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Poster presentation

Recognition of Isopentenylpyrophosphate and Daudi Tumor Cells By Distinct Subsets of Vγ2/Vδ2 T Cells

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Gammadelta (γδ) T cells account for 1–10% of CD3+ lymphocytes in the peripheral blood and mostly express a heterodimeric T cell receptor (TCR) with Vγ2+ and Vδ2+ chains. Although the Vγ2/Vδ2 subset is defined by the shared expression of common TCR gene segments, these TCRs are highly diverse due to characteristic N nucleotide insertion and deletion at the complementarity-determining region 3 (CDR3) of both γ- and δ-chains. Vγ2/Vδ2 T cells recognize alkylphosphates that are ubiquitous intermediates in isoprenoid biosynthesis and tumor cells derived from hematopoietic malignancies in a non MHC-restricted, TCR-dependent manner. Previous work from our lab demonstrated that a model alkylphosphate, isopentenylpyrophosphate (IPP), specifically selects Jγ1.2+ chains and selectively skews the Vγ2 repertoire toward longer chain lengths. We assumed that Vγ2/Vδ2 recognition of alkylphosphates and tumor cells was common and hypothesized that Daudi B cells, the model tumor target for Vγ2/Vδ2 T cells, would similarly promote the outgrowth of Vγ2/Vδ2 lymphocytes with longer, Jγ1.2 Vγ2 TCRs. Peripheral blood mononuclear cells (PBMC) from 6 donors were stimulated *in vitro* with interleukin-2 (IL2) alone, IL2 and IPP, or IL2 and irradiated (120 Gy) Daudi tumor cells. The frequency of Vγ2/Vδ2 lymphocytes increased from 5.8 ± 7.8% on Day 0 to 5.5 ± 5.9%, 34 ± 32%, 47 ± 27% after 2 weeks in culture with IL2, IL2+IPP or IL2+Daudi, respectively. RNA was extracted before and after stimulation, Vγ2 and ζδ2 chains were amplified from reverse transcribed cDNA, and spectratype analysis was performed to assess changes in the distribution of Vg2 CDR3 lengths. IPP and Daudi similarly skewed the Vγ2 repertoire toward longer chain lengths, while not affecting the overall distribution of Vδ2 chain lengths. Comparison of Vγ2 CDR3 sequences from three donors suggest that recognition of IPP and Daudi is mediated by two distinct subsets of Vγ2/Vδ2 T cells, thus overturning the prevailing model for gd T cell recognition of tumors. Collectively, these experiments help clarify the role of Vγ2 CDR3 specificity in alkylphosphate and tumor recognition and demonstrate that discrete subsets of Vγ2/Vδ2 T cells mediate alkylphosphate and tumor responsiveness.