P65. Minor-histocompatibility-antigen UTY as target for graft-versus-leukaemia and graft-versus-haematopoiesis in the canine-model

D Bund1, FG Gökmen1, J Zorn2, R Buhmann1, HJ Kolb1, H Schmetzer1

From 1st Immunotherapy of Cancer Conference (ITOC1)
Munich, Germany. 12-14 March 2014

Background
In haploidentical-SCT male-patients with female-donors have better prognosis compared to female-to-male-combinations due to Y-encoded minor-histocompatibility-antigens recognised by female-allo-immune effector-lymphocytes in the context of a graft-versus-leukaemia-(GvL)-effect. We provide data in a dog-model that the minor-histocompatibility-antigen UTY might be a promising target to further improve GvL-immune-reactions after allogeneic-SCT.

Materials and methods
Canine (c) purebred-beagle-dogs' PB and BM were studied. T2-cells (HLA-A2+, T AP-deficient) were used. These human-(h)-UTY-sequence-derived HLA-A2-binding-peptides were investigated: W248 (WMHHNMDLV), T368 (TLAARIKFL), K1234 (KLFEMIKYC). In vitro: Autologous-cDCs were generated with best of three DC-methods (Calcium-Ionophore, Picibanil, Cytokines). Generation cUTY-specific-CTLs: CD3+ T-cells were co-cultured with autologous-mature cDCs+hUTY-peptides (weekly restimulation for 21 days; +hIL-2, +hIL-7). Cytoxicity and antigen-specificity were determined in 3/6 female-dogs. CTLs specifically recognised/lysed autologous-female peptide-loaded-DCs (900 spots/100,000 T-cells (median)/≤47.9%), but not naive autologous-female-DCs and -monocytes (p≤0.026). They mainly recognized BM and to a lower extent DCs, monocytes, PBMCs and B-cells from DLA-identical-male-littermates and peptide-loaded T2-cells in an MHC-I-restricted manner (up to p≤0.046). UTY-mRNA was only expressed in male-cells. A UTY-/male-specific-reactivity was also obtained in vivo after stimulation of a female-dog with DLA-identical-male-PBMCs.

Results
Female cUTY-specific-CTLs were stimulated in vitro using autologous-DCs loaded with three HLA-A2-restricted UTY-derived-peptides (≤2.9-fold-expansion) and specific T-cell-responses were determined in 3/6 female-dogs. CTLs specifically recognised/lysed autologous-female peptide-loaded-DCs (900 spots/100,000 T-cells (median)/≤47.9%), but not naive autologous-female-DCs and -monocytes (p≤0.026). They mainly recognized BM and to a lower extent DCs, monocytes, PBMCs and B-cells from DLA-identical-male-littermates and peptide-loaded T2-cells in an MHC-I-restricted manner (up to p≤0.046). UTY-mRNA was only expressed in male-cells. A UTY-/male-specific-reactivity was also obtained in vivo after stimulation of a female-dog with DLA-identical-male-PBMCs.

Conclusions
We demonstrated natural UTY-processing/presentation in dogs. Female-dog-CTLs were specifically stimulated by HLA-A2-restricted UTY-peptides, thereby enabling recognition of DLA-identical-male-cells, mainly BM-cells. These observations suggest UTY as a promising candidate-antigen to improve GvL-reactions in the course of immunotherapy. Next-generation-sequencing and specialised-bioinformatics-algorithms are now focus for human-individualised-leukaemia-treatment (T-cell-receptor-Profiling, detection/selection of T-cell-receptor-clones or DC-based-immunotherapies).

Authors' details
1University of Munich-Grosshadern, Haematopoietic Cell Transplantation MED III, Munich, Germany. 2Helmholtz Center Munich, CCG Haematopoietic Cell Transplantation, Munich, Germany.

© 2014 Bund et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
http://www.immunotherapyofcancer.org/content/2/S2/P39

Published: 12 March 2014


Submit your next manuscript to BioMed Central and take full advantage of:

• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit