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Dendritic Cells Induce Memory-Like Characteristics in Activated Natural Killer Cells

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Natural killer (NK) cells are innate lymphocytes that defend host cells against pathogens and malignancies through their robust cytokine production and cytotoxic properties. One method of enhancing anti-tumor functionality is through the generation of cytokine-induced memory-like NK cells, a promising therapeutic approach for the treatment of hematologic cancers through adoptive cellular transfer. Memory-like character in NK cells has been thoroughly documented upon the pre-activation of naïve NK cells with exogenous cytokines (IL-12, IL-15, IL-18), but further investigation into mechanisms underlying NK cell biology and memory-like modulation is required, especially in the physiologic context. Dendritic cells are innate effector cells and antigen-presenting cells that produce abundant cytokines, including IL-12/15/18 and have been implicated in the physiologic mechanism of NK cell activation. To study the effects of dendritic cell stimulation and cytokine production on memory-like NK cell differentiation, dendritic cells were first generated *in vitro* from peripheral blood mononuclear cells and matured in the presence of CD-40 ligand expressing leukemia cells and cytokines. Mature dendritic cells were irradiated and subsequently co-cultured with naïve, autologous NK cells in a brief 'pre-activation,' which was followed by a cytokine-washout and seven-days rest *in vitro* permitting NK cells to return to their basal state. It was found that upon subsequent re-stimulation with tumor targets or cytokines, dendritic cell-activated NK cells showed enhanced IFN-g responses as compared to control NK cells. These findings suggest that NK cells previously stimulated by dendritic cells express similar characteristics to memory-like NK cells generated by incubation with purified cytokines alone, thus exhibiting superior anti-tumor effects over control NK cells when measured by flow cytometry. Future work aims to use cytokine-blocking assays and *in vivo* models to further elucidate the role of dendritic cells and pro-inflammatory cytokines in physiologically inducing memory-like NK cell functionality.