Dendritic cells in cancer immunotherapy

Akademisk avhandling

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av Karin Gustafsson

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Avhandlingen baseras på följande arbeten:

I. Recruitment and activation of natural killer cells *in vitro* by a human dendritic cell vaccine
Gustafsson K, Ingelsten M, Bergqvist L, Nyström J, Andersson A and Karlsson-Parra A.
Cancer Research, 2008. 68(14):5965-71.

II. Tumor-loaded α-type 1-polarized dendritic cells from patients with chronic lymphocytic leukemia produce a superior NK, NKT and $CD8^+$ T cell attracting chemokine profile
Gustafsson K, Junevik K, Werlenius O, Holmgren S, Karlsson-Parra A and Andersson P,O.
Submitted

III. Allogeneic αDC1s induce recruitment of monocytes from chronic lymphocytic leukemia patients *in vitro* and enhance their phenotypical and functional differentiation towards Th1-deviating DCs
Gustafsson K, Junevik K, Werlenius O, Holmgren S, Kovacka J, Andersson P,O and Karlsson-Parra A.
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Dendritic cells in cancer immunotherapy

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Abstract

Dendritic cells (DCs) play a central role in the initiation and regulation of innate and adaptive immune responses and have increasingly been applied as vaccines for cancer patients. *Ex vivo* generation and antigen loading of monocyte-derived DCs allows a controlled maturation, with the aim of imprinting different DC functions that are essential for their subsequent induction of a T cell-mediated anti-tumor response. A better understanding of how DCs control T cell immunity is important for the design of novel DC-based cancer vaccines with improved clinical efficiency. The aim of this thesis was to evaluate how different maturation conditions used for generation of clinical grade DC-based cancer vaccines affect their capacity to assist type-1 polarized immune responses, important for elimination of cancer.

Monocyte-derived DCs from healthy blood donors and chronic lymphocytic leukemia (CLL) patients were matured using two different types of cocktails; the "standard" maturation cocktail for human DC-based cancer vaccines consisting of TNF-α, IL-1β, IL-6 and PGE_2 (PGE_2DCs) and the more recently established α-type 1-polarized DC cocktail consisting of TNF-α, IL-1β, IFN-γ, IFN-α, and p-I:C (αDC1s).

Recent data from mouse models indicate that the ability of vaccine DCs to induce a desirable type 1-polarized immune response is strongly dependent on their ability to induce a CXCR3-dependent recruitment of IFN-γ-producing natural killer (NK) cells into vaccine-draining lymph nodes. We found that αDC1s from healthy blood donors secrete substantial amounts of the CXCR3 ligands (CXCL9/CXCL10/CXCL11). In contrast, no measurable production of these chemokines was found in PGE_2DCs. Functional studies revealed that supernatants from mature αDC1s recruited NK cells and further, αDC1s induced IFN-γ production in autologous NK cells, but only if concurrent CD40 ligation was provided.

Despite previous reports of dysfunctional DCs in CLL patients, we found that αDC1s generated from CLL patients also produced substantial amounts of CXCR3-ligands in a sustained fashion. Functional studies demonstrated that αDC1s from CLL patients were superior recruiters of NK cells and potential CD40 ligand-expressing NKT cells compared to PGE_2DCs. Importantly, loading of αDC1s with necrotic CLL cells had no negative impact on chemokine production.

It has most recently been shown that autologous DC vaccines indirectly prime naïve T cells *in vivo* by acting as immune adjuvant that transfer antigens to recruited endogenous DC-precursors. In our final study we investigated the ability of allogeneic (foreign) DCs to recruit and differentiate "bystander" monocytes into functional DC-like cells *in vitro*. We found that allogeneic αDC1s efficiently recruited monocytes and Th1-associated lymphocytes from CLL patients. Finally, monocytes primed in such αDC1 but not PGE_2DC-induced environment seem to undergo maturation toward Th1-deviating DCs.

In conclusion, this thesis supports the therapeutic use of αDC1-based vaccines in the traditional autologous setting and further indicates that allogeneic αDC1s could be used as a source of adjuvant and a vehicle for tumor antigen delivery to evoke Th1-polarized immune responses against human cancers.

Keywords: αDC1, PGE_2DC, dendritic cells, natural killer cells, T cells, CLL, vaccines
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