

Low Socioeconomic Status, Adverse Gene Expression Profiles, and Clinical Outcomes in Hematopoietic Stem Cell Transplant Recipients

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Abstract

Purpose: Low socioeconomic status (SES) is associated with adverse outcomes among unrelated donor hematopoietic stem cell transplant (HCT) recipients, but the biologic mechanisms contributing to this health disparity are poorly understood. Therefore, we examined whether social environment affects expression of a stress-related gene expression profile known as the conserved transcriptional response to adversity (CTRA), which involves upregulation of proinflammatory genes and downregulation of genes involved in type I IFN response and antibody synthesis.

Experimental Design: We compared pretransplant leukocyte CTRA gene expression between a group of 78 high versus low SES recipients of unrelated donor HCT for acute myelogenous leukemia in first remission. *Post hoc* exploratory analyses also evaluated whether CTRA gene expression was associated with poor clinical outcomes.

Results: Peripheral blood mononuclear cells collected pre-HCT from low SES individuals demonstrated significant CTRA upregulation compared with matched HCT recipients of high SES. Promoter-based bioinformatics implicated distinct patterns of transcription factor activity, including increased CREB signaling and decreased IRF and GR signaling. High expression of the CTRA gene profile was also associated with increased relapse risk and decreased leukemia-free survival.

Conclusions: Low SES is associated with increased expression of the CTRA gene profile, and CTRA gene expression is associated with adverse HCT clinical outcomes. These findings provide a biologic framework within which to understand how social environmental conditions may influence immune function and clinical outcomes in allogeneic HCT. *Clin Cancer Res*; 22(1); 69–78. ©2015 AACR.

See related commentary by Turcotte and Verneris, p. 6

Introduction

Low socioeconomic status (SES), independent of race, has a negative impact on unrelated (1) and related (2) donor hematopoietic stem cell transplant (HCT) outcomes, including worse overall survival (OS) and higher transplant-related mortality (TRM). This effect has been demonstrated in multiple other solid tumor populations as well (3, 4). The biologic, psychosocial, and environmental mechanisms accounting for

the relationship between SES and outcomes in cancer are poorly understood. While health disparities between patients with varying SES levels are in part attributable to differences in health behaviors, biologic processes resulting in altered central nervous system and immune activation also contribute (5). There is an increasing literature linking biobehavioral factors more prevalent in those of lower SES, such as chronic stressors, depressed mood, and lower levels of social integration and support (6), to higher levels of inflammatory burden (7), potentially through physiologic stress mechanisms (8). SES is inversely related to morbidity and mortality in a variety of diseases and populations, with inflammation implicated as a key biologic pathway mediating this association (7, 9).

Adverse social conditions are associated with worse outcomes and cancer progression in several populations (10, 11), including HCT (12). However, while interactions between behavioral, neural, and immune function continue to be identified in other cancer populations (13), these pathways are just beginning to be explored among HCT recipients (14, 15). Social environmental influences on human health are well established, with previous studies indicating that circulating immune cells demonstrate a systematic shift in basal gene expression profiles during extended periods of stress, threat, or uncertainty (16–19). This shift, termed the "conserved transcriptional response to adversity" (CTRA), is characterized by increased expression of genes involved in inflammation (e.g., proinflammatory cytokines such as *IL1B*, *IL6*, *IL8*, and *TNF*) and decreased

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Translational Relevance

Low socioeconomic status (SES) accounts for a 15% to 21% difference in overall survival and transplant-related mortality among HCT recipients as compared with recipients of high SES. SES-related health disparities persist after controlling for differences in access to care and health behaviors. Lifestyle and stress associated with low SES can activate psychobiologic processes leading to altered neural, endocrine, and immune activation. Here, we identify that pretransplant gene expression profiles of allogeneic HCT recipients from lower SES backgrounds display significantly increased expression of the conserved transcriptional response to adversity (CTRA) gene expression profile. Furthermore, our *post hoc* analyses indicate that this increased CTRA expression is associated with a greater likelihood of relapse and decreased leukemia-free survival. These transcriptomic differences provide useful therapeutic biologic targets to improve outcomes in socially at-risk populations through targeted pharmacologic intervention.

expression of genes involved in type I IFN antiviral responses (e.g., *IFI-*, *OAS-*, and *MX-* family genes) and IgG antibody synthesis (e.g., *IGJ*; refs. 17, 20, 21).

There are several biologic pathways through which CTRA gene expression dynamics might influence HCT-related biology and clinical outcomes. Inflammation plays a role in acute and chronic graft-versus-host-disease (a/cGVHD; ref. 22), whose incidence has been described as increased among HCT recipients with low SES (2). Inflammation is also associated with other adverse health outcomes post-transplant, including graft rejection and failure (23), severe infection (24), and increased symptom burden (25). Type I IFN and IgG1 antibody responses are also implicated in posttransplant complications (26, 27).

Previous research demonstrates increased CTRA gene expression profiles in circulating leukocytes from low SES individuals in healthy populations (7, 16); however, it is not known how such results might apply in the complex biologic milieu of HCT. Given previous work demonstrating the impact of SES on HCT outcomes, the current study sought to determine whether biologic factors, such as CTRA expression profiles, may partially explain the relationship between SES and outcomes. Therefore, we hypothesized that CTRA gene expression profiles from pretransplant blood samples would be increased among HCT recipients of low SES. *Post hoc* exploratory analyses evaluated whether SES and CTRA profiles were associated with adverse clinical outcomes. Given the extreme immunologic perturbations HCT recipients endure, it is important to understand how preexisting social environmental factors such as SES may impact clinical outcomes.

Materials and Methods

Data sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program Office of Research (NMDP) established in 2004 that comprises a voluntary working group of more than 450

transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantation to the Coordinating Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED data include disease type, age, sex, pretransplant disease stage, and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplant disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR teams contribute TED data. More detailed disease and pre- and posttransplant clinical information were collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF level data were collected pretransplant, 100 days and 6 months after transplant, annually until year 6 after transplant, and biannually thereafter until death.

Participants

The present sample of 78 participants was selected from the population evaluated in the study by Baker and colleagues that identified SES as an independent predictor of OS and TRM among unrelated donor allogeneic transplant recipients (1). The Baker and colleagues' population included 6,207 patients with acute or chronic leukemia or myelodysplastic syndrome who underwent an unrelated donor transplant in the United States using either a bone marrow or peripheral blood stem cell (PBSC) source with a myeloablative preparative regimen between 1995 and 2004 and who also had an available residential postal zip code. Patient income was estimated by the mean household income of their residential zip code from the 2004 U.S. Census. The package "Zip Code Deluxe" (28) was used to obtain income and location data by zip code. To achieve a homogeneous population for comparison purposes in the current study as well as to control for factors that may affect inflammation, our further inclusion criteria limited eligible subjects to adults ages 20 to 59 years with a diagnosis of acute myelogenous leukemia (AML) in their first complete remission (CR1) who had an available pretransplant whole blood sample and complete data for body mass index (BMI; height and weight), comorbid conditions, sex, age, race, Karnofsky performance status (KPS), and residential distance from transplant center. Pretransplant/baseline blood samples are routinely collected and banked at the NMDP for all U.S. allogeneic transplant recipients. The relevant samples for the current study were withdrawn and immediately sent to University of California Los Angeles (UCLA, Los Angeles, CA). Subjects with preexisting comorbid autoimmune disorders were excluded to remove the potential for extreme influence

on inflammation. Finally, we restricted the cohort to those individuals from the lowest SES quartile (<\$34,700) and a comparison group of individuals from the highest SES quartile (>\$56,300; quartiles as per Baker and colleagues, 2009). Patient race was reported by transplant centers and was categorized according to the U.S. Office of Management and Budget classification as White, African American, Hispanic, or Asian/Pacific-Islander. The initial plan was to analyze racial groups separately; however, there were insufficient samples meeting the above criteria to warrant separate analysis, so the analysis is limited to whites only. This selection resulted in 100 individuals.

We then performed a matching procedure using the MatchIt R package (29) among these 100 eligible participants to ensure similar groups with respect to variables that could affect inflammation. We matched individuals from the lowest SES quartile with a comparison group of individuals from the highest SES quartile based on BMI (BMI<30 vs. BMI≥30) and age (closest within 10 years). Additional matching on other variables such as comorbid conditions, KPS, or gender was not feasible because of limited numbers. The final population available to be analyzed for gene transcription meeting the above criteria included 39 low SES and 39 high SES recipients matched for BMI group and age within 10 years. For the current sample size, the detectable fold changes in gene expression levels between patients with low and high SES were calculated on the basis of the method described by Jung and colleagues (30). We assume testing of 20,000 genes, of which approximately 200 are differentially expressed. We target 90% average sensitivity, or the expected proportion of differentially expressed genes that are identified as significant. The univariate significance level corresponding to this setting and a 5% false discovery rate is $\alpha = 0.009$. The current sample size on average will detect 90% of differentially expressed genes with fold changes of approximately 1.5 to 2 depending on the coefficients of variation. Furthermore, the current sample of 39 in each group is larger than sample sizes that have evaluated gene expression as a function of psychosocial factors and yielded hundreds of differentially expressed genes that generate statistically significant results in higher order bioinformatics (18, 31). All study procedures were approved by the Institutional review board of the Medical College of Wisconsin (Milwaukee, WI).

Transcriptome analysis

Genome-wide transcriptional profiling was performed on isolated peripheral blood mononuclear cells (PBMC) from all 78 participants in one batch. Assays were conducted as previously described (32), with PBMCs isolated by density gradient centrifugation and total RNA extracted (RNeasy, Qiagen), tested for suitable mass (Nanodrop ND1000) and integrity (Bioanalyzer; Agilent), and converted to fluorescent cRNA for hybridization to Illumina Human HT-12 v4 BeadArrays following the manufacturer's standard protocol in the University of California, Los Angeles, Neuroscience Genomics Core Laboratory. Gene expression values were quantile-normalized, \log_2 -transformed, and subject to general linear model analyses relating the expression of each assayed gene to SES (0 = high SES, 1 = low SES; results are interpretable in terms of the effects of low SES) while also controlling for age, sex, BMI, and presence of predefined coexisting medical conditions at the time of preparative regimen. Primary analyses tested an *a priori*-defined contrast score represent-

ing the 53-gene CTRA profile of upregulated expression of 19 proinflammatory genes (*IL1A*, *IL1B*, *IL6*, *IL8*, *TNF*, *PTGS1*, *PTGS2*, *FOS*, *FOSB*, *FOSL1*, *FOSL2*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *REL*, *RELA*, and *RELB*) and downregulated expression of 31 genes involved in type I IFN responses (*GBP1*, *IFI16*, *IFI27*, *IFI27L1-2*, *IFI30*, *IFI35*, *IFI44*, *IFI44L*, *IFI6*, *IFIH1*, *IFIT1-3*, *IFIT5*, *IFIT1L*, *IFITM1-3*, *IFITM4P*, *IFITM5*, *IFNB1*, *IRF2*, *IRF7-8*, *MX1-2*, *OAS1-3*, and *OASL*) and three genes involved in antibody synthesis (*IGJ*, *IGLL1*, and *IGLL3*; refs. 17, 20, 21, 33) to evaluate whether low SES might be associated with increased expression of this CTRA profile. Contrast coefficient-weighted association statistics were averaged to summarize the magnitude of association over the entire CTRA gene set, and standard errors were derived from 200 cycles of bootstrap resampled residual vectors (to account for potential correlation among residuals across genes; ref. 34).

To identify transcription control pathways that may mediate observed transcriptional differences, initial "low-level" genome-wide analyses identified all transcripts showing a model-adjusted point estimate of $\geq 20\%$ difference in expression between low-versus high-SES HCT recipients. Those putatively associated genes were subject to Transcription Element Listening System (TELiS) promoter-based bioinformatic analysis (35) to assess activity of NF κ B, AP-1, IRF, and CREB and GR family transcription factors previously linked to CTRA transcriptional dynamics (TRANSFAC V\$CREL_Q1, V\$AP1_Q4, V\$ISRE_Q1, V\$CREB_Q4, V\$GR_Q6; ref. 35), with results averaged over nine parametric variations of MatInspector scan stringency and promoter length (35). To ensure that results were not confounded by individual differences in the prevalence of specific leukocyte subtypes within the PBMC pool (36), analyses also controlled for the prevalence of transcripts marking T-lymphocyte subsets (*CD3D*, *CD3E*, *CD4*, *CD8A*), B lymphocytes (*CD19*), natural killer cells (*CD16/FCGR3A*, *CD56/NCAM1*), and monocytes (*CD14*; ref. 18). Transcript origin analysis (TOA) was applied to the low-level association data to identify the specific PBMC subtypes mediating the observed differences in gene expression, as previously described (32). Low-level transcript-phenotype associations were estimated solely as inputs into high-level TELiS and TOA gene set expression analyses and are not tested for statistical reliability at the level of individual genes.

Clinical outcome study definitions

While the aim of the primary analysis was to understand the relationship between SES and CTRA gene expression, exploratory secondary analyses assessed the impact of SES and CTRA expression on clinical outcomes, including neutrophil engraftment at day +28, acute and chronic GVHD, TRM, relapse, leukemia-free survival (LFS), and OS. Neutrophil engraftment at day +28 was defined as the presence or absence of absolute neutrophil count (ANC) $> 0.5 \times 10^9/L$ sustained for three consecutive days. Patients were assessed for aGVHD and cGVHD by standard criteria (37, 38). TRM was defined as death in complete remission. Relapse was defined as disease recurrence at any site. LFS was defined as survival in complete remission after HCT. For OS, death from any cause was considered an event.

HLA matching status was categorized as well-matched, partially matched, or mismatched based on the NMDP classification of HLA matching status that allows adequate adjustment for donor-recipient HLA compatibility while accounting for best available

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resolution of typing. Well-matched patients had no identified mismatches at HLA-A, -B, -C, and -DRB1 with low-intermediate- or high-resolution data available at HLA-A, -B and high-resolution -DRB1. Partially matched patients had a single locus mismatch at any of the 4 loci and/or missing HLA-C data. Mismatched patients had 2 or more allele or antigen mismatches.

Statistical analysis of patient characteristics and outcomes

The χ^2 statistic was used to compare categorical patient, disease, and HCT-related variables and the Kruskal-Wallis test was used to compare continuous variables. Because of the dramatically different variances among gene expression values (often >10-fold range), we stabilized their variance by converting each gene expression value into a single z-score. Z-scores for each individual were then averaged over the CTGA genes to compute a single gene expression composite score for each individual. These values were then split at the median and dichotomized as low versus high CTGA expression, as no biologically based cut-points have yet been defined. CTGA profiles were unable to be compared to historic nondiseased populations as the normalization process performed within a given set of assays removes differences between sets of assayed samples. Clinical outcome variables were compared between the low versus high SES groups as well as the low versus high CTGA expression groups. Probabilities of neutrophil recovery, acute and chronic GVHD, TRM, and relapse were calculated by the cumulative-incidence function method and compared between groups using Gray test. Probabilities of LFS and OS were calculated using the Kaplan-Meier method and compared between groups using the log-rank test. Multivariate analyses were not performed due to sample size limitations. We also conducted stratified log-rank tests to account for the potential impact of matching, but the results were similar to the unstratified tests so they are not reported.

Results

Patient characteristics

Seventy-eight HCT recipients from the population sampled met study inclusion and matching criteria. Table 1 describes patient, disease, and treatment characteristics for low versus high SES. All patients had AML in first CR. Only distance to transplant center was significantly different between the two groups, with individuals of lower SES significantly more likely to live further away from the transplant center ($P < 0.001$). Table 2 describes the cohort's characteristics by low versus high CTGA expression level. Individuals with lower levels of CTGA gene expression were more likely to be older ($P = 0.04$) and have received a higher infused cell dose if receiving a peripheral blood HCT ($P = 0.02$).

CTGA transcriptome profile

CTGA gene expression varied significantly as a function of SES, with HCT recipients of lower SES expressing the CTGA gene profile significantly more than those of high SES (Fig. 1A; $P = 0.009$). Follow-up analysis of specific gene subsets identified downregulated expression of the type I IFN response genes as the primary driver of the overall reduction in CTGA gene expression in low SES ($P = 0.012$); proinflammatory and antibody genes were not significantly associated with low SES ($P = 0.418$ and 0.481 , respectively). The magnitude of the within-sample differences (e.g., by SES) are similar to those observed in other studies (7, 16), though direct comparison is not valid as previously described.

Table 1. Patient, disease, and treatment characteristics by low versus high socioeconomic status

A	B High SES (%)	C Low SES (%)	D P
Age, median (range), y	44 (21-59)	40 (21-59)	0.26
Age			0.71
20-29	6 (15)	10 (26)	
30-39	10 (26)	10 (26)	
40-49	16 (41)	13 (33)	
50-59	7 (18)	6 (15)	
Sex			0.36
Male	21 (54)	17 (44)	
Female	18 (46)	22 (56)	
Median income, 2000 ^a	61,814	30,259	<0.001
Distance to transplant center			<0.001
<17 miles	13 (33)	8 (21)	
17-55 miles	15 (38)	4 (10)	
55-150 miles	3 (8)	17 (44)	
>150 miles	8 (21)	10 (26)	
KPS			0.08
≥90	32 (82)	29 (74)	
<90	2 (6)	8 (20)	
Missing	5 (12)	2 (6)	
Comorbid conditions			1
No	21 (54)	21 (54)	
Yes	18 (46)	18 (46)	
BMI, median (range), kg/m ²	26 (20-41)	26 (18-51)	0.9
BMI, kg/m ²			0.47
0 < 18.5	0 (0)	2 (5)	
18.5-24.9	11 (28)	14 (36)	
25-29.9	19 (48)	14 (36)	
≥30	9 (24)	9 (23)	
CTGA profile expression			0.02
High	14 (36)	25 (64)	
Low	25 (64)	14 (36)	
Cytogenetics			0.8
Good risk	1 (2)	0 (0)	
Intermediate risk	19 (48)	18 (46)	
Poor/adverse risk	11 (28)	10 (26)	
Unknown	8 (20)	11 (28)	
HLA match status			0.59
Well matched	23 (48)	24 (62)	
Partially matched	9 (24)	11 (28)	
Mismatched	7 (18)	4 (10)	
Race match (donor/recipient)			0.83
Match	31 (80)	33 (84)	
Mismatch	4 (10)	3 (8)	
Unknown	4 (10)	3 (8)	
Donor age, median (range), y	33 (21-56)	37 (20-56)	0.5
Donor age at transplant, y			0.45
18-29	14 (36)	11 (28)	
30-39	13 (33)	15 (38)	
40-49	6 (15)	10 (26)	
≥50	6 (15)	3 (8)	
Sex match (donor/recipient)			0.16
Male/male	12 (30)	15 (38)	
Male/female	10 (26)	12 (30)	
Female/male	9 (24)	2 (6)	
Female/female	8 (20)	10 (26)	
CMV match (donor/recipient)			0.82
Negative/negative	12 (31)	14 (36)	
Negative/positive	14 (36)	11 (28)	
Positive/negative	5 (13)	5 (13)	
Positive/positive	8 (20)	8 (20)	
Unknown	0 (0)	1 (3)	
Year of transplant			0.64
1995-1999	13 (34)	15 (38)	
2000-2004	26 (66)	24 (62)	

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Table 1. Patient, disease, and treatment characteristics by low versus high socioeconomic status (Cont'd)

A	B High SES (%)	C Low SES (%)	D P
Conditioning regimen			0.25
Bu + Cy ± other	7 (18)	5 (13)	
Cy + TBI ± other	28 (72)	26 (67)	
TBI ± other	0 (0)	4 (10)	
Flu ± other	3 (8)	4 (10)	
Other	1 (2)	0 (0)	
GVHD prophylaxis			0.46
T-cell depletion	7 (18)	6 (15)	
CSA + MTX ± others	13 (33)	18 (46)	
CSA ± others	0 (0)	2 (6)	
Tacrolimus + MTX	15 (38)	10 (26)	
Tacrolimus	4 (10)	3 (8)	
Graft type			1
Bone marrow	28 (72)	28 (72)	
Peripheral blood	11 (28)	11 (28)	
Infused BM cell dose			0.18
> 2 × 10 ⁸	17 (39)	12 (43)	
≤ 2 × 10 ⁸	11 (61)	16 (57)	
Missing	0 (0)	0 (0)	
Infused PB cell dose			0.45
> 5 × 10 ⁸	6 (27)	9 (1)	
≤ 5 × 10 ⁸	3 (55)	1 (9)	
Missing	2 (18)	9(1)	
Time from diagnosis to transplant, median (range), months	5 (3-17)	6 (3-12)	0.82
Donor search time, median (range), months			
Diagnosis to preliminary search	2 (<1-10)	2 (<1-10)	0.62
Preliminary search to formal search	<1 (<1-12)	<1 (0-3)	0.29
Formal search to transplant	3 (2-11)	3 (2-6)	0.25
Follow-up of survivors, median (range), months	28 (12-86)	36 (12-132)	0.53
Cause of death			0.43
Infection	4 (10)	6 (15)	
Interstitial pneumonia	4 (10)	2 (6)	
aGVHD	3 (8)	4 (10)	
Recurrence or persistence of primary disease	3 (8)	6 (16)	
Organ failure	5 (12)	5 (12)	
Hemorrhage	4 (10)	0 (0)	
Other	16 (42)	16 (41)	

Abbreviations: BM, bone marrow; Bu, busulfan; CMV, cytomegalovirus; CSA, cyclosporine; CTra, conserved transcriptional response to adversity; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; KPS, Karnofsky Performance Status; MTX, methotrexate; PB, peripheral blood; TBI, total body irradiation.

^aBased on 2004 Census tract data linking income to residential ZIP code.

Transcription control pathways

To assess the role of immunoregulatory transcription factors previously implicated in CTra-related gene expression [proinflammatory NFκB, activator protein 1 (AP-1), and cAMP response element-binding protein (CREB) factors as well as interferon response factor (IRF) and glucocorticoid receptor (GR) activity; refs. 17, 20, 21], we applied TELiS promoter-based bioinformatics analyses (35) to all genes showing ≥20% difference in average expression between the low vs. high SES groups (Figure 1B). Consistent with findings from the CTra analyses, results showed significantly decreased activity of IRF transcription factors (the primary mediators of type I IFN response; $P = 0.003$)

Table 2. Patient, disease, and treatment characteristics by low versus high CTra gene expression profile

A	B High CTra (%)	C Low CTra (%)	D P
Age, median (range), y	37 (21-59)	44 (21-59)	0.04
Age			0.16
20-29	10 (26)	6 (15)	
30-39	13 (33)	7 (18)	
40-49	11 (28)	18 (46)	
50-59	5 (13)	8 (21)	
Sex			0.65
Male	18 (46)	20 (52)	
Female	21 (54)	19 (48)	
Median income, 2000 ^a	32,300	58,257	0.02
Distance to transplant center			0.58
<17 miles	12 (33)	9 (23)	
17-55 miles	7 (18)	12 (33)	
55-150 miles	11 (28)	9 (23)	
>150 miles	9 (23)	9 (23)	
KPS			0.38
≥90	33 (84)	28 (72)	
<90	4 (10)	6 (16)	
Missing	2 (6)	5 (12)	
Comorbid conditions			0.17
No	24 (62)	18 (46)	
Yes	15 (38)	21 (54)	
BMI, median (range), kg/m ²	27 (18-51)	26 (20-44)	0.9
BMI, kg/m ²			0.68
0 < 18.5	2 (5)	0 (0)	
18.5-24.9	13 (33)	12 (30)	
25-29.9	16 (41)	17 (44)	
≥30	8 (21)	10 (26)	
SES			0.02
High	14 (36)	25 (64)	
Low	25 (64)	14 (36)	
Cytogenetics			0.64
Good risk	0 (0)	1 (2)	
Intermediate risk	19 (48)	18 (46)	
Poor/adverse risk	9 (24)	12 (30)	
Unknown	11 (28)	8 (20)	
HLA match status			0.95
Well matched	23 (59)	24 (62)	
Partially matched	10 (26)	10 (26)	
Mismatched	6 (15)	5 (13)	
Race match (donor/recipient)			0.87
Match	32 (82)	32 (82)	
Mismatch	3 (8)	4 (10)	
Unknown	4 (10)	3 (8)	
Donor age, median (range), y	37 (20-56)	35 (21-56)	0.97
Donor age at transplant, y			0.48
18-29	14 (36)	11 (28)	
30-39	11 (28)	17 (44)	
40-49	10 (26)	6 (15)	
≥50	4 (10)	5 (13)	
Sex match (donor/recipient)			0.78
Male/male	13 (33)	14 (36)	
Male/female	13 (33)	9 (23)	
Female/male	5 (13)	6 (15)	
Female/female	8 (21)	10 (26)	
CMV match (donor/recipient)			0.71
Negative/negative	14 (36)	12 (33)	
Negative/positive	11 (28)	14 (36)	
Positive/negative	6 (15)	4 (10)	
Positive/positive	7 (18)	9 (23)	
Unknown	1 (3)	0 (0)	
Year of transplant			0.64
1995-1999	15 (38)	13 (33)	
2000-2004	24 (62)	26 (67)	

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Table 2. Patient, disease, and treatment characteristics by low versus high CTRA gene expression profile (Cont'd)

A	B High CTRA (%)	C Low CTRA (%)	D P
Conditioning regimen			0.74
Bu + Cy ± other	5 (12)	7 (18)	
Cy + TBI ± other	28 (72)	26 (67)	
TBI ± other	3 (8)	1 (3)	
Flu ± other	3 (8)	4 (10)	
Other	0 (0)	1 (3)	
GVHD prophylaxis			0.84
T-cell depletion	7 (18)	6 (15)	
CSA + MTX ± others	17 (44)	14 (36)	
CSA ± others	1 (3)	1 (3)	
Tacrolimus + MTX	12 (31)	13 (33)	
Tacrolimus	2 (5)	5 (12)	
Graft type			0.31
Bone marrow	30 (77)	26 (67)	
Peripheral blood	9 (31)	13 (33)	
Infused BM cell dose			0.41
>2 × 10 ⁸	14 (47)	15 (58)	
≤2 × 10 ⁸	16 (53)	11 (42)	
Missing	0 (0)	0 (0)	
Infused PB cell dose			0.02
>5 × 10 ⁸	4 (44)	11 (85)	
≤5 × 10 ⁸	4 (44)	0 (0)	
Missing	1 (11)	2 (15)	
Time from diagnosis to transplant, median (range), months	6 (3-17)	5 (3-15)	0.28
Donor search time, median (range), months			
Diagnosis to preliminary search	2 (<1-10)	2 (<1-10)	0.45
Preliminary search to formal search	<1 (0-12)	<1 (0-3)	0.44
Formal search to transplant	3 (2-8)	3 (2-11)	0.45
Follow-up of survivors, median (range), months	28 (12-81)	36 (23-132)	0.52
Cause of death			0.18
Infection	5 (13)	5 (13)	
Interstitial pneumonia	3 (8)	3 (8)	
aGVHD	3 (8)	4 (10)	
Recurrence or persistence of primary disease	8 (21)	1 (3)	
Organ failure	5 (13)	5 (13)	
Hemorrhage	3 (8)	1 (3)	
Other	12 (31)	20 (51)	

Abbreviations: BM, bone marrow; Bu, busulfan; CMV, cytomegalovirus; CSA, cyclosporine; CTRA, conserved transcriptional response to adversity; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; KPS, Karnofsky Performance Status; MTX, methotrexate; PB, peripheral blood; TBI, total body irradiation.

^aBased on 2004 Census tract data linking income to residential ZIP code.

but no significant alterations in NFκB or AP-1 activity in the low SES group. With respect to neural/endocrine processes that might regulate these immunobiologic pathways, we also saw indications of increased CREB activity (which mediates β-adrenergic signaling from the sympathetic nervous system (ref. 17; $P < 0.001$) and decreased activity of the GR (decreased activity often occurs secondary to stress-induced desensitization of the GR via β-adrenergic signaling (ref. 17; $P = 0.068$) in this group that was not statistically significant.

Cellular origins

To determine whether the transcriptional correlates of SES might occur within the same leukocyte subpopulations (i.e., monocytes, dendritic cells, and B lymphocytes) previously shown

to mediate the CTRA transcriptional effects of other adverse life circumstances (20, 21, 31, 32), we conducted transcript origin analysis (TOA; 32) on differentially expressed genes (Figure 1C). These results indicate that differentially expressed genes derived predominately from dendritic cells (both upregulated and downregulated genes) and from monocytes (downregulated genes). To ensure that differential prevalence of these subsets did not confound analyses of transcription factor activity, all CTRA gene set analyses and transcription factor bioinformatics results reported above were adjusted for leukocyte subset marker transcripts (*CD3D/E*, *CD4*, *CD8A*, *CD19*, *CD16/FCGR3A*, *CD56/NCAM1*, and *CD14*).

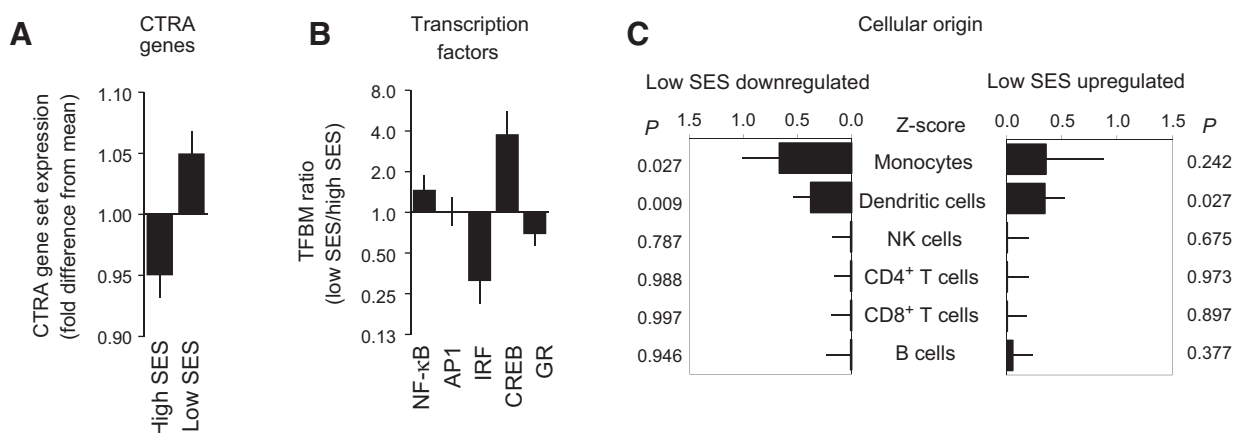
Clinical outcomes

Increased expression of the CTRA gene profile was significantly associated with increased overall relapse ($P = 0.04$; Fig. 2) and decreased overall LFS ($P = 0.04$; Fig. 3) as compared with the low CTRA group in unadjusted analyses (Table 3). Relapse at 3 years was 31% and 11% in the high and low CTRA groups, respectively, while LFS at 3 years was 26% and 45%. Exploratory analyses demonstrated no significant differences between low versus high SES groups on any of the clinical outcome variables.

Discussion

The results of this study show that low SES is associated with a marked activation of the CTRA gene expression profile in leukocytes from hematologic cancer patients receiving HCTs from unrelated donors. These results are consistent with studies of other stressed populations suggesting that extended exposure to life adversity is associated with upregulated expression of the CTRA gene profile. While increased CTRA gene expression has been observed among healthy individuals of low SES (7, 16), these are the first data to demonstrate the robustness of this relationship in an immunologically compromised and diseased population. These data are the first to suggest a potential neuro-immune mechanism for the previously reported adverse clinical outcomes among HCT recipients of lower SES (1). Descriptive analyses suggest that greater CTRA gene expression is associated with increased relapse and decreased LFS, which is the first indication in the literature to directly link the CTRA profile with clinical outcomes.

The provocative differences between CTRA among those with low versus high SES may explain differences in outcomes, and could lead to mechanistic targets for future interventions. β-Adrenergic signaling is known to affect the transcription pathways differentially expressed between low versus high SES groups in this study, including upregulation of CREB activity, inhibition of IRF signaling, and desensitization of the GR (16). Therefore, this profile of results is consistent with the possibility that increased sympathetic nervous system activity associated with exposure to chronic stress may contribute to the differential gene expression profiles observed. β-Adrenergic signaling may regulate multiple cellular processes contributing to cancer progression (39). Retrospective epidemiologic studies have linked the use of β-adrenergic antagonists (β-blockers) to reduced rates of progression for several solid tumors (40-42). Preclinical pharmacologic and biomarker studies in animals support translation of β-blockade as a novel adjuvant to existing therapeutic strategies in clinical

**Figure 1.**

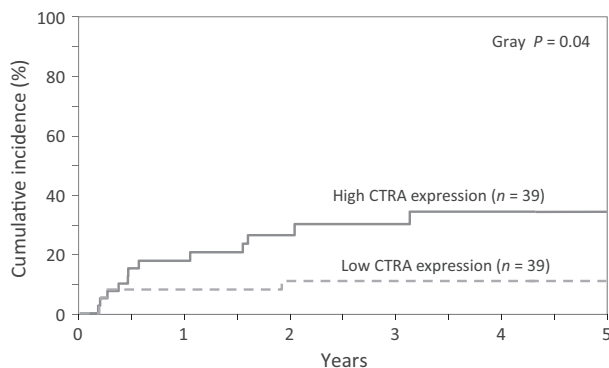
Expression of the CTRA gene set, transcription control pathways and cellular origin. A, linear model-based estimates of fold-difference from the mean in expression in a 53-gene CTRA contrast score in PBMCs from individuals with low versus high SES (adjusting for age, gender, race, BMI, number of comorbid conditions at time of transplant, and mRNA markers of major leukocyte subsets). Genes showing $\geq 20\%$ difference in expression between HCT recipients of low versus high SES were tested for differential activity of specific transcription factors as indicated by TELIS analysis of transcription factor-binding motifs (TFBM) in proximal promoter sequences of up- vs. downregulated genes (ref. 35; B) and PBMC cell type of origin as indicated by TOA cell-type diagnosticity z-scores (ref. 32; C). Error bars indicate SE.

oncology, linking the use of β -blockers with reduced disease progression (16, 40–46). This effect has been demonstrated in malignant hematologic cells as well (16, 45). The identification of altered gene transcription patterns among HCT recipients exposed to varying levels of chronic stress may provide a biologic target for the novel use of β -blockers in the HCT setting.

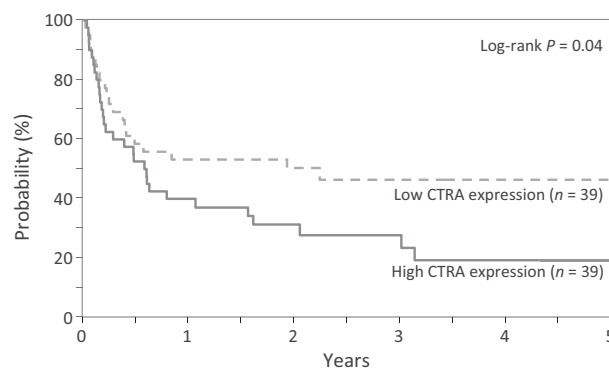
In addition to β -adrenergic signaling, prostaglandin synthesis may be another mechanistic drug target for stress-associated cancer control. Animal models demonstrate that COX2 inhibitors attenuate tumor-promoting effects of surgery (43, 47), though gene expression studies have not been done in this setting. Finally, behavioral interventions targeted at stress management can modulate leukocyte transcriptional activity among cancer patients (20). The CTRA gene profile may represent a useful molecular biomarker for assessing pharmacologic or behavioral intervention treatment response.

Though this study was not powered to examine the relationship between CTRA expression and clinical outcomes in multivariate analysis, the data are provocative in identifying a molecular

signature that could serve as a cumulative stress biomarker. Such a biomarker may be useful in stratifying disease risk. Social and physical stressors other than SES may affect overall gene transcription as well as specific expression of the CTRA gene profile; this, in addition to low power, may explain why CTRA expression, but not SES, was associated with clinical outcomes in our exploratory analyses. While SES was significantly associated with OS and TRM in the Baker and colleagues study (1), this finding was not replicated in the current study either due to lack of statistical power or to the fact that, by design, the present sample was purposefully selected as a homogeneous subset and therefore not representative of the Baker cohort. The significant age difference between the high versus low CTRA expression groups is contrary to what might be expected given the known positive association between aging and inflammation. If this confounded the present findings it should have been in the direction of the null hypothesis. Further studies assessing clinical outcomes while controlling for age as well as other patient-, disease-, and treatment-related variables that impact HCT outcomes (including

**Figure 2.**

Cumulative incidence of relapse by CTRA expression.

**Figure 3.**

Probability of LFS by CTRA expression.

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Table 3. Clinical outcomes as a function of high versus low CTRA gene expression

A Outcome	B High CTRA expression % of cohort (95% CI) N = 39	C Low CTRA expression % of cohort (95% CI) N = 39	D P
Neutrophil recovery @ 100 days	92 (83–98)	85 (72–94)	0.27
aGVHD @ 100 days	49 (33–64)	62 (46–76)	0.25
cGVHD			0.08
@ 1 y	30 (16–45)	35 (21–51)	0.61
@ 3 y	30 (16–45)	47 (31–63)	0.13
TRM			0.61
@ 100 days	33 (20–49)	23 (12–38)	0.33
@ 1 y	44 (29–59)	40 (25–56)	0.74
@ 3 y	44 (29–59)	44 (28–60)	0.98
Relapse			0.04
@ 1 y	18 (8–31)	8 (2–19)	0.2
@ 3 y	31 (17–46)	11 (3–23)	0.04
LFS			0.04
@ 1 y	38 (24–54)	52 (36–68)	0.23
@ 3 y	26 (13–41)	45 (29–62)	0.09
OS			0.09
@ 1 y	44 (29–59)	54 (38–69)	0.36
@ 3 y	25 (12–42)	47 (31–63)	0.14

Abbreviations: CTRA, conserved transcriptional response to adversity; GVHD, graft-versus-host disease (a = acute, c = chronic); LFS, leukemia-free survival; OS, overall survival; TRM, transplant-related mortality.

cytogenetics; HLA match; donor age; donor/recipient match on race, gender, and CMV status; year of transplant; conditioning regimen; GVHD prophylaxis; graft type; cell dose; and time from diagnosis to transplant) are needed.

This study found differences in relapse and LFS, whereas TRM and OS were different between SES groups in the study done by Baker and colleagues (1). This difference may be explained by the subset selection or the different independent variables used for analysis (CTRA rather than SES). SES is only one etiology of chronic stress, and the biologic sequelae may be similar but not identical to that predicted by an overall stress biomarker. The significant clinical outcomes in the present analysis are, however, consistent with the pathophysiology of β -adrenergic-mediated tumor progression as previously discussed. Finally, the sample size in this subgroup was not powered to evaluate clinical outcomes; therefore, these interesting findings require validation in adequately powered multivariate analyses.

This study's findings are limited in several respects. These results are from a cross-sectional analysis, and it is possible the observed associations are attributable to factors other than SES. This study focuses on a one-time assessment of leukocyte gene expression in a Caucasian-only sample; future studies are needed to determine whether the same gene expression effects exist in other races, vary between racial groups, change throughout the transplant process, or are affected by social environmental factors experienced by the donor. The current findings are from extreme SES quartiles and may overestimate the magnitude of SES-related differences within the population as a whole; robustness of this relationship should be confirmed in future studies assessing SES as a continuous variable. We were unable to control for smoking status, though previous research has failed to demonstrate an effect of smoking status on outcomes among unrelated donor recipients for chronic myelogenous leukemia (48). As inflammation is a large component of the CTRA profile, and low SES is associated with higher levels of smoking (49), it is feasible this could have artificially enhanced

the relationship between SES and CTRA expression. However, IFN and antibody expression are also significant contributors to the overall CTRA profile and there is substantially less research available to suggest a significant relationship between IFN/antibody responses and SES or smoking. Furthermore, our results are consistent with those from other studies of social adversity that were able to control for smoking (16–19). Finally, it will also be important to validate the present bioinformatic indications of monocyte and dendritic cell involvement in future studies using physical isolation of cell subsets.

This study demonstrates significant SES-related differences in immune system gene expression among unrelated donor HCT recipients consistent with that of other populations confronting significant life adversity (46). Given prior evidence for worse overall survival and transplant-related mortality among low SES transplant recipients (1) and possible association between CTRA gene expression and relapse and leukemia-free survival, these findings provide a molecular framework within which to understand potential social environmental influences on immune function and clinical outcomes in the setting of cancer and HCT.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. government.

Authors' Contributions

Conception and design: J.M. Knight, J.D. Rizzo, B.R. Logan, S.W. Cole
Development of methodology: J.D. Rizzo, B.R. Logan, S.W. Cole
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.W. Cole
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Knight, J.D. Rizzo, B.R. Logan, T. Wang, J.M.G. Arevalo, J. Ma, S.W. Cole
Writing, review, and/or revision of the manuscript: J.M. Knight, J.D. Rizzo, B.R. Logan, S.W. Cole

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Low Socioeconomic Status, Adverse Gene Expression Profiles, and Clinical Outcomes in Hematopoietic Stem Cell Transplant Recipients

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