducible hematopoiesis, while a possible implication of the H_4 receptor (H4R) has been considered only recently. The preferential expression of this receptor subtype in the bone marrow is consistent with its intervention during hematopoiesis. Furthermore, more selective and potent receptor ligands are now available or about to be developed to address this issue. Indeed, the use of specific pharmacological tools will be a prerequisite in unraveling the complex interactions through which histamine can modulate hematopoiesis. In the following we will summarize the data that support a regulatory function of histamine during inducible hematopoiesis in both murine and human systems, focusing on H4R-mediated activities.

3. MODULATION OF HEMATOPOIESIS BY ENDOGENOUS AND EXOGENOUS HISTAMINE

We have established some time ago that histamine is newly synthesized in the bone marrow during skin allograft rejection or expulsion of the nematode *Nippostrongylus brasiliensis* (13,14). Later on, interleukin (IL)-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) were identified as major inducers of this biological activity and characterized the histamine-producing cells as basophils (15-17). Addressing the physiological role of endogenous medullary histamine, we found that it was requisite for IL-3-induced entry of stem cells (CFU-S: cells forming colonies in the spleen of irradiated recipients) into cell cycle (18,19), which failed to occur in the presence of a specific HDC inhibitor.

This result is in agreement with a previous report by J. Byron, who showed that 4-methylhistamine, considered a specific H2R agonist at the time, promoted CFU-S cycling (20). We came to a similar conclusion regarding bone marrow-derived histamine, since H2R antagonists abolished this typical biological activity of IL-3 (18). The finding that extramedullary hematopoietic recovery after gamma irradiation is impaired in HDC-deficient mice (21) provides an additional argument in favor of a growth-promoting function of endogenous histamine during inducible hematopoiesis. However, these data need to be reappraised considering the preferential expression of the H4R in the bone marrow, in particular with respect to the cell cycle arrest in CFU-S ascribed to H1R activation (22) and the effect on other more lineage-committed progenitor cells.

4. EVIDENCE FOR FUNCTIONAL H4R EXPRESSION IN HEMATOPOIETIC PROGENITOR SUBSETS

4.1. H4R expression in murine and human hematopoietic progenitor cells

Until now the H4R has been chiefly investigated as a potential pharmacological target for anti-inflammatory therapy (23), given its originally reported functions, i.e. recruitment of immune cells, such as eosinophils, mast cells, neutrophils and dendritic cells (24-28), mediator release and exacerbation of inflammatory diseases like experimental allergic asthma (29,30). However, the fact that the H4R is detected most easily in the bone marrow supported a possible expression in the progenitor compartment of this organ (31). This is effectively the case, as assessed not only by RT-PCR, but also by flow cytometry analysis that revealed a progressive increase in the percentage of positive cells from total to the most primitive c-kit$^+$Sca1$^+$ bone marrow cells, reaching over 70% and more than 90% among sorted human CD34^{high} cells (32). Conversely, whatever their degree of purification, hematopoietic progenitors do not express the H_3 receptor (H3R) subtype. This is an important point, because of the high degree of homology between the two receptors and the fact that most H4R ligands used so far recognized both subtypes (33).

4.2. H4R-mediated blockade of growth factor-induced entry of hematopoietic progenitors into cell cycle

Hematopoietic progenitor cells are mostly quiescent during steady state (34), entering the cell cycle only upon stimulation. Activation of the H4R by agonists, such as clobenpropit, a partial agonist, initially developed as an H3R antagonist, before exposure to growth factors leads to a drastic decrease in the percentage of cycling cells from around 50 to 10%. This inhibition is not followed by apoptosis, as assessed by Annexin-V staining and a return to cell cycle progression after removal of H4R agonists and re-exposure to growth factors. Several experimental approaches, such as tracking of cell divisions after CFSE staining, cell cycle analysis after incorporation of fluorescent dyes into DNA and cell counts, confirmed that H4R stimulation blocks progenitor cell proliferation and/or differentiation by preventing G1/S cell cycle transition (Figure 1). It does so not only by downregulating cyclins D3 and E that are essential for passing this restriction point, but by modulating the transcription of many other genes involved in cell cycle regulation (32).

H4R agonists inhibit both myeloid (CFU-GM) and lymphoid (CLP) colony formation in the standard methylcellulose assay, indicating that the receptor is functional in primitive populations. A comparable inhibition occurred in a proliferation assay set up with different growth factor cocktails to reveal myeloid and erythroid progenitors, based on luminescence readout (32).

5. H4R SIGNALING

5. 1. cAMP/PKA-dependent cell cycle arrest in response to H4R activation

As reported for other cell types, H4R signaling in murine hematopoietic progenitors is initiated by coupling to the Pertussis toxin (PTX)-sensitive $G_{i/o}$ protein (31,33,35). It is followed by downregulation of adenylyl cyclase and a decrease of cAMP that is critical for cell cycle arrest. H4R signaling through cAMP has mainly been reported for transfected cells so far, while in mature primary cells Ca^{2+} appears to be the chief second

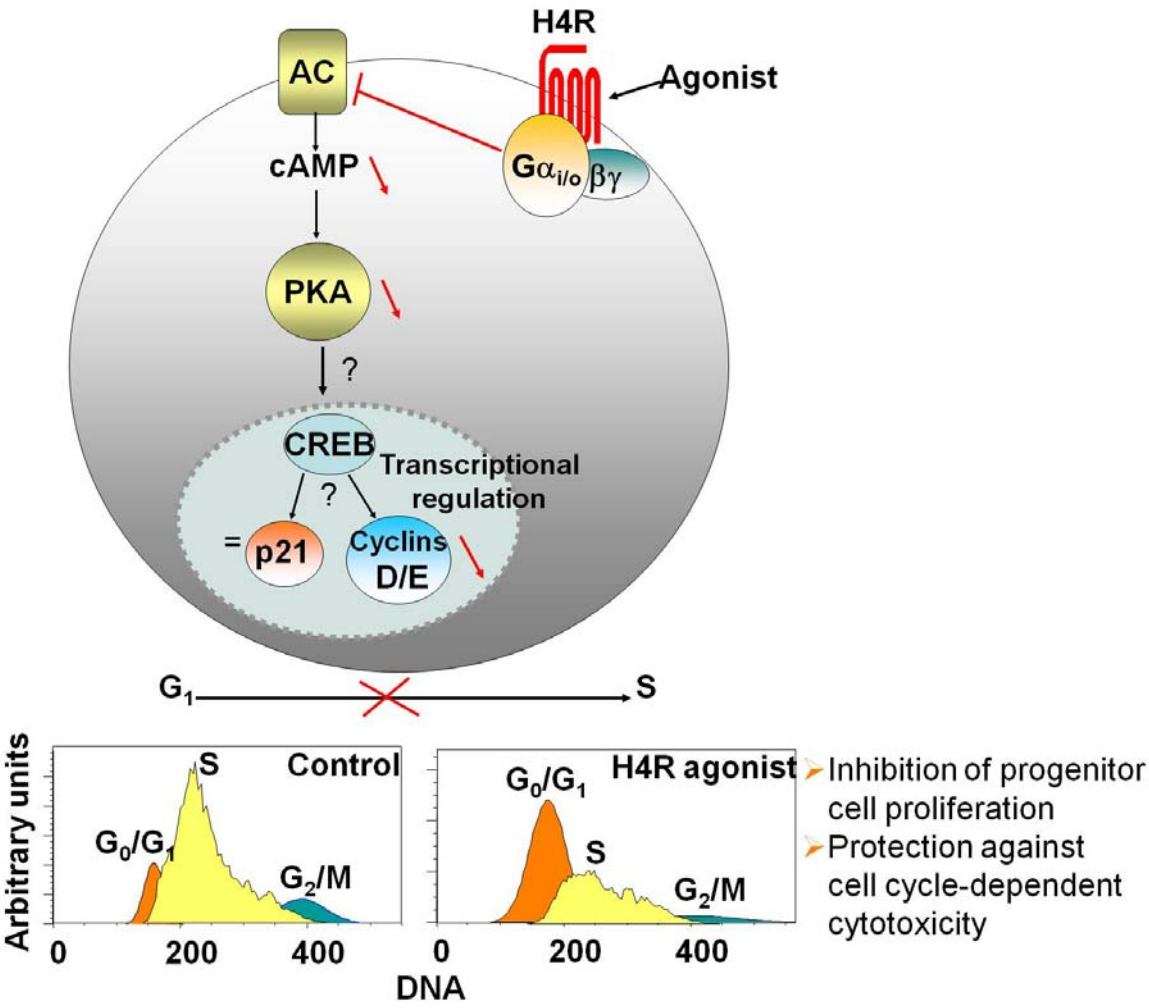

Figure 1. Schematic representation of the signal transduction pathway induced by histamine H_4 receptor (H4R) activation in hematopoietic progenitor cells (sorted $CD34^+$ cells). H4R ligation triggers coupling to $G_{i/o}$ protein followed by downregulation of adenylyl cyclase (AC) and decrease of adenosine 3':5'-cyclic monophosphate (cAMP), which is followed by decreased protein kinase A (PKA) activity, resulting in decreased cyclin D and E expression and maintenance of p21, probably relayed by cAMP response element-binding (CREB). = maintained expression.

messenger (24,26). Further downstream, cAMP-dependent PKA transduces the signal since cell cycle arrest is mimicked by a specific inhibitor of this enzyme. Erk expression was not modified by exposure to H4R agonists, notwithstanding the increased evidence for a crosstalk between cAMP and the ERK/MAPK pathway (36). It is therefore most likely that decreased cell cycling is promoted through PKA/CREB signaling, as proposed previously (37).

5. 2. Cell cycle arrest through H4R-induced maintenance of $p21^{Cip1/Waf1}$ expression

Passing the restriction point between G_0/G_1 and S in response to growth factor stimulation requires decreased expression of cyclin-dependent kinase inhibitors. H4R activation prevents the downregulation of one of these inhibitors, namely $p21^{Cip1/Waf1}$, a cell cycle regulator with important functions in self-renewal, differentiation and apoptosis of progenitor cells (38). By contrast, the expression of $p27^{Kip1}$ that has been associated with the regulation of growth and/or differentiation of more lineage-restricted progenitor cells (39) was diminished in the same conditions. However, it is generally agreed on that both mediators need to be suppressed to ensure the entry of hematopoietic progenitor cells into cell cycle (40), as the maintenance of one compensates for the loss of the other.

6. H4R-INDUCED CELL CYCLE ARREST AS A MEANS OF MYELOPROTECTION

6.1. H4R-mediated *in vitro* and *in vivo* protection of hematopoietic progenitor cells against the toxicity of anti-cancer drugs

The reversibility of the cell cycle arrest together with the lack of apoptosis qualified the H4R as a potential pharmacological target to protect clonogenic cells from the

hematotoxicity of anti-cancer drugs, which limits the benefit of chemotherapy (41). Several methods are currently applied to prevent these complications, such as autologous bone marrow transplantation at high-dose chemotherapy (42) or treatment with growth factors like G-CSF or Epo to alleviate neutropenia or to prevent anemia, respectively (43, 44). Yet, even though the period of hematopoietic recovery is shortened by these treatments that allow a more intensive drug regimen, they are difficult to handle and not devoid of side effects. It has also been suggested that growth factor administration post chemotherapy may deplete the stem cell compartment and give rise to genomic alterations, even though these issues remain controversial (45, 46). For all these reasons a preventive intervention to protect rather than regenerate hematopoietic progenitors would obviously be preferable.

Previous studies have attempted to render hematopoietic cells resistant to anti-neoplastic drugs by slowing down their cell cycle progression, while improving anti-tumor activity by dose intensification (47-50). Some of these cell cycle inhibitors have proved quite effective *in vitro* or in murine *in vivo* models (48,49), but turned out to be less beneficial in preclinical trials because of a number of side effects (50). A myeloprotective effect has also been reported for catecholamines (51), while Broxmeyer *et al.* established that chemokines act in synergy to decrease the percentage of progenitors in S phase, thus accelerating hematopoietic recovery (52). It is not clear so far whether this effect is direct or indirect and how chemokine receptors are distributed in different hematopoietic progenitor subsets.

A potential therapeutic application of H4R agonists as a means of myeloprotection during chemotherapy was consistent with *in vitro* experiments, which showed that following H4R activation the proportion of murine and human clonogenic progenitors that survive treatment with anti-cancer drugs like cytarabine (AraC) or 5- fluorouracil (5-FU) is significantly increased. It was also supported by the induction of cell cycle arrest in hematopoietic progenitor cells *in vivo* in mice having received repeat injections of H4R agonists. In a model of chemotherapy with the cell cycle-dependent drug AraC, the aplasia appearing 2 days post-treatment was significantly reduced by a prior exposure to the partial H4R agonist clobenpropit and clonogenic progenitor frequencies in the bone marrow were maintained. The agonist did not modify either of these parameters *per se* and had no other adverse effects. In further support of a potential clinical usage, H4R activation *in vivo* provided also a partial protection of clonogenic cells against cyclophosphamide, a mobilizing agent that is only partially cell cycle-dependent (32).

6. 2. Lack of H4R expression and function in common carcinoma cell lines

Treatment with H4R agonists during chemotherapy can only be envisaged if it does not impair the anti-tumoral cytotoxicity. It is obvious that in a clinical setting H4R expression in cancer cells should be verified in each patient before treatment and avoided when positive. Note that the studies investigating the effect of H4R activation on tumor cell proliferation have given rise to conflicting results until now. For example, in the MDA-MB-231 breast cancer cell line H4R activation has been shown to result in G_0/G_1 cell cycle arrest followed by apoptosis (53), while in another report histamine receptor-mediated cell cycle arrest occurred in G2/M, once again followed by apoptosis and enhanced radio-sensitivity, which would increase the therapeutic efficiency rather than protect malignant cells (54). It has also been proposed that H4R expression is downregulated in colorectal tumor cells (55), as compared with healthy tissue, which underscores once again the requirement of individual tests.

We failed to confirm the expression of H4R in the colon carcinomas, HT29 and HCT116, and the mammary carcinoma MDA-MB-231. In accordance with this result, we found that the H4R agonist clobenpropit affected neither the proliferation of these malignant cells nor their sensitivity to *in vitro* treatment with the antineoplastic drug 5-FU, which raises the question of the reliability of results obtained with long-established cell lines.

7. CONCLUSIONS AND PERSPECTIVES

In conclusion, in addition to its pro-inflammatory functions in terms of chemotaxis and cytokine production, H4R activation affects hematopoiesis by inhibiting cell cycle progression in progenitor cells. For the time being, we do not understand the relevance of this activity in pathological situations, such as helminth infection, that lead to the generation of high histamine levels in hematopoietic organs. It is possible that the cell cycle arrest mediated through the H4R facilitates the mobilization of hematopoietic progenitor cells to extramedullary sites, as proposed by a previous study (56). Knowing that bone marrow cells express H1R, H2R and H4R subtypes, we postulate that newly synthesized medullary histamine might preferentially target the H4R on progenitors with short-term repopulating activity, while promoting the proliferation of more primitive stem cells through activation of the H2R. This would be a means of replenishing the lineage-committed compartment depleted by mobilization.

The reversible cell cycle arrest in response to H4R activation provides a potential therapeutic strategy to alleviate the side effects of chemotherapy by decreasing the myelotoxicity of anti-cancer drugs. According to our results, the cell cycle arrest will protect mainly the progenitors that ensure short-term hematopoietic recovery, while the quiescent stem cell population will not be affected, being insensitive to the toxicity of the cell cycle-dependent drugs (57). Hence, our approach will limit the period of aplasia by accelerating reconstitution from more lineage-restricted clonogenic progenitors without impairing the efficiency of the anti-cancer treatment. These clinical perspectives, which might eventually facilitate chemotherapy dose and schedule intensification, call for the development of new, more selective H4R agonists.

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Abbreviations: 5-FU: 5- fluorouracil, AC: adenylyl cyclase, AraC: cytarabine, cAMP: adenosine 3':5'-cyclic monophosphate, CLP: lymphoid colony formation, CFU-GM: myeloid colony formation, CFU-S: cells forming colonies in the spleen of irradiated recipients, CREB: cAMP response element-binding, ERK: extracellular signal-regulated kinases, GM-CSF: granulocyte-macrophage colony-stimulating factor, HDC: histidine decarboxylase, HXR: histamine H_X receptor, IL: interleukin, MAPK: mitogen-activated protein kinases, PKA: protein kinase A, PTX: pertussis toxin

Key Words H4 Histamine Receptor, Hematopoietic Progenitor Cells, Cell Cycle Arrest, Myeloprotection, Review

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