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Balance is a key for happiness

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Abbreviations: α-GalCer, α-galactosylceramide; NKT, natural killer T; Treg, regulatory T cell

Eliminating one immunosuppressive mechanism is rarely sufficient to overcome cancer. One of reasons underlying this fact is that whether regulatory T cells (Tregs) or Type II natural killer T (NKT) cells dominate immunosuppression depends on the mutual interactions between the latter and their Type I counterparts. Thus, the balance among three immunomodulatory cell types dictates whether eliminating Tregs relieves or not immunosuppression.

Immunotherapies targeting tumor-associated antigens, such as anticancer vaccines and the adoptive transfer of tumor antigen-specific T cells, do not always generate clinical benefits. One of the reasons underlying such a limited therapeutic success lies in the fact that tumors get help to evade the immune system from immunosuppressive cells including myeloid-derived suppressor cells (MDSCs), natural killer T (NKT) cells and regulatory T cells (Tregs). Along with recent advances in the understanding of these immunosuppressive cell populations, many approaches to block or eliminate them have been tested or are currently under investigation in clinical settings. These strategies include the use of monoclonal antibodies or fusion proteins targeting molecules that are expressed on the surface of immunosuppressive cells as well as the use of agents that specifically block the molecular mechanisms of suppression. Recent data indicate that some types of chemotherapy also exert a selective inhibitory effect on immunosuppressive cells.[1]

However, blocking one single mechanism of immunosuppression does not always allow for the re-establishment of antitumor immune responses. For example, the blockade of Tregs does not protect mice against the development of some tumor types and has achieved minimal success in patients, suggesting that other mechanisms of immunosuppression are in place.[2] Why in some, but not all, tumor models Tregs seem to play a critical role in suppressing anticancer immunity? What determines which immunosuppressive mechanism dominates in a given tumor? Our recent study provides some insights into these issues.[3] We found indeed that blocking one single immunosuppressive cell type, notably Tregs, is not always sufficient to protect mice against tumor progression because the dominant mechanism of immunosuppression depends on the balance between other regulatory cells, namely Type I and Type II NKT cells.

NKT cells are a subset of T cells recognizing lipid antigens presented by CD1d.[4] NKT cells can be subdivided into two subsets. Type I NKT cells express an invariant T-cell receptor (TCR)-α chain coded by the Vα14Jα18 recombined gene segments in mice and the Vα24Jα18 sequences in humans. The prototypic activator of Type I NKT cells is α-galactosylceramide (α-GalCer), and these generally promote antitumor immunity. In contrast, Type II NKT cells express a diverse TCRα repertoire, in both humans and mice. Type II NKT cells, which have been less well characterized than their Type I counterparts (owing to the lack of tools allowing for their precise identification) can be activated by lipids other than α-GalCer, such as sulfatide, and have been found to suppress antitumor immune responses. Of note, Type I and Type II NKT cells are able to cross-regulate each other.[5]

We observed that blocking Tregs is sufficient to induce tumor rejection in wild-type mice, but has no effects on tumor growth in Type I NKT cell-deficient ($J\alpha18^{-/-}$) animals.[3] The adoptive transfer of Type I NKT cells as well as the blockade of Type II NKT cell activation restored the antineoplastic effects of Treg-blocking interventions in $J\alpha18^{-/-}$ mice. These data suggest two things. First, in the absence of Type I NKT cells, their Type II counterparts efficiently suppress antitumor immunity, together with Tregs, so that the blockade of both of these immunosuppressive cell populations is required for the re-establishment of tumor-specific immune responses. Second, Type I NKT cells suppress the immunomodulatory activity of their Type II counterparts, so that the balance between the two types of NKT cells determines whether blocking Tregs allows for tumor rejection. Thus, a third type of T cell, Type I NKT cells, determines whether Tregs or Type II NKT cells dominate the scene of immunosuppression and hence "regulates the regulators" (**Fig. 1**). This conclusion is also supported by the observation that the specific activation of Type II NKT cells, which shifts the tip of the balance in their own favor, eliminated the anticancer effects of Treg-blocking measures in wild-type mice, even though

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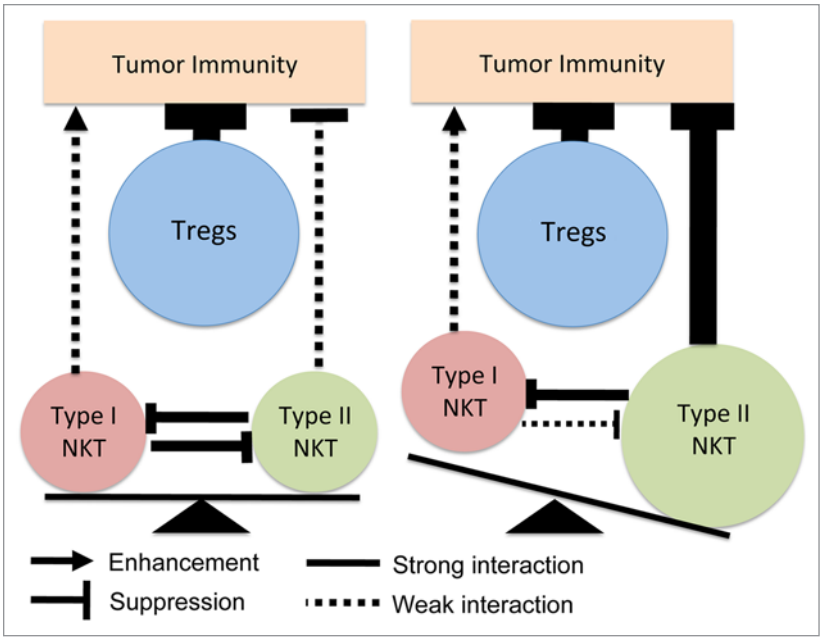

Figure 1. The balance between Type I and Type II natural killer T cells and regulatory T cells in the control of antitumor immunity. Type I natural killer T (NKT) weaken the immunosuppressive activity of their Type II counterparts, leaving regulatory T cells (Tregs) as dominant immunosuppressors (left panel). In the absence of a balance between Type I and II NKT cells, the former are unable to effectively inhibit the latter, so both Tregs and Type II NKT cells exert strong immunosuppressive effects (right panel).

these animals have Type I NKT cells.[3] The functions and/or numbers of Type I NKT cells appear to be reduced in cancer patients.[4] Thus, the immunological status of cancer patients might resemble that of *Jα18*$^{-/-}$ mice, possibly accounting for the limited clinical success of Treg-targeting immunotherapies. It will be interesting to study the balance between Type I and Type II NKT cells in patients that fail to respond to Treg-targeting therapies. Moreover, simultaneously blocking Tregs and Type II NKT cells may turn out to constitute a valuable immunotherapeutic approach against cancer.

How can we overcome the multiple immunological defects that generally affect cancer patients? Various approaches can be envisioned to restore the balance between Type I and Type II NKT cells. One possibility is to recover the functions of Type I NKT cells by specifically activating them with α-GalCer. The results of some clinical studies indicate that the administration of α-GalCer-pulsed dendritic cells efficiently stimulate the production of interferon γ (IFNγ), a critical effector cytokine.[6] Recent studies suggest that combining this approach with the blockade/depletion of Tregs might increase the efficacy of anticancer vaccines.[7,8] A second possibility is to adoptively transfer Type I NKT cells to cancer patients, similar to what we did in mice. Indeed, clinical trials based on Type I NKT cells expanded ex vivo and then adoptively transferred to patients achieved promising results.[9] Finally, interventions for the specific blockade of Type II NKT cells can be envisioned. This might be achieved by administrating a specific antagonistic antigen or monoclonal antibodies that selectively recognize Type II NKT cells. An analogous approach has previously been suggested for the targeting of Type I NKT cells in the setting of some autoimmune diseases in which Type I NKT cells are pathogenic.[10] As it stands, candidate agents to specifically target Type II NKT cells are lacking, but we are currently striving to identify them.

Tumors harness multiple immunosuppressive pathways to evade the anticancer activity of the host immune system. Therefore, blocking one single immunosuppressive mechanism may not always be sufficient to allow for the re-establishment of antitumor immune responses. Rather, we may need to restore the proper balance among multiple immunoregulators to achieve successful anticancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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