in HSCs and CMPs. A rise in *BCR-ABL* levels in GMP populations signified impending relapse. Post-SCT patients harbored more residual CML cells in CD34+ subpopulations than TKI-treated patients. Our findings suggest that in patients with persistent MRD-positivity post-SCT, the graft-versus-leukemia (GVL) effect may eliminate mature leukemic CD34+ subpopulations in vivo more readily. Primitive leukemic HSCs and CMPs, although persistent, are presumably constrained by GVL in patients who do not fulfill criteria for relapse. Conversely, TKI reduces the number of *BCR-ABL*-positive GMPs and CMPs more efficiently. Our data support adjuvant TKI-treatment for CML relapse post-SCT, and concurrent vaccination strategies which can target surface proteins on HSCs to eradicate CML.

HEMATOPOIESIS/MESENCHYMAL CELLS

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TIE2 + BONE MARROW ENDOTHELIAL CELLS REGULATE HEMATOPOIETIC RECONSTITUTION IN VIVO

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Radiation and chemotherapy cause myelosuppression in patients via damage to bone marrow (BM) hematopoietic stem/progenitor cells (HSCs). HSCs reside adjacent to BM sinusoidal vessels but the function of BM endothelial cells (BM ECs) in regulating HSC fate in vivo remains less well understood. We hypothesized that BM ECs are critical in regulating BM hematopoietic reconstitution following radiation stress. To test this hypothesis, we used Cre-LoxP recombination to create targeted deletion of the pro-apoptotic genes, Bak and Bax, in Tie2 + BM ECs (Tie2Cre;Bak-/-;BaxFl/- mice) and measured hematopoietic response to total body irradiation (TBI). Tie2Cre;Bak-/-;BaxFl/- mice were compared with Tie2Cre; Bak-/-; BaxFl/+ mice which have constitutive Bak deletion but retain Bax in Tie2 + BM ECs. After exposure to 100 cGy TBI, Tie2Cre; Bak-/-;BaxFl/- mice displayed a 2-fold increase in total viable BM cells ($p = 0.04$), 4-fold increase in BM ckit+sca+lineage- (KSL) progenitor cells ($p < 0.0001$), 3-fold increase in colony-forming unit-spleen day 12 content ($p = 0.0003$) and a 2-fold increase in 12-week competitive repopulating units (CRUs) ($p = 0.002$) compared to Tie2Cre;Bak-/-;BaxFl/+ mice. Comparable radioprotection was observed after 300 cGy TBI. Since Tie2 is expressed by BM ECs and a subset of BM HSCs, we wanted to determine whether the radioprotection we observed in Tie2Cre;Bak-/-;BaxFl/- mice was caused autonomously by protection of Tie2 + BM ECs or Tie2 + HSCs. We transplanted 4×10^6 BM cells from Tie2Cre; Bak-/-;BaxFl/- mice into lethally irradiated (950 cGy) wild type B6.SJL mice such that the recipient mice were chimeric for Bak and Bax deletions only in hematopoietic cells while retaining a wild type BM microenvironment, verified by qRTPCR. At 16 weeks post-transplant, the chimeric recipient mice were then exposed to 100 and 300 cGy TBI and we compared the hematopoietic response of these mice to that of Tie2Cre;Bak-/-;BaxFl/- mice. After 100 cGy TBI, the hematopoietic response of the chimeric mice revealed a significant reduction in total viable BM cells (1.3-fold), BM KSL cells (7.4-fold) and 12-wk CRU weeks (1.6-fold, $p = 0.008$) compared to 100 cGy-irradiated Tie2creBak-/-;BaxFl/- mice. These results demonstrate that Tie2 + BM ECs positively regulate hematopoietic reconstitution following injury and indicate that BM ECs are a novel mechanistic target for therapies to augment hematopoietic recovery in patients undergoing radiation and/or chemotherapy.

HISTOCOMPATIBILITY/ALTERNATIVE STEM CELL SOURCES

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PATIENT ETHNICITY MARKEDLY AFFECTS THE PROBABILITY OF FINDING AN HLA-A, -B, -C, AND DRB1 ALLELE MATCHED UNRELATED DONOR FOR HEMOPOIETIC CELL TRANSPLANTATION

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The adult unrelated volunteer registries include more then 14 million donors worldwide; however, the required precision of patient and donor matching for high resolution HLA determinants, and the ethnic variation of the patient population put a yet unknown constraint to the probability of finding a suitable donor. We evaluated the results of unrelated searches for 398 consecutive patients. Patients and donors were typed by HLA sequencing. Searches were assisted by NMDP histocompatibility specialists for patients to identify an HLA-A, B, C, DRB1 match (8/8) or a partial match (7/8). HLA-DQB1 was considered in the search, but was not evaluated in this analysis. For the purpose of this study, the search was completed when confirmatory typing on a freshly drawn donor sample identified the first suitable donor. Such a donor was found for 336 (85%) patients after a median of 20 [95% C.I. 11-59] days: this was an 8/8 match for 209 (53%) patients and a 7/8 for 127 (32%) patients, with no difference in search duration observed by matching grade. With a 7/8, the mismatch was at -A (35%), -B (26%), -C (28%), or -DRB1 (11%). The probability of finding a donor was not affected by patient age or diagnosis, but was affected by the patient ethnicity. An 8/8 match was found for 181/293 (62%) Caucasians, 22/65 (34%) Hispanics, and 6/40 (15%) African-Americans, and a 7/8 match was found for 80 (27%) Caucasians, 28 (43%) Hispanics and 19 (48%) African-Americans ($p < 0.0001$). Therefore, only 11% of Caucasians had no suitable donor compared to 23% of Hispanics and 37% of African Americans.

Consistent with overall NMDP data, among those with a suitable match, 161/336 (48%) patients reached transplantation after a median of 101 [95% C.I.; 56-258] days from the search inception. The interval from finding the first donor to transplant was a median of 81 [95% C.I.: 45-199] days, about 4-fold longer than the search itself. Reaching transplant was affected by the match grade, 107/209 (51%) for 8/8, 54/127 (43%) for 7/8, and 3/62 (5%) for those without a match ($p < 0.0001$). The low probability of reaching transplant despite a suitable donor is alarming: 40% deteriorated or died, 17% received other treatment modalities, 14% declined or failed to make a decision, 14% waited for a better match, 16% other reasons. A suitably matched unrelated donor is available for the large majority of the patients, however, Hispanic or African-American ethnicity represents a barrier to find a suitable donor.

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CAN HISTOCHECK ALGORITHM PREDICT HIGH-RISK HLA ALLELE MISMATCH COMBINATIONS RESPONSIBLE FOR SEVERE ACUTE GRAFT-VERSUS-HOST DISEASE?

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HLA polymorphism remains a major hurdle for hematopoietic stem cell transplantation (HSCT). In 2004 Elsner et al (BMT) proposed the "HistoCheck" web-based tool to estimate the allogeneic potential between HLA-mismatched stem cell recipient/donor pairs expressed as a matching score (dissimilarity score, DSS). DSS is based on the structural data of HLA molecules and the functional similarity of amino acids. A high DSS score represents high dissimilarity between MHC molecules.

Objective: We sought to investigate the potential of DSS to predict high-risk HLA allele mismatch combinations responsible for severe acute graft-versus-host disease (aGvHD grades III and IV) from data recently published by Kawase et al, Blood, 2007 by comparing DSS in low and high risk combinations.

Method: DSS were calculated for 110 HLA allele mismatch combinations observed in 3830 donor/recipient pairs using the HistoCheck tool available on the Web (WWW.histocheck.org). We compared ranges and means of DSS among high risk versus low risk allele combinations.

Results: An example of a higher risk combination is Cw*0303 (donor) – 1502 (patient) that was observed in 25 pairs with HR of 3.22 ($p < 0.001$). A lower risk combination containing the same recipient allele but a different donor option is Cw*0801 – 1502 (observed in 36 pairs) with HR of 1.59 ($p = 0.19$). DSS for these 2