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Enrichment of functional CD8 memory T cells specific for MUC1 in Bone Marrow of Multiple Myeloma Patients

M Witzens*[1], C Choi[2], M Bucur[2], M Feuerer[3], N Sommerfeldt[2], A Trojan[4], A Ho[1], V Schirrmacher[2], H Goldschmidt[1] and P Beckhove[2]

Address: [1]Department of Hematology and Oncology, The University Hospital Heidelberg, Germany, [2]Tumor Immunology Program, The German Cancer Research Center, Heidelberg, Germany, [3]Department of Experimental Rheumatology, Medical Clinic, Charité, Humboldt University, Berlin, Germany and [4]Department of Oncology, University Hospital Zurich, Switzerland

Email: M Witzens* - mathias_witzens@med.uni-heidelberg.de

* Corresponding author

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Objective

Recently, the bone marrow was shown to be a site were T cells are primed against blood borne antigens and tumor associated antigens. The common tumor-associated antigen (TAA) MUC1 has been shown to be expressed on about 90% of malignant plasma cells in multiple myeloma (MM). This study was performed to investigate the content and reactivity of MUC-1 specific memory T cells in BM compared to PB from MM patients with respect to possible use in immunotherapeutic strategies.

Methods

Paired BM and PB samples from 42 HLA-A2 pos. MM patients and 11 HLA-A2 pos. normal donors were tested for frequency of TAA-specific CD8 T cells by HLA-A2 tetramer-analysis using MUC1 derived peptide LLLTVLTV (12–20) as TAA or for frequency of tumor-reactive CD8 memory T cells in 40 h short term IFNy ELISPOT assay. Antigen specific cytotoxic potential of 6 patients T cells was evaluated by Chr^{51} chromium release assay following single restimulation with MUC1 peptide pulsed DCs. Presence of MUC1 expressing cells and CD8 T cells in BM biopsies from MM patients was detected by immunohistochemistry.

Results

The frequencies of MUC1-specific CD8 T cells in PB and BM of 42 tested patients varied between 0–6.4% of CD8 T cells. In contrast, PB and BM of 11 normal donors contained only 0–0.25% tetramer binding CD8 T cells. Enrichment of MUC1 specific CD8 T cells (> 0.3% of CD8 T cells) was found in PB and BM from 16 out of 30 patients (53%).

Using short term IFNγ ELISPOT functional-assay we detected enrichment of MUC1-reacticve CD8 memory T cells in BM from 6 out of 12 patients (50%). In contrast, in corresponding PB, MUC1-reactive T cells were detected in only 1 out of 9 patients (11%). The frequencies of MUC1-reactive CD8 memory T cells varied between 1:390–1:3350 (BM) and 1:3340 (PB). BMTCs from MM patients were able to kill MUC1-peptide loaded Target cells in a dose dependent manner in contrast to corresponding PB T cells from the same patients. CD8 T cells were co-localized together with MUC1 expressing cells in the BM of MM patients.

Conclusions

MUC1 specific T cells are highly enriched in PB and BM of about 50% of MM patients indicating induction and maintainance of tumor cell directed immune responses during the course of disease. We detected high amounts of MUC1-derived peptide specific CD8 memory T cells capable of IFNγ secretion and cytotoxicity upon appropriate restimulation in BM but not PB of MM patients. Thus, autologous BM-derived memory T cells reactivated *in vitro* with MUC1 pulsed dendritic cells might be useful for future immunotherapy of MM.