Requirements for common chain family cytokines for adoptively transferred \( \gamma \delta \) T cell function and homeostasis \textit{in vivo} 

Kazuhiro Kakimi1*, Takamichi Izumi1, Makoto Kondo1, Nao Fujieda1, Atsushi Kondo1, Naohisa Tamura1, Ryuji Maekawa2, Hirokazu Matsushita1

Abstract

We have conducted clinical trials of adoptive \( \gamma \delta \)T cell therapy for the treatment of cancer. Peripheral blood mononuclear cells (PBMC) were harvested by apheresis and \( \gamma \delta \)T cells had been expanded ex vivo for 14 days by culture with zoledronate (5 \( \mu \)M) and IL-2 (1000 IU/ml). Patients received >1x10^9 \( \gamma \delta \)T cells every 2 weeks. Infused \( \gamma \delta \)T cells gradually accumulated in patients’ peripheral blood and accounted for 10% of PBMC as late as 3 months after the final injection, even without IL-2 administration in vivo. These cells maintained the ability to release cytotoxic granules (detected by CD107 assay) and produce IFN-\( \gamma \) in response to re-stimulation. To determine the factors contributing to \( \gamma \delta \) T cell survival in vivo, we investigated their expression of receptors for common \( \gamma \) chain (\( \gamma_c \)) family cytokines at the time of infusion. IL-2R\( \beta \) and \( \gamma_c \), but not IL-7R \( \alpha \), IL-15R\( \alpha \) or IL-21R, were present on these cells, and although the IL-2R\( \alpha \) was upregulated at the initiation of culture, it was only very weakly expressed at the time of transfer. When \( \gamma \delta \) T cells were maintained for longer periods in culture, IL-15 but not low dose IL-2 and IL-7 supported their survival. Because IL-15 can be transpresented with IL-15Ra, \( \gamma \delta \) T cell expressing IL-2R\( \beta \) and \( \gamma_c \) can respond more efficiently to IL-15 than IL-2. These results suggest that tissue-specific \( \gamma_c \)-dependent signals in response to IL-15 might affect the survival and function of infused \( \gamma \delta \) T cells, and hence materially influence the success of immunotherapy.