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Histamine antagonists promote cancer immunosurveillance

Peng Liu[a,b], Guido Kroemer[a,b,c], and Oliver Kepp[a,b]

[a]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Center, Université Paris Saclay, Villejuif, France; [b]Centre de Recherche des Cordeliers, Equipe Labellisée Par la Ligue Contre le Cancer, Université Paris Cité, Sorbonne Université, Inserm U1138, Institut Universitaire de France, Paris, France; [c]Institut du Cancer Paris CARPEM, Department of Biology, APHP, Hôpital Européen Georges Pompidou, Paris, France

ABSTRACT

Recently, a cellular mini-immune system comprising infinitely expandable dendritic cells and T cells led to the discovery that histamine receptor H1 antagonists act on T cells to stimulate their proliferation and polarization toward a Th1/Tc1 phenotype and to increase their anticancer activity in the context of immunochemotherapy.

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Main text

For a decade, immunostimulatory agents, in particular, monoclonal antibodies targeting immune checkpoints, have entered into clinical routine practice for cancer therapy. Immune checkpoint inhibitors (ICIs) acting on the programmed cell death-1 (PD-1)–programmed cell death ligand 1 (PD-L1) axis, as well as on cytotoxic T lymphocyte antigen-4 (CTLA-4), cause durable effects in a wide range of malignant diseases. Moving ICIs into the frontline of cancer treatments, in particular, into the neoadjuvant setting, is increasing their therapeutic advantage over conventional chemotherapeutics or targeted agents that directly act on cancer cells. Altogether, the success of ICI-based interventions underlines the importance of T cell-mediated anticancer immunity for long-term therapeutic efficacy[1]. Nevertheless, despite the fact that ICIs can achieve complete eradication of advanced stage disease in certain cases of neoplasia, such beneficial effects are still limited to a fraction of patients.

Immunogenic cell death (ICD) triggers the emission of danger-associated molecular patterns by cancer cells that act as adjuvant signals on pattern recognition receptors (PRRs) expressed on antigen presenting dendritic cells (DCs) to stimulate tumor infiltration, phagocytosis and antigen presentation. Moreover, cellular stress and death in the course of ICD can facilitate the generation of tumor-associated antigens by transcriptional shifts, alternative splicing or complementary protein modifications[2]. The resulting priming and clonal expansion of tumor-antigen-specific cytotoxic T lymphocytes (CTLs) in lymphoid structures facilitate tumor lysis, which together with the generation of memory T cells confers tumor regression and therapeutic efficacy that last beyond treatment discontinuation[3,4]. Several lines of evidence from preclinical and clinical studies show that ICD can be beneficially combined with subsequent treatment with ICIs targeting the PD-1/PD-L1 axis[5]. Enhancing the perception of ICD by immune cells can further increase the amplitude of the immune response and thus ameliorate therapeutic anticancer efficacy[6]. In sum, leveraging the curative potential of ICIs makes ICD induction and enhancement an interesting arena for drug development.

We recently built a screening system for ICD enhancers that confronts antigen-presenting DCs differentiated from induced immortalized (iniDC) precursors with interleukin-2 (IL2)-producing B3Z T cell hybridomas expressing a transgenic TCR specific for the ovalbumin (OVA)-derived SIINFEKL peptide[7]. Using OVA-pulsed DCs, we screened chemical compound libraries for ICD enhancers that increase the production of IL2 by B3Z T cells (Figure 1a). In this campaign, we attempted to identify agents that enhance antigen presentation by DC and confer T cell activation. Target deconvolution revealed that the histamine receptor H1 (HRH1) antagonist astemizole elicited IL2 production by B3Z that was independent of cognate antigen exposure or DC-mediated co-stimulation. In fact, astemizole conferred broad T cell stimulation as detectable by CD69 expression and interferon-γ (IFN-γ) secretion by B3Z hybridoma cells as well as by primary T cells from mice[8]. In line with this, we found that injection of astemizole into the footpads of immunocompetent animals induced the expression of T-box transcription factor 21 (TBX21 better known as T-bet) by T cells in the draining (popliteal) lymph nodes with the consequent production of IFNγ, the expression of CD69 and inducible T cell costimulator (ICOS) in $CD4^+$ and $CD8^+$ T cells[8].

At the mechanistic level, astemizole induced the phosphorylation of lymphocyte-specific protein tyrosine kinase (LCK) that binds and stabilizes phosphorylated Zeta-chain-associated protein kinase 70 (ZAP70), which in turn leads to the phosphorylation of key downstream signaling molecules such as linker for activation of T cells (LAT), altogether orchestrating stimulatory TCR signaling. Accordingly, pharmacological

CONTACT Oliver Kepp captain.olsen@gmail.fr Gustave Roussy Cancer Center, Villejuif, France; Peng Liu kunzhiling@gmail.fr Gustave Roussy Cancer Center, Villejuif, France; Guido Kroemer kroemer@orange.fr Centre de Recherche des Cordeliers, Paris, France

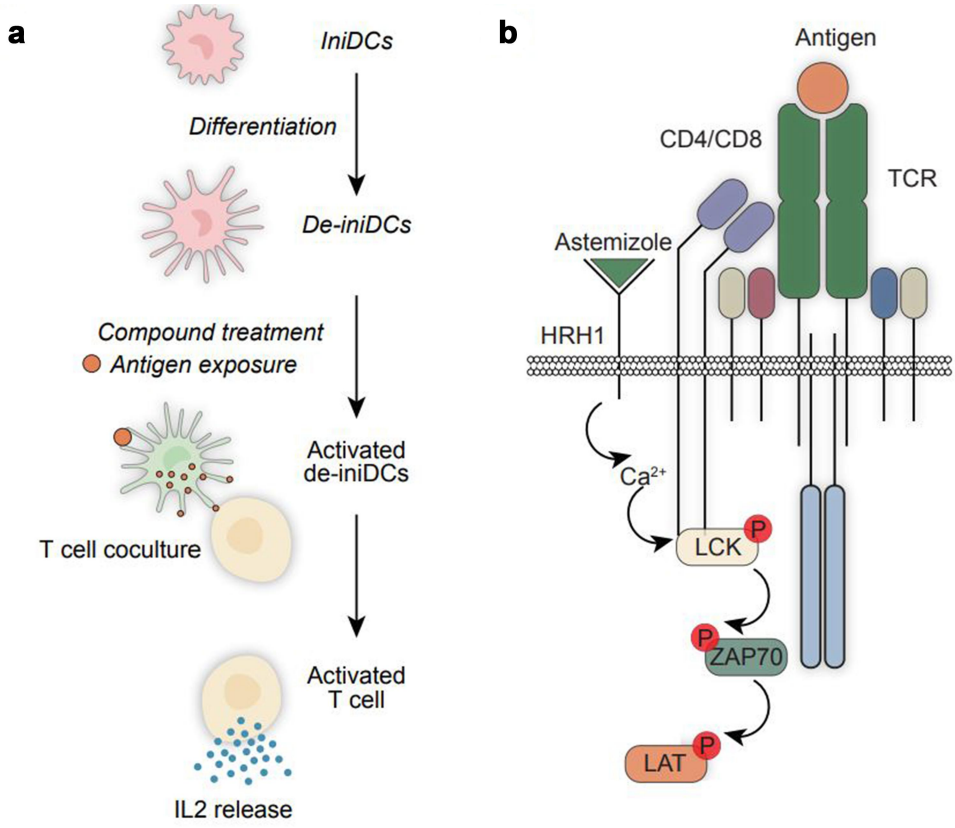

Figure 1. Schematic representation of the screening system and the effect of histamine receptor H1 on cancer immunosurveillance. (a) Inducible immortalized dendritic cell (DC) precursors (iniDC) are differentiated into functional de-iniDcs before being subjected to chemical compound libraries and pulsed with the model antigen ovalbumin. Coculture with antigen specific T cells allows for functional readouts such as the production of interleukin 2 (IL2) by ovalbumin-specific B3Z hybridoma. (b) Astemizole acts as a histamine H1 receptors (HRH1) antagonist, triggers an increase in intracellular Ca^{2+} and elicits LCK activation and downstream phosphorylation of ZAP70 and LAT at the T cell receptor, altogether increasing T cell activation.

inhibition of LCK as well as the use of Ca^{2+}-chelating agents abrogated astemizole-elicited T cell activation, IFN-γ secretion and IL2 production[8].

We found that astemizole acts *on target* as evidenced by a series of alternative HRH1 antagonists that all stimulated LCK activation. Moreover, molar excess of histamine and other HRH1 agonists outcompeted the binding of astemizole to HRH1, inhibited the activation of LCK and interfered with the production of IL2 by B3Z cells. Of note, $CD4^+$ and $CD8^+$ T lymphocytes isolated from the spleens of *Hrh1*$^{-/-}$ mice showed IFN-γ production above baseline that was not further increased by astemizole. Moreover, the abundance of $FOXP3^+CD4^+$ regulatory T cells (Tregs) in spleens from those mice was markedly reduced as compared to wild type littermates, altogether confirming that astemizole acts on HRH1 to induce LCK-mediated TCR signaling[8].

In immunocompetent mice bearing established orthotopic fibrosarcomas, monotherapy with astemizole exhibited no anticancer effects. However, astemizole synergized with the ICD inducer oxaliplatin to slow down the growth of fibrosarcomas. Similarly, triple-negative mammary carcinomas as well as orthotopic non-small cell lung cancers responded to oxaliplatin-based chemotherapy that became more efficient upon treatment with astemizole[8]. Of note, the effect of the combination was lost in immunodeficient animals lacking mature T-cells, as well as in conditions in which $CD4^+$ or $CD8^+$ T cells were depleted or IFN-γ was neutralized by means of suitable antibodies. The immune-enhancing antineoplastic effect of the combination treatment was also reflected by prominent changes in the tumor immune infiltrate, resulting in an increased ratio of tumor-infiltrating CTLs over Treg cells. Finally, bioinformatic analysis of public transcriptomic datasets revealed that, in human cancers, the expression of HRH1 markedly correlated with T cell exhaustion markers while showing an inverse correlation with the abundance of $CD4^+$ TH1 cells[8].

Altogether, the aforementioned data indicate that astemizole enhances ICD-ignited adaptive anticancer immunity by increasing the immune tone of T cells through antagonizing a latent inhibition of TCR signaling imposed by HRH1 (Figure 1b). These findings are in line with reports showing that HRH1 antagonists amplify the efficacy of PD-1/PD-L1-targeted ICIs in murine models of breast carcinomas, colorectal cancers and melanomas[9]. Moreover, retrospective epidemiological data revealed that the use of HRH1 antagonists correlated with overall survival in patients with localized ovarian cancer or metastatic disease and generally ameliorated the response to anticancer immunotherapy[10,11]. These findings have been corroborated

in a recent basket trial revealing that circulating histamine levels inversely correlate with clinical response to PD-1-targeted ICI[9]. Prospective clinical trials evaluating the combination effect of HRH1 antagonists with (ICD-mediated) immunotherapy are urgently awaited.

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Disclosure statement

OK is a cofounder of Samsara Therapeutics. GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys and Vascage. GK has been consulting for Reithera. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's wife, Laurence Zitvogel, has held research contracts with 9 Meters Biopharma, Daiichi Sankyo, Pilege, was on the on the Board of Directors of Transgene, is a cofounder of everImmune and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim.

ORCID

Oliver Kepp http://orcid.org/0000-0002-6081-9558

Data availability statement

All data that led to the conclusions in this manuscript have been referenced and all sources have been described.

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