immunosuppressive therapy (n = 7), donor unavailable (n = 8), early relapse (n = 2), or other (n = 2). Hematologic relapse was 16% in MRD+ patients, 6% in MRD+DLI+ patients, and 63% in MRD+DLI+ patients (P < .001; Figure 1); the actuarial 3-year survival in these 3 groups was 78%, 80%, and 26%, respectively (P = .001; Figure 1). Mortality due to acute GVHD following DLI was 12%. In multivariate Cox analysis, the MRD group predicted relapse (P < .001) and survival (P = .01), together with disease phase and chronic GVHD. In MRD+ patients, DLI protected against relapse (P = .003) and improved survival (P = .01).

In conclusion, we confirm that MRD detected after transplantation is a significant predictor of relapse. Treatment of MRD with DLI is appears to protect against leukemia relapse, although caution with DLI dosing needs to be used because of the potential risk of GVHD.

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The influence of KIRs in the proliferation of a control CD4+CD158b+ T-cell line and P1 cells was evaluated. On control T cells, CD158b engagement led to a dramatic inhibition of their CD3-induced proliferation. In contrast, coligation of CD3 and CD158a or CD158b on the P1 cell line or on PBMCs resulted in an increased proliferation when compared with CD3 triggering alone (Figure 1C).

Further expression analysis demonstrated that both CD158a and CD158b were expressed under their inhibitory (KIR-L) and activating (KIR-S) isoforms in P1 cells, while only CD158b KIR-S was found on normal CD4+CD158b+ T cells, and consequently interacted with SHP-1. In contrast, no tyrosine-phosphorylated CD158a or CD158b, nor coprecipitated SHP-1, were detected with DLI dosing needs to be used because of the potential risk of GVHD.

To the editor:

Killer cell Ig-like receptors CD158a and CD158b display a coactivatory function, involving the c-Jun NH2-terminal protein kinase signaling pathway, when expressed on malignant CD4+ T cells from a patient with Sézary syndrome

Sézary syndrome (SS) is an aggressive leukemic and erythrodermic variant of cutaneous T-cell lymphomas characterized by the presence of a clonal T-lymphocyte population in the skin, lymph nodes, and peripheral blood.1 We recently identified KIR3DL2/CD158b as the first cell-specific marker for the evaluation of the circulating tumoral burden and for the follow-up of patients with SS.2,4 We next investigated the expression of additional killer cell Ig-like receptors (KIRs) on the peripheral blood mononuclear cells (PBMCs) of patients with SS and detected the simultaneous expression of CD158a and CD158b on all malignant cells from a unique patient (P1; Figure 1A, left panel).

To study the relevance of CD158a and CD158b expression by P1 malignant cells, a long-term cell line was generated. The identity of the in vitro-derived clone with the circulating tumoral clone was assessed by characterizing the CDR3-size Vβ distribution and the T-cell receptor (TCR) Vβ/Jβ junction (Figure 1B). Cell immunolabeling indicated that the derived T-cell line corresponded to the major TCR-Vβ8+CD158k+ circulating clone, and similarly expressed CD158a and CD158b (Figure 1A, right panel).

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References


11. van Dongen JJ, Macintyre EA, Gabert JA, et al. Standardized RT-PCR analysis of fusion gene transcripts from chromosome aberrations in acute leukaemia for detection of minimal reCorrespondence: Andrea Bacigalupo, Divisione Ematologia 2, Ospedale San Martino, Largo Rosanna Benzi 10, 16132 Genova, Italy; e-mail: andrea.bacigalupo@hsanmartino.it.

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signaling was apparently generated following CD158a or CD158b triggering of P1 cells.

Stimulatory receptors usually interact with adaptor molecules to promote the downstream recruitment of Syk family protein tyrosine kinases. However, expression of the regular adaptor proteins DAP10 and DAP12 was undetectable in P1 cells, and no ζ was found associated with CD158a or CD158b in activated Sézary cells (not shown). In CD4+ T cells, CD158j/KIR2DS2 was identified as a costimulatory molecule using the DAP12-independent JNK pathway. We observed that CD158a- or CD158b-mediated stimulation of P1 cells resulted in phosphorylation of MKK4 and JNK, and to a lesser extent, of c-Jun and ATF2 (Figure 1E). In addition, while a suboptimal CD3 activation of the cells did not lead to protein phosphorylation, the coengagement of CD158a or CD158b resulted in the detection, for all proteins tested, of phosphorylation levels equivalent to that reached upon optimal CD3-mediated activation (Figure 1E).

In conclusion, we showed that CD158a and CD158b could act as costimulatory receptors on Sézary cells through the recruitment of the DAP12-independent JNK pathway. The delivery of costimulatory signals through both KIRs, specific for all HLA-C alleles, might therefore contribute to Sézary cell clonal outgrowth in vivo.

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A.M.-C. and D.H. contributed equally to this work.

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References
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