Cancer Cell International

Poster presentation

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Identification of a novel epitope derived from the cancer-germline antigen, HAGE, displaying both in-vitro and in-vivo immunogenicity

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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):S50

This article is available from: http://www.cancerci.com/content/4/S1/S50

It is now well established that both CD4+ and CD8+ tumour-specific T-lymphocytes play critical roles in anti-tumour immunity; thus there is a desirability to identify both MHC class I and II-restricted tumour antigens that induce immunogenic responses in both in-vitro models and more significantly in an in-vivo environment. Many current tumour antigens that are potential targets fall into the category of cancer-germline (CG) antigens, and are considered to represent good candidate antigens for tumour immunotherapy based on their lack of expression on normal somatic tissues. HAGE is a novel CG gene expressed in a wide range of solid tumour tissue (eg. around 20% of melanomas, one-third of lung cancers) but also in haematological malignancies (in >50% and >20% of chronic and acute myeloid leukaemias, respectively). Here we describe the use of a combination of computer algorithms to identify potentially immunogenic peptides from the HAGE protein based on both predicted HLA affinity and proteosomal cleavage sites. An HLA-A2-binding motif contained within a longer HLA-DR-binding sequence was identified. Two peptides representing either the class I motif alone, or a longer peptide containing the class I motif within the class II motif, were then screened in in-vitro T cell sensitisation experiments using PBMC or monocyte-derived dendritic cells from healthy donors or CML patients; the class I peptide was also used in-vivo to vaccinate HLA-A2-transfected mice. We demonstrate that both these peptides are immunogenic in-vitro not only for T cells from healthy donors, but also from CML patients, as assessed by functional assays such as cytokine secretion and cytotoxicity. Moreover, immunogenicity was confirmed by using MHC/peptide tetramers to show specific expansion of sensitised T-cells. Furthermore, the class I peptide also demonstrates immuno-genicity in-vivo following vaccination of HLA-A2-transfected mice. Spleen cells isolated from these mice showed specific cytotoxicity ex-vivo. We conclude that the HLA-DR-binding peptide and the HLA-A2 motif contained therein may represent potential vaccines for the immunotherapeutic treatment of cancer, particularly CML, targeting the HAGE expression of a high proportion of tumours.