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AUTHOR'S VIEW

Harnessing the IL-7/IL-7Rα axis to improve tumor immunotherapy

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ABSTRACT
IL-7 and IL-15 are critical for supporting T cells transferred into a lymphopenic environment. As activated $CD8^+$ T cells downregulate IL-7Rα, it is thought IL-15 is more important. However, we find that $CD8^+$ T cells activated with IL-12 have elevated IL-7Rα and rely on IL-7 for persistence and antitumor immunity.

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The adoptive transfer of activated $CD8^+$ T cells can be highly efficacious in treating select cancers.[1,2] An important component of many adoptive cellular therapy (ACT) protocols is lymphodepleting chemotherapy prior to T cell transfer. Such preconditioning is thought to aid the persistence and function of adoptively transferred T cells through multiple mechanisms including the removal of suppressor cells, the induction of microbial TLR ligands, and the release of tumor antigens.[2] Perhaps most importantly, the depletion of host lymphocytes also leads to elevated levels of the T cell growth factors IL-7 and IL-15.[3] These cytokines are critical for supporting the survival and proliferation of different T cell subsets transferred into a lymphopenic environment. However, it is thought that activated $CD8^+$ T cells, which downregulate IL-7Rα and concomitantly increase IL-2/IL-15Rβ, would be more dependent on IL-15 than IL-7 in the context of ACT.[1,4,5]

To test the cytokine responsiveness of adoptively transferred activated $CD8^+$ T cells in the context of tumor immunity, we used a lymphodepletion-dependent model.[6-8] In this murine melanoma tumor model, activated tumor-reactive $CD8^+$ T cells are derived from pmel-1 TCR transgenic mice. These pmel-1 $CD8^+$ T cells recognize an H-$2D^b$-restricted peptide from the endogenous gp100 tumor antigen that is expressed on the transplantable mouse B16 tumor cells. Using this model, we have previously shown that IL-12 conditioning of the activated T cells prior to adoptive transfer significantly (10–100 fold) improved their ability to persist and mediate antitumor immunity.[6,7] Importantly, the IL-12-conditioned T cells (Tc1) depended on lymphodepletion for optimal antitumor immunity.[6,7] Therefore, this model represents a powerful system for assessing the role of host IL-7 and IL-15 on activated $CD8^+$ T cells.

We tested the cytokine requirements of donor pmel-1 Tc1 cells in IL-15 knockout mice or mice depleted with antibodies targeting either IL-7 or IL7Rα.[8] Tc1 cells transferred into irradiated mice had severely impaired persistence at one week in the absence of IL-7. In contrast, Tc1 cells persisted normally in IL-15 knockout mice. Removing both IL-7 and IL-15 did not have any additional impact over IL-7 deprivation alone. Interestingly, in contrast to initial T cell engraftment, the ability of activated Tc1 cells to mediate antitumor immunity was severely compromised in the absence of either IL-7 or IL-15. This finding may be explained by our observation that long-term persistence and memory formation of donor Tc1 cells was compromised in the absence of IL-15.

The critical role of IL-7 in IL-12-conditioned activated $CD8^+$ T cells was not expected. IL-12 conditioning during T cell activation is thought to lead to the development of short-lived effector cells which are characterized by low IL-7Rα expression.[9] To test whether IL-7Rα was reduced in our system, we evaluated activated $CD8^+$ T cells conditioned with (Tc1) or without (Tc0) IL-12.[8] Strikingly, IL-12 conditioning led to significantly elevated IL-7Rα expression in Tc1 versus Tc0 cells. This IL-7Rα expression led to markedly enhanced IL-7 sensitivity in Tc1 cells compared to Tc0 cells, as measured by proliferation and intracellular cytokine signaling. In the absence of IL-12 conditioning, we also observed enhanced functionally relevant IL-7Rα expression, albeit at lower levels, by increased TCR stimulation during activation. This was in contrast to the expected TCR activation-induced downregulation of IL-7Rα. Overall, our findings suggest an unappreciated importance of IL-7Rα expression on activated $CD8^+$ T cells.

To directly evaluate whether elevated IL-7Rα on activated Tc1 cells was functionally important *in vivo*, we generated Tc1 cells from pmel-1 IL-$7R\alpha^{+/-}$ or wildtype mice.[8] IL-$7R\alpha^{+/-}$ Tc1 cells phenocopied wildtype Tc1 cells *in vitro*, except for expressing approximately half as much IL-7Rα and responding less robustly to IL-7. Consistent with our predictions, infused IL-$7R\alpha^{+/-}$ Tc1 cells were impaired in their capacity to persist

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and mediate antitumor immunity compared with wildtype Tc1 cells. Thus, these experiments demonstrate that relatively modest differences in IL-7Rα expression on activated CD8$^+$ T cells can have important biological consequences for T cells transferred into a lymphopenic environment.

Similar to murine Tc1 cells, we found a critical role for the IL-7/IL-7Rα axis for human CD8$^+$ T cells activated in the presence of IL-12 compared to cells activated without IL-12.[8] Unlike the murine cells, we detected low IL-7Rα expression on human T cells after activation with IL-12. However, when these IL-12-conditioned human T cells were removed from stimulation and expanded (in the absence of IL-12), they re-expressed IL-7Rα at high levels, unlike their counterparts primed without IL-12. Finally, using a protocol for generating human TCR-modified tumor-reactive T cells similar to that in certain clinical ACT settings, we showed that adding IL-12 during the rapid expansion step led to upregulation of IL-7Rα after removal of TCR stimulation.

In summary, our findings shed new light on the importance of IL-7Rα in cancer immunotherapy. From a clinical perspective, our results suggest an unappreciated role of IL-7Rα expression (or re-expression) in supporting engraftment of adoptively transferred activated CD8$^+$ T cells. As clinically used lymphodepleting strategies are thought to induce a transient window of enhanced IL-7 availability, the ability to induce a relatively brief upregulation of IL-7Rα on donor T cells may be sufficient to improve their engraftment (Fig. 1). Given the importance of this pathway, IL-7Rα expression prior to or after adoptive T cell transfer may serve as a useful biomarker predictive of T cell persistence or efficacy. From the standpoint of understanding T cell biology, it is intriguing that adoptively transferred activated murine CD8$^+$ T cells were not only IL-7 dependent but initially IL-15-independent *in vivo*. These results are markedly different from those obtained with CD8$^+$ memory T cells transferred into lymphopenic recipients where IL-7 and IL-15 play compensatory roles in supporting T cell engraftment.[10] One tempting possibility to explain these seemingly different results is that activated CD8$^+$ T cells do not initially localize to IL-15-rich areas, although other possibilities warrant investigation. Overall, these results provide a better understanding of the cytokine requirements of adoptively transferred T cells, which will aid in the development of improved ACT strategies.

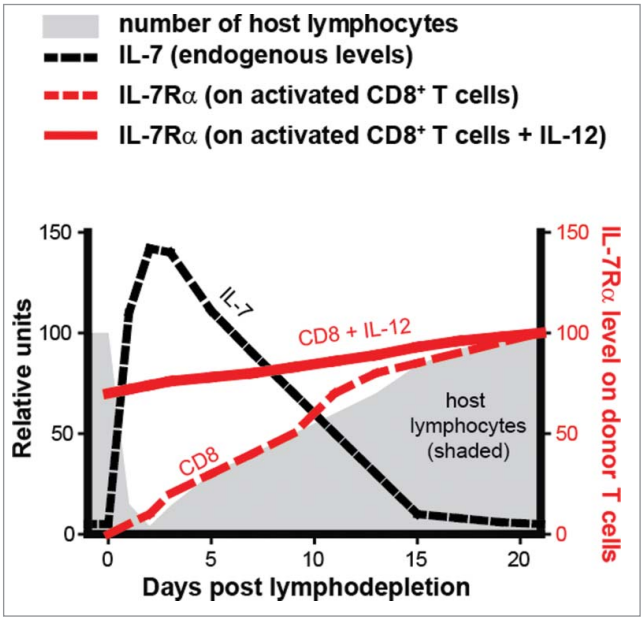

Figure 1. Activated CD8$^+$ T cells with IL-12 conditioning have elevated IL-7Rα and maximal ability to utilize host IL-7 after transfer into a lymphodepleted host. In this schematic diagram, the shaded area indicates theoretical change in host lymphocyte numbers after cytoreductive therapy. As a consequence of lymphodepletion, serum IL-7 levels are greatly and transiently increased (dotted black line). The red lines indicate expression of IL-7Rα on either standard activated (red dotted line) or IL-12-conditioned (red solid line) CD8$^+$ T cells. Unlike standard activated CD8$^+$ T cells, IL-12-conditioned activated CD8$^+$ T cells have elevated IL-7Rα at transfer and can maximally respond to high serum IL-7 levels during the critical lymphopenic window.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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