Role of Notch Signaling in anti-Tumor-Associated Antigen T Cell Activation with Artificial Antigen Presenting Cells

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Adoptive cell transfer of ex vivo-expanded tumor infiltrating lymphocytes (TILs) is currently an effective tool in the treatment of metastatic melanoma. While promising, it is not a widely applicable immunotherapy due to limitations in proliferative potential and access to TILs and endogenous antigen presenting cells (APCs) that are required for TIL expansion. Unlike patient-derived natural APCs, such as dendritic cells, "artificial" APCs (aAPCs) are a readily accessible and easily manipulated cell source that has been shown to support priming and activation of tumor-associated antigen (TAA)-specific $CD8^+$ cytotoxic T lymphocytes (CTLs). Here we addressed whether Notch signaling would influence the expansion and lead to enhanced cytotoxic function of TAA-specific CTLs obtained from human naïve peripheral blood $CD8^+$ CTLs. K562 erythroleukemia-derived cells (aAPCs) expressing costimulatory ligands and presenting a TAA peptide (Mart-1) were modified to express Delta-like-4 (DLL4), a member of the family of ligands for Notch receptors. We hypothesize that provision of Notch signaling during priming and early activation will generate an increased pool of Mart-1- specific CTLs with enhanced effector function. Our preliminary results using $DLL4^+$ aAPCs point to an important role for adopting Notch-driven CTL expansion strategies, and earlier polyclonal stimulations suggest the effect of DLL4 may manifest at the effector cell stage. Others have shown that provision of DLL4 to mouse $CD4^+$ T lymphocytes during priming generates lymphocytes with greater anti-tumor activity, thus induction of this phenomenon in lymphocytes capable of inducing direct lysis of tumor cells, such as CTLs, is an attractive therapeutic avenue. An important goal of our work is to address the current practical limitations in cancer immunotherapy and generate a translatable strategy to render all patients eligible for immunotherapy.