Abstract

IL-15 may have a role in the development of T cell large granular lymphocyte (T-LGL) or NKT leukemias. However, the mechanisms of action and the identity of the cell subset that undergoes leukemic transformation remain elusive. Here we show that in both mice and humans, NKp46 expression marks a minute population of WT NKT cells with higher activity and potency to become leukemic. Virtually 100% of T-LGL leukemias in IL-15 transgenic mice expressed NKp46, as did a majority of human T-LGL leukemias. The minute NKp46+ NKT population, but not the NKp46$^-$ NKT population, was selectively expanded by overexpression of endogenous IL-15. Importantly, IL-15 transgenic NKp46$^-$ NKT cells did not become NKp46+ in vivo, suggesting that NKp46+ T-LGL leukemia cells were the malignant counterpart of the minute WT NKp46+ NKT population. Mechanistically, NKp46+ NKT cells possessed higher responsiveness to IL-15 in vitro and in vivo compared with that of their NKp46$^-$ NKT counterparts. Furthermore, interruption of IL-15 signaling using a neutralizing antibody could prevent LGL leukemia in IL-15 transgenic mice. Collectively, our data demonstrate that NKp46 identifies a functionally distinct NKT subset in mice and humans that appears to be directly susceptible to leukemic transformation when IL-15 is overexpressed. Thus, IL-15 signaling and NKp46 may be useful targets in the treatment of patients with T-LGL or NKT leukemia