Zeng et al. www.jem.org/cgi/doi/10.1084/jem.20041057

Synergistic expansion of CD8$^+$ T cells is diminished in both IL-15$^{-/-}$ and IL-21R$^{-/-}$ mice.
We examined the effect of IL-15 and IL-21 on splenocytes derived from IL-15$^{-/-}$ or IL-21R$^{-/-}$ mice. Consistent with previous papers, IL-15$^{-/-}$ mice had reduced numbers of CD8$^+$ T cells (Fig. S2, lane 13 vs. 1, and reference 1), whereas IL-21R$^{-/-}$ mice had essentially normal numbers of CD8$^+$ T cells (Fig. S2, lane 25 vs. 1; references 2, 3). IL-15 had less of an effect on CD8$^+$ T cell expansion in IL-15$^{-/-}$ mice (Fig. S2, lane 17) than in wild-type mice (Fig. S2, lane 5), consistent with only partial reversion of the IL-15$^{-/-}$ phenotype by IL-15 as observed previously (1). The basis for this is unclear, but we speculate

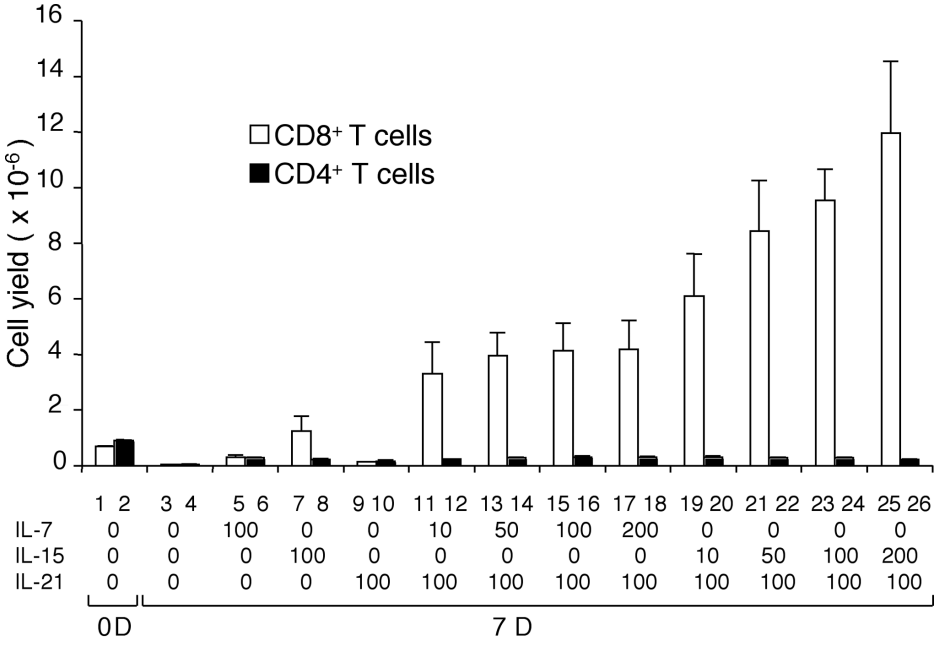

Figure S1. IL-21 cooperated with IL-15 more potently than with IL-7 to expand CD8$^+$ T cells. 5×10^6 splenocytes pooled from three wild-type mice were cultured for 7 d in medium containing IL-7, IL-15, IL-21, or combinations of these cytokines, as indicated. CD8$^+$ T, CD4$^+$ T cell subsets were identified as CD8$^+$CD4$^-$ and CD8$^-$CD4$^+$, respectively. Results shown are means ± SD from three experiments.

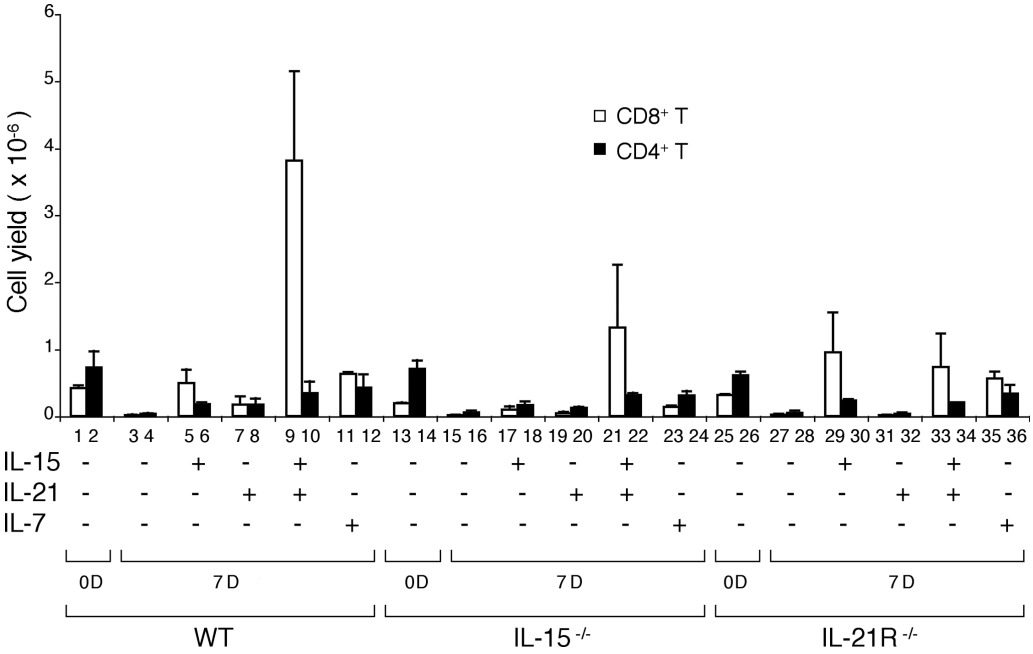

Figure S2. Both IL-15 and IL-21 are essential for maximal expansion of CD8$^+$ T cells. 5×10^6 splenocytes were pooled from wild-type, IL-15$^{-/-}$, or IL-21R$^{-/-}$ mice and cultured for 7 d with 100 ng/ml of IL-15, IL-21, or IL-7, as indicated. CD8$^+$ T, CD4$^+$ T cell subsets were identified as CD8$^+$/CD4$^-$ and CD8$^-$/CD4$^+$, respectively.

that it might result from developmental defects in these animals preventing their full response. Correspondingly, IL-15 and IL-21 exhibited a synergistic effect on $CD8^+$ T cells in IL-$15^{-/-}$ mice (Fig. S2, lane 21 vs. 17 and 19), although the effect was less than in wild-type mice (Fig. S2, lane 9). Interestingly, IL-15 had a slightly greater effect on $CD8^+$ T cells from IL-$21R^{-/-}$ mice (Fig. S2, lane 29) than from wild-type mice (Fig. S2, lane 5). Because the defect in IL-21 signaling in IL-$21R^{-/-}$ mice cannot be rescued by the addition of IL-21, in these animals there was no effect of IL-21 alone (Fig. S2, lane 31) or synergistically with IL-15 (Fig. S2, lane 33 vs. 29). Interestingly, in wild-type and IL-$21R^{-/-}$ mice, IL-7 expanded or supported survival of both $CD8^+$ and $CD4^+$ splenic T cells (Fig. S2, lanes 11 and 12 vs. 3 and 4 and lanes 35 and 36 vs. 27 and 28). The effect of IL-7 on $CD8^+$ T cells was reproducibly impaired in IL-$15^{-/-}$ splenocytes, although its effect on $CD4^+$ T cells was intact (Fig. S2, lanes 23 and 24). Thus, the effect of IL-7 on $CD8^+$ T cell expansion or survival appears to require normal IL-15 function.

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