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C. Bryce Johnson, John Wrangle, Shikhar Mehrotra, Zihai Li, Chrystal M. Paulos, David J. Cole, Charles D. Surh & Mark P. Rubinstein

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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.

The adoptive transfer of activated CD8+ T cells can be highly efficacious in treating select cancers. 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. Perhaps most importantly, the depletion of host lymphocytes also leads to elevated levels of the T cell growth factors IL-7 and IL-15. 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.

To test the cytokine responsiveness of adoptively transferred activated CD8+ T cells in the context of tumor immunity, we used a lymphodepletion-dependent model. 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-2Dβ-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. Importantly, the IL-12-conditioned T cells (Tc1) depend on lymphodepletion for optimal antitumor immunity. 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 IL-7Rα. 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. To test whether IL-7Rα was reduced in our system, we evaluated activated CD8+ T cells conditioned with (Tc1) or without (Tc0) IL-12. 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-7Rα+/+ or wildtype mice. IL-7Rα−/− 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-7Rα−/− Tc1 cells were impaired in their capacity to persist...
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. 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 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 appreciated 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. 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.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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