Cancer Cell International

CANCER CELL INTERNATIONAL

BioMed Central

Poster presentation

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Biological characterization of CD40-activated B cells as a prerequisite for their use as cellular adjuvant in cancer vaccines

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from Association for Immunotherapy of Cancer: Cancer Immunotherapy – 2nd Annual Meeting
Mainz, Germany, 6–7 May 2004

Published: 1 July 2004

Received: 28 April 2004

Cancer Cell International 2004, **4**(Suppl 1):S49

This article is available from: http://www.cancerci.com/content/4/S1/S49

Cellular immunotherapy is a promising approach to specific treatment of cancer. Dendritic cells (DC) are the best-studied antigen presenting cells (APC) and have been tested in multiple clinical trials over the last years. To extend this strategy to clinical situations in which DC therapy might be more challenging, e.g. pediatric patients or to approaches with frequent vaccinations, we have established CD40-activated B cells (CD40-B cells) as a complementary autologous APC, due to the simple generation of large amounts of highly efficient CD40-B cells from small amounts of peripheral blood. Similar to the pharmaceutical development of DC to become a standardizable adjuvant, several important biological aspects need to be addressed for CD40-B cells prior to "product development" according to GMP conditions.

We have identified efficient presentation of antigen in the context of MHC class I and MHC class II as well as homing capabilities to secondary lymphoid organs as essential biological criteria for this cellular adjuvant to merit further development. Recently, we showed that antigen-loaded CD40-B cells expand memory and induce primary $CD8^+$ T cell responses in healthy donors and cancer patients alike.

Here we address, whether CD40-B do process antigens in the context of MHC class II and induce secondary as well as primary $CD4^+$ T-cell responses: We developed a T-cell expansion system that uses CD40-B cells as sole APC to induce antigen-specific responses of purified $CD4^+$ T-cells: 1) tetanus toxoid (TT) and keyhole limpet hemocyanin (KLH), were used as a model for whole protein antigens, 2) the artificial promiscuous MHC class II binding peptides PADRE-AKF and PADRE-AKX served as model peptide-neoantigens. After 2 to 5 rounds of stimulation with antigen-loaded CD40-B cells ELISPOT technology was used to determine the presence of antigen specific $CD4^+$ T-cells. While specific cells were successfully expanded for all antigens studied, INF-γ and IL-4 cytokine secretion profiles did not indicate a dominant polarization towards TH_1 or TH_2 lineage.

Similarly important, we addressed, if CD40-B cells have the potential to home to lymph nodes and induce T-cell chemotaxis: CD40-B lack receptors important for relocating to peripheral tissue but do express CD62L, LFA-1, CCR7 and CXCR4, receptors implied in homing to secondary lymphoid organs. Migration experiments using their cognate ligands CXCL12, CCL19 and CCL21 demonstrated that these receptors are fully functional and mediate migration of CD40-B cells. Furthermore, CD40-B cells express several important T-cell attractants including IP-10, Rantes, MCP-1 and ENA-78. Correspondingly supernatant from CD40-B cultures induces strong chemotaxis of $CD4^+$ and $CD8^+$ T-cells.

Taken together, CD40-B cells efficiently induce primary MHC class I and II restricted T-cell responses and have

potential to home to secondary lymphoid organs. Based on these findings pre-clinical models have been developed to assess the *in vivo* capacity of these cells to efficiently migrate to T cell rich areas of secondary lymphoid organs and to induce efficient T cell activation.