Cancer Cell International

Poster presentation

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Chimeric carrier proteins for targeted delivery of tumor antigens to professional antigen presenting cells

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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):S36

This article is available from: http://www.cancerci.com/content/4/S1/S36

Tumor-specific T lymphocytes can be regarded as a highly effective mechanism for tumor rejection. A substantial number of T-cell defined tumor antigens including mutated oncoproteins and differentiation antigens have been identified. However, while most spontaneous tumors appear to be antigenic, few are immunogenic. Activation of tumor-specific cytotoxic T cells (CTL) requires presentation of tumor antigens by professional antigen presenting cells (APCs) via MHC I molecules. Due to their crucial role in T-cell activation, APCs are being exploited for active cancer immunotherapy. Present experimental strategies include the incubation of dendritic cells with synthetic, tumor specific peptides to achieve uptake of tumor antigens and presentation in the context of MHC molecules. Alternatively, gene therapeutic approaches are aimed at the endogenous expression of tumor antigens in APCs upon transfer of suitable vector constructs.

Our strategy for the presentation of tumor antigens by APCs is based on the intracellular delivery of tumor antigens as part of a fusion protein specifically targeted to APC cell surface receptors. We have constructed prototype molecules that contain a soluble fragment of CTLA-4 for cell binding via interaction with B7 molecules, genetically fused to a protein fragment derived from the tumor-associated antigen ErbB2. To improve uptake and direct the antigenic determinant preferentially to the MHC class I pathway, in one of these protein vaccines also the translocation domain of the bacterial *Pseudomonas* exotoxin A has been included. In the parental toxin this protein domain facilitates escape from the endosomal compartment to the cytosol upon receptor mediated endocytosis.

Here we have investigated the *in vitro* cell binding activity of such reagents and their antitumoral activity in immunocompetent murine model systems. Specific binding to B7 molecules and uptake of bacterially expressed protein vaccines could be demonstrated. *Ex vivo* restimulation with an ErbB2-derived peptide of splenocytes from Balb/c mice injected with the fusion proteins resulted in enhanced IFN-γ production by T cells. Protective and therapeutic effects of ErbB2 protein vaccines were also investigated. Vaccinated animals were protected against subsequent challenge with syngeneic ErbB2 expressing tumor cells. Likewise, s.c. injection of ErbB2 protein vaccines in the vicinity of established tumors resulted in tumor rejection and long lasting protection indicating that immunological memory was induced.

Our results suggest that chimeric proteins combining a tumor antigen and specific recognition of APCs in a single molecule are suitable for targeted delivery of antigens to professional APCs and might become valuable tools for cancer immunotherapy.