Low socioeconomic status in hematopoietic cell transplant recipients is associated with increased treatment-related mortality and relapse, resulting in reduced survival. No biologic mechanism has been identified for these associations. The stress-related gene expression profile, termed the "conserved transcriptional response to adversity," may be a predictor of these negative outcomes. *Clin Cancer Res; 22(1); 6–8. ©2015 AACR. See related article by Knight et al., p. 69*

In this issue of *Clinical Cancer Research*, Knight and colleagues examine the relationships between socioeconomic status (SES), stress-related gene expression profiles, and hematopoietic cell transplantation (HCT) outcomes (1). Previous literature shows that individuals of lower SES experience inferior HCT outcomes, including increased rates of transplant-related mortality and relapse, resulting in decreased overall survival (2, 3). These troubling findings have not previously been linked by an underlying biologic mechanism. Interestingly, as described by Knight and colleagues, low SES and many other biobehavioral factors, such as chronic stress, depression, and decreased levels of social support, are all associated with increased inflammation (Fig. 1). This, in turn, has been associated with increased morbidity and mortality in many conditions, including cancer, asthma, and heart disease, and remarkably early life exposures to these factors can have persistent impact into adulthood (4–8).

During periods of stress, peripheral blood immune cells exhibit changes in gene expression, and this shift has been termed "the conserved transcriptional response to adversity (CTRA) gene expression profile" (9, 10). The CTRA is characterized by the upregulation of 19 genes involved in inflammation (i.e., IL1B, IL6, IL8, and TNF) and downregulation of 31 genes involved in type 1 IFN antiviral responses (IFN-α, -β, and -ω, and MX-family genes) and 3 genes involved in antibody synthesis (IGJ, IGLL1, and IGLL3). Given the important role that inflammation plays in many post-HCT health outcomes, such as graft versus host disease (GVHD), infection, and graft versus leukemia/lymphoma reactions, it is reasonable to suspect that the CTRA gene profile may have bearing on HCT outcomes.

In order to investigate this association, Knight and colleagues utilized a cohort of patients from a study previously performed by Baker and colleagues through the Center for International Bone Marrow Transplant Research (2). The cohort was composed of Caucasian adults (20–59 years) with acute myeloid leukemia, who underwent unrelated myeloablative HCT in first remission between 1995 and 2004. Individuals were divided into quartiles, based on SES, as estimated by residential zip code, and those from the highest and lowest quartiles were included. Individuals were also matched on age and body mass index (BMI; n = 78). Transcriptional profiling was performed on pretransplant, recipient peripheral blood mononuclear cells, and CTRA gene expression values were analyzed, controlling for age, sex, BMI, and coexisting medical conditions. HCT recipients of low SES were significantly more likely to express the CTRA gene profile than those of high SES (P = 0.009). Differences between these two groups were predominantly driven by type 1 IFN response genes, which were downregulated in low SES patients (P = 0.012). When specific transcriptional control pathways were considered, increased CAMP response element-binding protein (CREB) activity, which, among its multiple roles, mediates β-adrenergic signaling from the sympathetic nervous system, was seen in the low SES group (P < 0.001). Regardless of SES, increased expression of the CTRA gene profile was associated with increased relapse (P = 0.04) and decreased leukemia-free survival (P = 0.04). No significant differences in clinical outcomes were observed based on SES status.

The authors make the compelling case that differences in this stress-related gene expression profile, the CTRA, prior to transplantation, was significantly associated with important transplant outcomes. The association between SES and CTRA gene expression profile was not surprising, as it has been previously described among otherwise healthy individuals (9). However, the association of CTRA with HCT outcomes is novel and warrants further attention. Certainly, as the authors point out within the article, the sample size was limited, prohibiting a more extensive, multivariable analysis to better define these relationships, particularly in regard to clinical outcomes, but the univariate findings are too interesting to ignore. The results from this study suggest that increased sympathetic nervous system activity associated with chronic stress may lead to the observed differences between the high and low SES groups, perhaps refining the previously described association between SES and transplant outcomes.

From the clinician’s perspective, these findings are somewhat defeating on first glance, as they may imply that patients with...
high CTRA gene expression are doomed before even beginning the HCT process. On the surface, there seems to be little we can do as clinicians and scientists to alleviate the potentially chronic and multifactorial stress faced by many of our patients, particularly in a timely manner prior to transplant. However, Knight and colleagues suggest potentially using the CTRA profile as a stress biomarker, which could, in turn, be incorporated into pre-HCT disease risk stratification. The authors further posit that the use of β-adrenergic antagonists (β-blockers) or behavioral therapy may be of potential benefit in individuals with altered gene transcription patterns and that CTRA expression could be monitored over time to assess treatment response. Potentially, as we more fully understand the utility of this marker in predicting HCT outcomes, it may be incorporated into other scoring systems that predict outcome, such as the HCT-Comorbidity Index (11).

Thinking ahead, the future directions for this line of investigation are plentiful. As the authors suggest, along with recruiting a larger, more diverse sample size to better evaluate and potentially validate the present findings, it may also be useful to interrogate the CTRA gene expression profile of HCT donors as well as recipients. It is intriguing, in the setting of myeloablative transplantation, that the CTRA gene profile would exert ongoing control over outcomes, even once the recipient cells are replaced by the donor immune system. One is led to question whether environmental stressors can alter the CTRA gene expression profile in the engrafted donor cells? And if the donor cells ultimately exhibit a shift in gene expression, at what point would it occur? If this is the case, perhaps there is a window of opportunity for intervention prior to this shift. Behavioral modifications in the early post-HCT period may be an important nonpharmacologic approach with potential for significant benefits. Moreover, these data might get to the core of an untapped area in cancer therapeutics: understanding how to manage chronic stress to positively influence outcomes.

Utilization of the CTRA gene profile provides yet another means for identifying patients at risk for inferior outcomes following HCT and creates opportunity to intervene. The CTRA profile may not only prove useful for identifying patients at increased risk for relapse, but also potentially for early morbidities, such as GVHD or treatment-related mortality. In addition, it may identify patients warranting increased screening for long-term side effects of HCT therapy, such as cardiovascular disease and metabolic syndrome, all of which have been associated with chronic inflammation (12). If validated, the next steps are to determine whether behavioral, pharmacologic, or environmental modifications influence the CTRA gene profile and ultimately improve clinical outcomes.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.
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