

POSTER PRESENTATION

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Selective costimulation by IL-15R/IL-15, but not IL-2R/IL-2, allows the induction of high numbers of tumor-specific CD8⁺ T cells by human dendritic cells matured in conditions of acute inflammation

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Conventional dendritic cells (DC) are believed to rely on membrane-bound IL-2R α to trans-present soluble IL-2 and costimulate T cell activation and expansion. In contrast, Langerhans cells have been shown to use membrane-bound IL-15R α /IL-15 complex to activate T cells. Here we show that, while the expansion of tumor-specific CD8⁺ T cells by DC matured in the presence of chronic inflammatory mediators (PGE₂, TNF α , IL-1 β , IL-6) fully depends on expression of IL-2R α , CD8⁺ T cell expansion induced by IL-12p70-producing DC matured by interferon's and Toll-Like receptor ligands (type-1-polarized; DC1) is both more effective and independent of IL-2R α expression. While DC1-expressed IL-15R α promotes the expansion of tetramer-specific CD8⁺ T cells, their secreted levels of IL-12p70 determines the degree of CD8⁺ T cell functionality as evidenced by tumor antigen-specific release of IFN γ and TNF α . In accordance with the *in vivo* advantage of utilizing an IL-2-independent pathway of costimulation of tumor-specific T cells, in a retrospectively analyzed cohort of patients with metastatic malignant melanoma treated with cyclophosphamide and tumor-antigen transfected DCs (NCT00978913) we observed a highly significant inverse relation between overall survival and expression of IL-2R α on DC vaccine products ($p = 0.009$). The differential usage of IL-2R α /IL-2 versus IL-15R α /IL-15 pathways by subsets of DCs helps to explain the role of different types of inflammation in memory formation, exhaustion of CD8⁺ T cell responses and progression of cancer. Furthermore, *ex vivo* induction of IL-15R α /IL-15 dependent

signaling might improve adoptive T cell therapies targeting tumors with well-defined and undefined tumor rejection antigens.

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