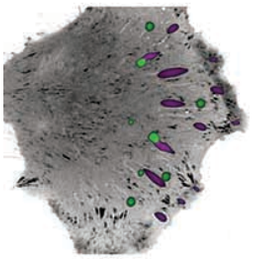
Autophagy



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AUTOPHAGIC PUNCTUM

Autophagy induction for the treatment of cancer

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ABSTRACT

Cancer can be viewed in 2 rather distinct ways, namely (i) as a cell-autonomous disease in which malignant cells have escaped control from cell-intrinsic barriers against proliferation and dissemination or (ii) as a systemic disease that involves failing immune control of aberrant cells. Since macroautophagy/autophagy generally increases the fitness of cells as well as their resistance against endogenous or iatrogenic (i.e., relating to illness due to medical intervention) stress, it has been widely proposed that inhibition of autophagy would constitute a valid strategy for sensitizing cancer cells to chemotherapy or radiotherapy. Colliding with this cell-autonomous vision, however, we found that immunosurveillance against transplantable, carcinogen-induced or genetically engineered cancers can be improved by pharmacologically inducing autophagy with caloric restriction mimetics. This positive effect depends on autophagy induction in cancer cells and is mediated by alterations in extracellular ATP metabolism, namely increased release of immunostimulatory ATP and reduced adenosine-dependent recruitment of immunosuppressive regulatory T cells into the tumor bed. The combination of autophagy inducers and chemotherapeutic agents is particularly efficient in reducing cancer growth through the stimulation of $CD8^+$ T lymphocyte-dependent anticancer immune responses.

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Autophagy can be viewed as a mechanism that allows cells to adapt to a stressful and changing environment by mobilizing energy reserves and remodeling/recycling their cytoplasmic organelles. In line with this vision, autophagy induction by nutritional, pharmacological or genetic manipulations can increase the longevity of model organisms. In our body, malignant cells form as a result of genetic and epigenetic alterations and acquire an unwarranted level of fitness (and de facto immortality) that is combatted by therapeutic measures including chemotherapy and radiotherapy. Many cell biologists working in the fields of autophagy and cancer have come to the conclusion that inhibition of autophagy would constitute a strategy for reducing the fitness of cancer cells and for sensitizing them to killing by chemotherapy or radiotherapy. Based on this assumption, biotechnological and pharmaceutical companies are developing autophagy inhibitors, and multiple clinical studies exploring chemosensitization or radiosensitization by rather nonspecific agents interfering with lysosomal functions (such as chloroquine and its derivatives) have been launched.

Although it has been common wisdom that chemotherapy and radiotherapy mediate tumor growth reduction by direct cytostatic and cytotoxic effects on cancer cells, recent preclinical experimentation and clinical observation indicates that the sustained long-term effects of successful treatments (that last beyond their discontinuation) can only be explained by anticancer immune responses. Indeed, cancers are antigenically distinct from normal cells because they accumulate mutations affecting the coding regions of cellular proteins and because they ectopically transcribe genes that are usually only expressed in embryonic development or in the testis. Moreover, during the process of transformation, cancer cells emit stress signals that may facilitate immune recognition by increasing their adjuvanticity. The combination of antigenicity and adjuvanticity renders cancer cells immunogenic, meaning that the usual (and desirable) fate of a cell that is transforming to a (pre-)malignant state is its elimination by immune effectors. When elimination is impossible, the initial malignant lesion is smoldering in a precarious equilibrium wherein cancer and immune cells engage in a battle of attempted elimination and localized immunosuppression. It is only when immunosurveillance fails that tumors can escape and progress toward a life-threatening state. In this scenario of the 3 "E"s of immunosurveillance (elimination→ equilibrium→ escape), the supreme goal of therapeutic intervention is not the shear reduction of

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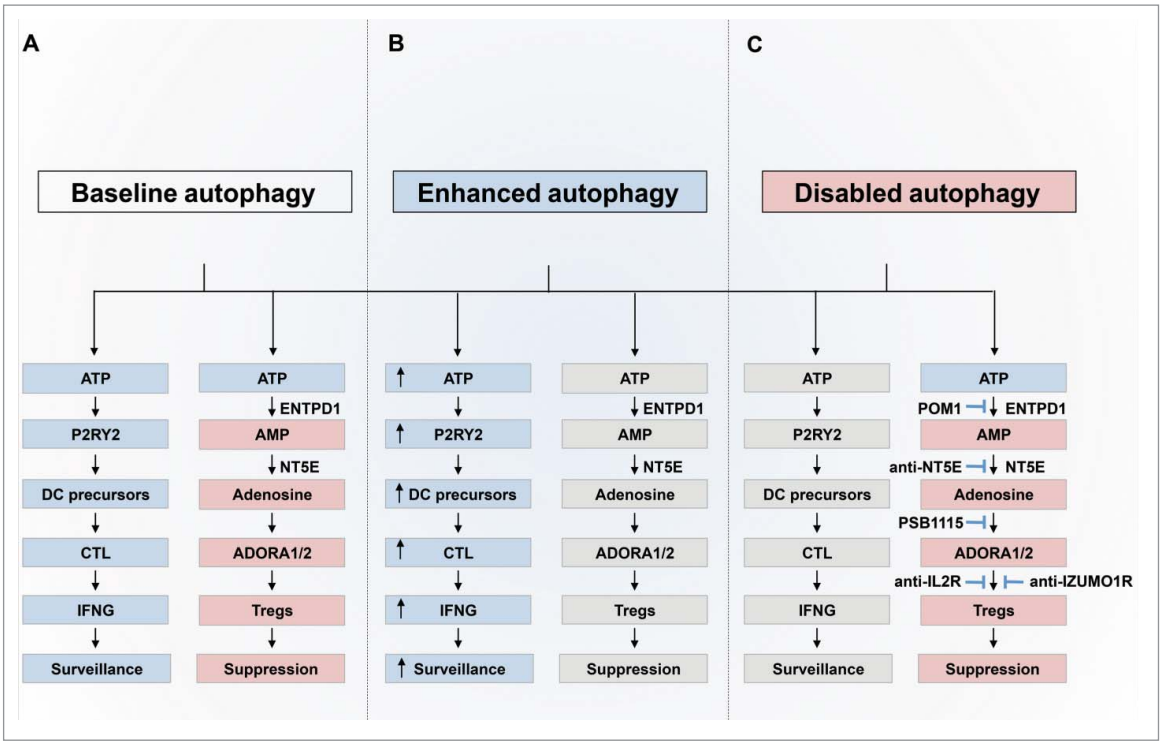

Figure 1. Extracellular ATP metabolism in cancer immunosurveillance. (A) Extracellular ATP metabolism from immunostimulatory ATP to immunosuppressive adenosine. ATP is released in an autophagy-dependent manner from tumor cells exposed to immunogenic chemotherapy. Extracellular ATP acts on the nucleotide receptor P2RY2 (Purinergic Receptor P2Y) expressed by dendritic cell (DC) precursors, ultimately leading to recruitment of IFNG (Interferon gamma)-producing cytotoxic T lymphocytes (CTLs) into the tumor bed. (B) Therapeutic improvement of anticancer immunosurveillance by enhancing autophagy leading to an increase in extracellular ATP. (C) Immunostimulation by suppression of the generation of adenosine or depletion of regulatory T cells (Treg). When autophagy is disabled, ATP undergoes 2-step degradation reactions to adenosine through the activity of the ectoATPase ENTPD1/CD39 and the ectonucleotidase NT5E/CD73. Adenosine acts on ADORA1/2 (adenosine A1/2 receptor) expressed by Treg thus mediating immunosuppression. Inhibition of adenosine generation (POM1 [polyoxometalate-1], anti-NT5E/CD73), treatment with an ADORA antagonist (PSB1115) or Treg depletion (anti-IL2R [interleukin 2 receptor], anti-IZUMO1R/FOLR4 [IZUMO1 receptor, JUNO) are therapeutic strategies that reinstate proficient antitumor immunesurveillance.

tumor mass. Rather, anticancer treatments aspire at resetting the state from immune escape toward equilibrium or (ideally) to elimination.

Surprisingly, there is ample evidence that effective chemotherapies or radiotherapies are actually reinstating immunosurveillance, both in mice and in patients. When mice bearing transplanted carcinomas, sarcomas or lymphomas are treated with anthracycline- or oxaliplatin-based chemotherapy, sustained tumor growth reduction is entirely dependent on cytotoxic T lymphocytes (CTLs), meaning that elimination of CTLs by genetic manipulations or by injecting T cell-depleting CD8-specific antibodies abolishes the treatment effects. In this context, starvation of mice for 48 h (which reduces their body weight by ~20%) improves tumor growth reduction by chemotherapy, and this effect is again dependent on the presence of T lymphocytes as well as on the autophagy competence of the tumors. Cancer cells in which ATG5 or ATG7 have been knocked down by shRNA transfection form tumors that are refractory to chemotherapy, alone or in combination with starvation.

We investigated the possibility to replace chemotherapy by pharmacological autophagy inducers that, in contrast to rapamycin or rapalogs, would not have any immunosuppressive side effects. Hence, we used a variety of caloric restriction mimetics (CRMs) that induce autophagy by virtue of their capacity of reducing the global acetylation of cytoplasmic protein. Co-administration of chemotherapy with CRMs to cancer-bearing mice improves tumor growth reduction in an autophagy- and T cell-dependent manner. These effects are observed for a variety of CRMs differing in their mode of action, namely hydroxycitrate (a competitive low-affinity inhibitor of the acetyl-CoA-generating enzyme ACLY [ATP citrate lyase]), SB204990 (a noncompetitive high-affinity inhibitor of ACLY), spermidine (a natural inhibitor of the acetyltransferase activity of EP300), C646 (a synthetic inhibitor of EP300) and resveratrol (an activator of the deacetylase function of SIRT1/sirtuin-1). In addition, an autophagy-inducing cell-permeable peptide designed to disrupt the inhibitory interaction between BECN1 and GLIPR2/GAPR1 is able to improve the efficacy of chemotherapy in an immune-dependent fashion.

Altogether, these results indicate that the induction of autophagy in cancer cells can improve immunosurveillance. The mechanisms of this positive effect could be linked to extracellular ATP metabolism (Fig. 1A). Autophagy favors the extracellular accumulation of ATP, which acts on purinergic receptors to attract immune effectors into the tumor bed, hence eliciting anticancer immune responses that ultimately are mediated by CTLs. In conditions of autophagy inhibition, extracellular ATP is degraded to adenosine by the sequential action of 2 ecto-enzymes (ENTPD1/CD39 [ectonucleoside triphosphate diphosphohydrolase 1], and then NT5E/CD73 [5′-nucleotidase ecto]). Adenosine favors the local immunosuppressive function of regulatory T cells (Tregs) via its action on adenosinergic receptors. Induction of autophagy

(Fig. 1B) or inhibition of adenosine generation, adenosinergic receptors or Treg depletion (Fig. 1C) synergize with chemotherapy to improve tumor growth reduction. With regard to tumor growth, autophagy induction, inhibition of extracellular ATP catabolism and Treg depletion are epistatic to each other, suggesting that these pathways are indeed functionally connected to each other. Accordingly, CRMs caused the depletion of Tregs from the tumor bed in an autophagy-dependent fashion.

Beyond these mechanistic details, our present study strongly argues in favor of therapeutic measures that combine conventional anticancer treatments with autophagy inducers. The future will tell which particular autophagy stimulators will prove efficient in the clinical setting.