NK and CD8⁺ T Cells Regulate Dendritic Cell Functions: DCs as Carriers of Signal 3 and Signal 4 for Tumor-specific T cells

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Professor Pawel Kalinski is a graduate of the University of Warsaw School of Medicine (AMW; MD 1990) and of the University of Amsterdam (UvA; PhD: 1998). He is the Director of Research of the Division of Surgical Oncology, University of Pittsburgh Cancer Institute (UPCI), and an Associate Professor in the Departments of Surgery, Immunology, and Infectious Diseases & Microbiology at the University of Pittsburgh. The research of Prof Kalinski’s group focuses on: 1) Development of DC-based vaccines with optimized Th1-, CTL-, and NK cell-activating properties for use as vaccines against cancer; 2) Developing the means of boosting the therapeutic efficacy of vaccination, by modifying the patterns of DC interaction with NK cells and CD8⁺ T cells in vivo; 3) Regulation of chemokine receptor expression on tumor-specific T cells and 4) the production of T cell-attracting chemokines within tumor tissues. Prof Kalinski is currently being supported by a total of 11 research grants from NCI, NIAID, and private foundations. Prof Kalinski is directing eight of them (as PI). The above grants include funding for 8 clinical trials of DC-based cancer vaccines in melanoma and colorectal cancer) developed by Prof Kalinski in collaboration with other members of the UPCI.

Abstract
NK cells and CD8⁺ T cells, traditionally considered as immune effector cells, can also play regulatory functions, either suppressing or enhancing the immunogenic properties of dendritic cells (DC). These opposed functions are performed at different stages of activation of NK- and CD8⁺ T cells and involve different molecular mechanisms, allowing us to selectively suppress or enhance them for therapeutic purposes. The “effector” pathway of activation of NK cells and the effector stage of CD8⁺ T cell activation are associated with the perforin- and granzyme B-mediated elimination of DCs. In contrast, IL-18-induced “helper” NK cells and memory-type CD8⁺ T cells, that both release TNFα and IFNγ-prior to acquisition of cytotoxic function, protect DCs from CTL-mediated killing and induce mature type-1 polarized DCs (DC-1) characterized by strongly-enhanced, rather than “exhausted”, ability to produce IL-12p70 and other CTL-, Th1-, and NK cell-activating cytokines. A single round of in vitro sensitization with DC-1s loaded with tumor-related antigens induces 40-70-fold higher numbers of functional CTLs against different types of tumors, when compared with nonpolarized mature DCs. Such polarized DC-1s are particularly effective in inducing tumoricidal activity of CD8⁺ T cells and NK cells and Th1 differentiation of CD4⁺ Th cells (delivery of “signal 3”). They also induce tumor-relevant homing properties of the immune cells (delivery of “signal 4”). DC1s generated ex-vivo (DC-based vaccines) or in vivo (by promoting DC interaction with memory-type virus-specific CD8⁺ T cells), have proven effective in multiple mouse tumor models, and show early promise in our ongoing phase I/I clinical trials. Modulation of helper and suppressive activities of NK- and CD8⁺ T cells is also a potential target for immunotherapy of chronic infections and autoimmune diseases.