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## $\gamma\delta$ T cells expansion and function stimulated with IL-18: Role of NK cells

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**Introduction:** Human  $\gamma\delta$  T cells display potent cytotoxicity against various tumor cells pretreated with zoledronic acid (Zol). Zol has shown benefits when added to adjuvant endocrine therapy for patients with early-stage breast cancer or to standard chemotherapy for patients with multiple myeloma. Although  $\gamma\delta$  T cells may contribute to this additive effect, the responsiveness of  $\gamma\delta$  T cells from early-stage breast cancer patients has not been fully investigated.

**Objective:** In this study, we determined the number, frequency, and responsiveness of V $\gamma$ 2V $\delta$ 2 T cells from early- and late-stage breast cancer patients and examined the effect of IL-18 on their ex vivo expansion.

**Methods:** Breast cancer patients (n=80) were enrolled after institutional review board approval and with written informed consent. Peripheral blood mononuclear cells (PBMC) were purified and stimulated with Zol/IL-2 or Zol/IL-2/IL-18 for 2 to 10 days. The expanded cells were assessed on flow cytometry and the production of IFN- $\gamma$  and TNF- $\alpha$  measured through ELISA.

**Results:** The responsiveness of V $\gamma$ 2V $\delta$ 2 T cells from patients with low frequencies of V $\gamma$ 2V $\delta$ 2 T cells was significantly diminished. IL-18, however, enhanced ex vivo proliferative responses of V $\gamma$ 2V $\delta$ 2 T cells and helper NK cells (CD3<sup>-</sup>CD56<sup>bright</sup>CD11c<sup>+</sup>CD14<sup>-</sup>CD16<sup>+</sup>NKGD2<sup>+</sup>NKp44<sup>low</sup>) from patients with either low or high frequencies of V $\gamma$ 2V $\delta$ 2 T cells. Cell-to-cell contact between  $\gamma\delta$  T and helper NK cells appeared to promote expansion of  $\gamma\delta$  T cells. Exogenous IL-18 markedly enhanced IFN- $\gamma$  and TNF- $\alpha$  production from PBMC stimulated by Zol/IL-2, whereas the addition of an anti-IL-18R $\alpha$  mAb reduced cytokine production.

**Conclusion:** These results demonstrate that Zol elicits immunological responses by  $\gamma\delta$  T cells from early-stage breast cancer patients and IL-18 enhances proliferative responses and effector functions of  $\gamma\delta$  T cells in the context of helper NK cells.

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