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Elimination of cDC1 cells by regulatory T cells jeopardizes cancer immunotherapy

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

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

ABSTRACT

Recent findings revealed that neoantigen-specific cytotoxic type 1 regulatory T (T_R1) CD4 T cells can subvert cancer immunotherapy by killing type 1 conventional dendritic cells (cDC1s) that present tumor antigens bound to MHC class II. This underlines the importance of cDC1s for eliciting anticancer immunity but poses a novel clinical challenge.

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Cancer immunotherapy has advanced to the frontline for the treatment of many aggressive malignancies in routine clinical practice. Immune checkpoint inhibitors, which target CTLA-4 or the PD-1/PD-L1 axis to (re)activate cytotoxic T lymphocyte (CTL) responses, highlight the crucial role of adaptive anticancer immunity in achieving durable therapeutic success.[1] The ignition of antitumor immune responses and the success of anticancer immunotherapy depend on the critical contribution of type 1 conventional dendritic cells (cDC1s). This has been demonstrated using cDC1-deficient *Batf3*$^{-/-}$ mice (and other methods of cDC1 depletion) in which chemotherapy, immunotherapy, and their combination (chemoimmunotherapy) fail due to the absent cross-presentation of tumor antigens to CTLs.[2,3]

Over the past decade, it has become evident that anticancer treatments capable of inducing immunogenic cell death (ICD) are crucial drivers of adaptive cDC1-mediated anticancer immune responses. ICD, which is triggered by certain antineoplastic agents or radiation therapy (but not standard-of-care cytotoxicants such as cisplatin that largely fail to elicit anticancer immunity), promotes a surge in adjuvanticity, with an increased antigenicity of cancer cells, which together facilitate the activation of dendritic cell-mediated adaptive immune responses.[4] Mechanistically, ICD induces changes in the immunopeptidome presented by MHC complexes, enhancing antigenicity, while simultaneously activating premortem stress pathways that promote the release and surface exposure of specific danger-associated molecular patterns (DAMPs), thereby boosting adjuvanticity. Eukaryotic translation initiation factor 2 subunit 1 (eIF2α) acts as a central switch integrating cellular stress pathways, facilitating the emission of DAMPs such as ATP, which is released during ICD and calreticulin (CALR), which is exposed on the cell surface. In addition, ICD is linked to the release of annexin A1 (ANXA1) and high-mobility group box 1 (HMGB1). All these DAMPs act on pattern recognition receptors expressed by tumor infiltrating cDC1s, triggering their chemotaxis, maturation, and activation.[4,5] Type I interferons (IFNs) produced by tumor cells undergoing ICD further stimulate the release of chemokines, facilitating the recruitment of T lymphocytes into the tumor microenvironment. In essence, ICD spurs tumor infiltration by cDC1s and T cells, thus igniting cDC1-mediated tumor antigen processing and presentation to CTLs. CTLs in turn induce the interferon-gamma (IFNγ)-dependent lysis of residual cancer cells and establish immune memory, which can limit tumor recurrence.[4] Several strategies have been proposed to amplify the immunostimulatory effect of immunogenic cell death (ICD). These strategies include the induction of autophagy to enhance ATP release by tumor cells, as well as the pharmacological stimulation of DCs.[6] Moreover, targeting immune checkpoints expressed by cDC1s, such as BCL2, can improve antigen cross-presentation by cDC1s, thus enhancing anticancer immune responses in vivo.[7]

In a recent article titled "Neoantigen-specific cytotoxic T_R1 CD4 T cells suppress cancer immunotherapy," published in *Nature*, Robert Schreiber and his team reported that cancer vaccines comprising high doses of MHC-II neoantigens (HDVax) inadvertently induce the differentiation of $CD4^+$ T cells into type 1 regulatory (T_R1) cells which then lyse cDC1s (but not cDC2s) in a granzyme B (GZMB)-dependent fashion. The consequent elimination of cDC1s jeopardizes the success of immunotherapies, including that of PD-1 blockade.[8]

The study further revealed three strategies for improving the outcome of cancer immunotherapy after HDVax (Figure 1). The first strategy consists in blocking the leukocyte immunoglobulin like receptor B4 (LILRB4), which is

CONTACT Oliver Kepp captain.olsen@gmail.com Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Center, Villejuif, France; Guido Kroemer kroemer@orange.fr Centre de Recherche des Cordeliers, Equipe Labellisée par la Ligue Contre le Cancer, Université de Paris Cité, Sorbonne Université, Inserm U1138, Institut Universitaire de France, Paris, France

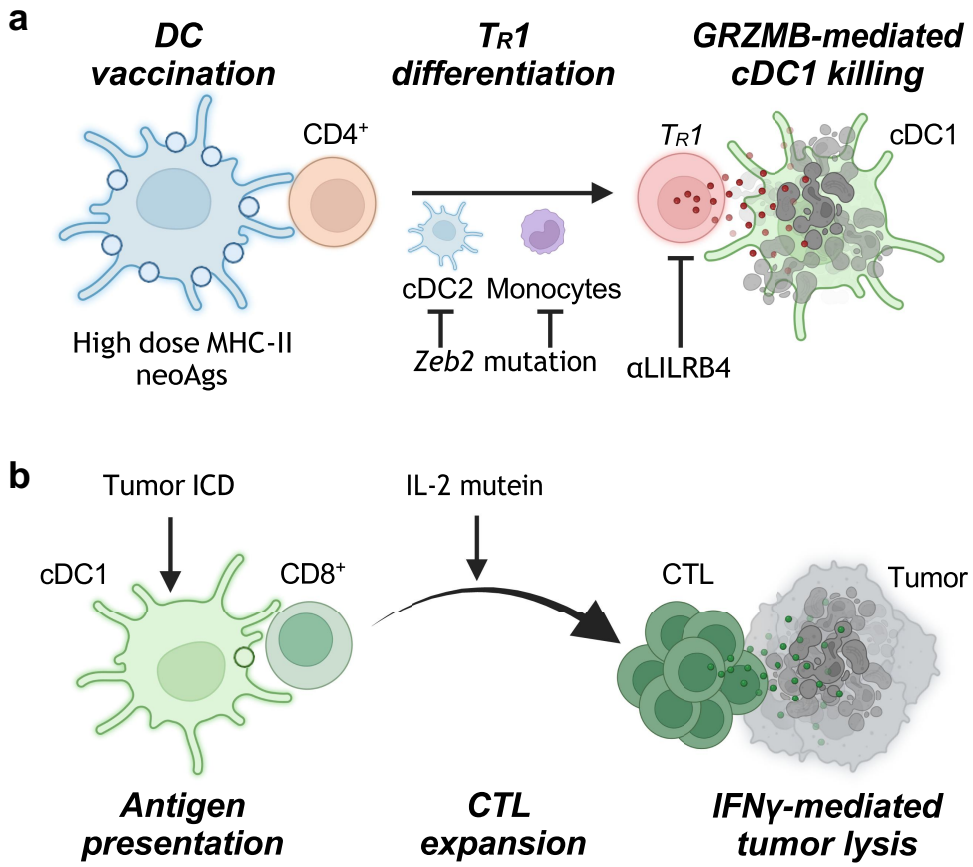

Figure 1. (A) induction of T_R1 cells induces cDC1 depletion and abolishes the effect of immunotherapy. The induction of cytotoxic $CD4^+$ type 1 regulatory T (T_R1) cell differentiation by cancer vaccines comprising high doses of MHC-II neoantigens in the presence of conventional type 2 dendritic cells (cDC2) and monocytes induces the granzyme B-mediated depletion of cDC1 (but not cDC2) and abolishes the effect of immunotherapy, including immune checkpoint blockade (ICI). Depletion of cDC2/monocytes by triple mutation of the *Zeb2* enhancer, inhibition of T_R1-mediated toxicity by blocking LILRB4 (A) or the use of IL-2 mutein for activating cytotoxic T cells (B), allows to overcome T_R1-mediated immune suppression and restores the therapeutic efficacy of cancer immunotherapies. On theoretical grounds, T_R1 cells should also interfere with immunogenic cell death (ICD) induced and cDC1-mediated anticancer immunity.

expressed on type 1 regulatory (T_R1) cells, by means of a monoclonal antibody that results in the downregulation of GZMB and the upregulation of cytokines (such as interleukin 2 (IL-2), IFNγ and tumor necrosis factor) in such cells. The second strategy involves an engineered IL-2 mutein (i.e., a $CD8^+$ T cell *cis*-targeted variant of IL-2 dubbed CD8-IL-2) that activates CTLs but not T_R1 cells and hence tips the balance toward successful cancer immunosurveillance.[8,9] The third strategy consists in the elimination of type 2 conventional dendritic cells (cDC2s) and monocytes by triple mutation of the *Zeb2* enhancer.[10] Such cDC2s/monocytes apparently are required for the induction of T_R1 cells.[8]

Altogether, these results underscore the critical role of different DC subpopulations in shaping the anticancer immune response. While cDC1s educate CTLs to eliminate cancer cells, cDC2s maliciously instigate T_R1 cells to kill cDC1 cells. This complex battle between friends (cDC1s, CTLs) and foes (cDC2s, T_R1 cells) offers ample opportunities for developing novel tactics of anticancer warfare.

Author contributions

PL and LZ collected data, designed display items, and edited the manuscript. GK and OK wrote the manuscript.

Disclosure statement

O.K. is a scientific co-founder of Samsara Therapeutics. GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sutro, Tollys, and Vascage. 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 in the scientific advisory boards of Hevolution, Institut Servier, Longevity Vision Funds and Rejuveron Life Sciences. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. GK's wife, Laurence Zitvogel, has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche, was 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. The funders had no role in the design of the study, in the writing of the manuscript, or in the decision to publish the results.

Data availability statement

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

ORCID

Guido Kroemer http://orcid.org/0000-0002-9334-4405
Oliver Kepp http://orcid.org/0000-0002-6081-9558

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