

Myeloma-Induced Alloreactive T Cells Arising in Myeloma-Infiltrated Bones Include Double-Positive CD8(+)CD4(+) T Cells: Evidence from Myeloma-Bearing Mouse Model

Laurence Catley, Derek N. J. Hart and Slavica Vuckovic Khalil, Nigel Waterhouse, Frank Vari, Alison M. Rice, Andreas Evdokiou, John Luff, Pooi-Fong Wong, Dalia Ali Salajegheh, Peter Diamond, Andrew Zannettino, Lisa M. Freeman, Alfred Lam, Eugene Petcu, Robert Smith,

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Abstract:

The graft-versus-myeloma (GVM) effect represents a powerful form of immune attack exerted by alloreactive T cells against multiple myeloma cells, which leads to clinical responses in multiple myeloma transplant recipients. Whether myeloma cells are themselves able to induce alloreactive T cells capable of the GVM effect is not defined. Using adoptive transfer of T naive cells into myeloma-bearing mice (established by transplantation of human RPMI8226-TGL myeloma cells into CD122(+) cell-depleted NOD/SCID hosts), we found that myeloma cells induced alloreactive T cells that suppressed myeloma growth and prolonged survival of T cell recipients. Myeloma-induced alloreactive T cells arising in the myeloma-infiltrated bones exerted cytotoxic activity against resident myeloma cells, but limited activity against control myeloma cells obtained from myeloma-bearing mice that did not receive T naive cells. These myeloma-induced alloreactive T cells were derived through multiple CD8(+) T cell divisions and enriched in double-positive (DP) T cells coexpressing the CD8 alpha and CD4 coreceptors. MHC class I expression on myeloma cells and contact with T cells were required for CD8(+) T cell divisions and DP-T cell development. DP-T cells present in myeloma-infiltrated bones contained a higher proportion of cells expressing cytotoxic mediators IFN-gamma and/or perforin compared with single-positive CD8(+) T cells, acquired the capacity to degranulate as measured by CD107 expression, and contributed to an elevated perforin level seen in the myeloma-infiltrated bones. These observations suggest that myeloma-induced alloreactive T cells arising in myeloma-infiltrated bones are enriched with DP-T cells equipped with cytotoxic effector functions that are likely to be involved in the GVM effect. *The Journal of Immunology*, 2011, 187: 3987-3996.

Keywords:

Graft-versus-Myeloma (GVM), alloreactive T cells, myeloma-bearing mice, T naive cells

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