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Experienced discrimination and racial differences in leukocyte gene expression

April D. Thames[1,2], **Michael R. Irwin**[3], **Elizabeth C. Breen**[3], and **Steve Cole**[3]

[1]Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles

[2]Present affiliation: April D. Thames, Ph.D. Department of Psychology, University of Southern California

[3]Cousins Center for Psychoneuroimmunology, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles

Abstract

Racial disparities in health outcomes between African Americans and European Americans have been well-documented, but not fully understood. Chronic inflammation contributes to several of the diseases showing racial disparities (e.g., Human Immunodeficiency Virus [HIV]), and racial differences in stress exposure (e.g., experiences of racial discrimination) that stimulate pro-inflammatory processes that may contribute to differential health outcomes.

We performed a cross-sectional bioinformatic analyses relating perceived discrimination (as measured by the Perceived Ethnic Discrimination Questionnaire [PED-Q]) to the activity of pro-inflammatory, neuroendocrine, and antiviral transcription control pathways relevant to the conserved transcriptional response to adversity (CTRA) in peripheral blood leukocytes. Subjects were 71 individuals (37 HIV-seropositive (HIV+); 34 HIV-seronegative (HIV-)) (mean age = 53 years, range 27–63), who self-identified either as African American/Black (n=48) or European American/White (n=23). This provided the opportunity to examine the independent effects of race and HIV, as well as the modifying role of perceived discrimination on pathways involved in CTRA. Exploratory analysis examined the interactive effects of HIV and race on pathways involved in CTRA. Relative to European Americans, African Americans showed increased activity of two key pro-inflammatory transcription control pathways (NF-κB and AP-1) and two stress-

Address correspondence to Dr. April D. Thames, Department of Psychology, University of Southern California, 3620 S. McClintock Drive, Bldg. Seeley G. Mudd, Los Angeles, CA 90075, thames@usc.edu. Phone: 213-740-4436.

Author Contributions

April D. Thames, Ph.D. – Dr. Thames was responsible for the conceptualization of the current study, data curation, funding acquisition, project administration, write-up of original draft and editing of draft.

Michael Irwin, M.D. – Dr. Irwin was responsible for the writing of manuscript drafts, input on study design and reviewing and editing of manuscript drafts.

Elizabeth Breen, Ph.D. – Dr. Breen was responsible for the methodology; project administration and reviewing and editing of manuscript drafts.

Steve Cole, Ph.D. – Dr. Cole was responsible for supervising the biological resources, formal data analysis, data curation, supervision, validation, writing of original draft and review and editing of subsequent drafts.

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responsive signaling pathways (CREB and glucocorticoid receptor); these effects did not differ significantly as a function of HIV infection (HIV x Race interaction, all $p > .10$). Results suggested that differences in experiences of racial discrimination could potentially account for more than 50% of the total race-related difference in pro-inflammatory transcription factor activity. In sum, differential exposure to racial discrimination may contribute to racial disparities in health outcomes in part by activating threat-related molecular programs that stimulate inflammation and contribute to increased risk of chronic illnesses.

Keywords

Racial discrimination; gene expression; HIV; African Americans

1. Introduction

Racism and racial discrimination has permeated the lives of many African Americans for decades, and is conceptualized as a chronic social stressor (Thoits, 2010). In a 2015 survey by the Kaiser Family Foundation, 35 percent of African Americans reported discriminatory experiences such as being denied a job or housing, or being prevented from voting, compared to about 11 percent of European Americans (see www.kff.org). Persistent racial inequality in areas of employment, housing, and other domains is a sobering reminder that racial discriminatory practices have yet to subside. As with other types of chronic stressors, racial discrimination may serve as a social pathway that contributes to Black-White disparities in a number of documented health and disease outcomes (Geronimus et al. 1996; Kochanek et al. 2004; Levine et al.2001; MMWR 2005; Smith et al. 1998; Williams & Jackson 2005).

Experiences with racial discrimination have been linked to several psychiatric and medical risk factors (e.g., depression, anxiety, cardiovascular disease, hypertension; Barnes et al., 2004; Brondolo et al., 2008; Lewis et al., 2006; Mozzaffarian et al., 2015; Williams & Mohammed, 2009; Sims et al., 2012; Kessler, Mickelson, & Williams, 1999; Mays, Cochran, & Barnes, 2007), mortality rates (Clark et al., 1999; Barnes et al., 2008), and cognitive compromise (Barnes et al., 2012; Thames et al., 2013). While perceived racial discrimination has been linked to socioeconomic status (SES) (Forman, Williams, & Jackson, 1997), it continues to be associated with race-related differences in health after SES is controlled (Williams, Neighbors, & Jackson, 2003), suggesting that poverty alone cannot explain these differences (Mays et al., 2007).

More recent evidence suggests that perceived racial discrimination is linked to premature aging (Diez Roux et al., 2009; Rewak et al., 2014; Chae et al., 2014, Lee et al., 2017; Liu & Kawachi, 2017), which may partly explain why certain groups have worse medical (e.g., cardiovascular disease, diabetes, hypertension) and psychiatric outcomes (e.g., depression, anxiety). In studies of premature aging, perceived racial discrimination was associated with shorter leukocyte telomere length (LTL) in African American men who demonstrated an implicit bias within their own group (Chae et al., 2014) and lower levels of depression (Chae et al., 2016), but the precise mechanisms of this effect remain unclear. This is particularly

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interesting since LTL has been found to be longer among African Americans when compared to European Americans/Whites (Lynch et al., 2016). The emerging field of social genomics may provide additional insights into racial disparities in disease risk by identifying specific types of human genes that are activated in association with racial discrimination (Cole, 2013; Cole, 2014). A number of studies have identified a common pattern of transcriptional alterations that is activated by chronic low-grade activation of the sympathetic nervous system (SNS) during experiences of socioeconomic disadvantage, social rejection, or threat. This "conserved transcriptional response to adversity" (CTRA) profile is characterized by increased expression of genes involved in inflammation, and decreased expression of genes involved in innate antiviral responses (e.g., Type I interferons) and genes encoding specific isotypes of antibodies (IgG in particular) (Cole, 2013; Cole, 2014). Experimental studies have shown that CTRA gene expression is mediated in part by activation of the sympathetic nervous system (SNS; Powell et al., 2013). Specifically, perceptions of social threat activate the SNS, leading to release of norepinephrine at SNS nerve terminals, activation of β-adrenergic receptors on adjacent cells, and stimulation or repression of specific transcription factors in response to the cyclic $3'-5'$ adenosine monophosphate/protein kinase A (cAMP/PKA) signaling pathway. β-adrenergic-responsive transcription factors stimulate transcription of genes that encode proinflammatory cytokines and suppressing transcription of genes encoding Type I interferons and IgG antibodies, which contribute to CTRA gene expression (Cole, 2014).

CTRA activation has been observed in a wide range of adverse life circumstances including chronic social isolation (Cole et al., 2007; 2011; 2015), imminent bereavement (Miller et al., 2008; Miller et al., 2014), low SES (Chen et al., 2009; Miller et al., 2009; Chen et al., 2011), and of relevance to the current study, animal models of low social rank and repeated social defeat (Cole et al., 2010; Powell et al., 2013; Tung et al., 2012; Irwin & Cole, 2011). Experiences of racial discrimination have not yet been examined as potential triggers for CTRA gene expression, but the key role of perceived threat in triggering CTRA responses in other contexts suggests that similar dynamics may occur in response to experiences of racial discrimination. If so, CTRA-related increases in pro-inflammatory gene expression could contribute to racial disparities in rates of inflammation-related chronic illnesses such as cardiovascular, neoplastic, and neurodegenerative diseases. Moreover, CTRA-related decreases in antiviral responses may contribute to racial disparities in infectious diseases such as HIV.

African Americans represent over 40% of the HIV US population, yet only account for 12% of the total US population, which reflects a substantial health disparity (www.kff.org/hivaids/fact-sheet). Innate immune responses are key determinants of HIV outcomes, which include critical events in the earliest stages of infection such HIV transmission, establishment of initial foci of infection and local virus replication/spread as well as virus dissemination, and subsequent level of ongoing viral replication and rate of disease progression (Borrow, Shattock, Vyakarnam et al., 2010; Yamamoto, Barre-Sinoussi, Pedersen et al., 1986). Therefore, African Americans may be, in part, vulnerable to HIV acquisition and poor disease outcomes as a function of CTRA responses.

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It is unknown if the presence of HIV infection increases vulnerability to CTRA activation as experiences of social adversity increase. HIV-infection results in a marked increase in immune activation, which involves both the adaptive and innate immune systems (Borrow, Shattock, and Vyakarnam et al., 2010). Myeloid lineage immune cells and their effector molecules are implicated in both HIV-infection and exposure to adverse socioenvironmental conditions (MacGillivray & Kollmann, 2014; Nicholson, 2016; Irwin & Cole, 2013). Thus, it is plausible that the presence of HIV may place individuals in adverse social circumstances at even higher risk for poor immune health.

In a recent study from our group, we found the effects of psychosocial stress on depression (Williamson et al., 2017) and cognitive/brain outcomes (Thames et al., 2017) to be greater among individuals with HIV. Previous research has also found that chronic activation of the SNS can promote the pathogenesis of HIV-1 infection (e.g., accelerating viral replication and inhibiting antiviral immune responses (Cole, 2008; Cole et al., 2003; Cole et al., 2001; Cole et al., 1998; Collado-Hidalgo et al., 2006), and experimental studies in animal models have linked CTRA activation to impaired antiviral response to the simian immunodeficiency virus (Cole, Capitanio, Chun et al., 2015).

The current study examined the effects of race in general, and perceived racial discrimination in particular, on the activity of key pro-inflammatory and antiviral transcription control pathways involved in generating CTRA responses, in a sample of HIV+ and HIV- African American and European Americans with similar income and employment status as well as perceived stress (other than racial discrimination). We hypothesized: 1) increased activity of pro-inflammatory and neuroendocrine-related transcription control pathways, and decreased activity of antiviral pathways, in African Americans relative to European Americans; 2) increased activity of pro-inflammatory and neuroendocrine-related transcription control pathways, and decreased activity of antiviral pathways in HIV+ relative to HIV- participants; and 3) differential experiences of racial discrimination might account, at least in part, for race- associated differences in CTRA-related transcription factor activity. As an exploratory analysis, we examined the interactive effects of race and HIV, and hypothesized that African Americans who were HIV+ would demonstrate the greatest activity of pro-inflammatory and neuroendocrine-related transcription control pathways, and decreased activity of antiviral pathways.

2. Methods

2.1 Participants

Participants were a total of 71 individuals, including 37 HIV+ persons and 34 HIV-persons, who either self-identified as African American (n = 48; 26 HIV+) or European Americans (n = 23; 11 HIV+), who were a subset of subjects enrolled in a larger study examining the effects of HIV on neurocognitive functioning and brain imaging among African American and European American individuals. Participants were recruited for the substudy if they had completed all procedures from the larger parent project and provided informed consent to be contacted by the research team about future studies. For this substudy, 71 subjects were randomly identified out of 180 total eligible participants in the parent study. There were no differences between participants in this substudy sample and those in the larger parent

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project sample with respect to a number of demographic and clinical characteristics such as age, ethnicity/race, gender, and education (all p's >.20). Participants were recruited from various local community clinics and HIV service agencies in the Greater Los Angeles area. All procedures received approval by the University of California, Los Angeles.

Participants were included in the parent study if they were over the age of 18 years (range 27–63), reported English as their primary language, scored ≥ 26 on the Mini-Mental Status Exam (MMSE; Folstein et al. 1975), self-identified as African-American or European American, and were able to provide informed consent, as indicated by the participant communicating their understanding of the consent form. Participants were excluded if they reported either current abuse/dependence of cocaine or amphetamines, past stimulant abuse/dependence, or current/past diagnosis of a psychotic-spectrum disorder, as assessed by the Structured Clinical Interview for DSM-IV (Spitzer et al. 1995). Recent illicit drug use was assessed via urine toxicology in addition to a self-report drug screen (i.e., Brief Drug History Questionnaire). Participants were excluded if they screened positive for stimulants or hallucinogens. Participants were surveyed about alcohol, tobacco and other substances using the Drug Use History Form (DHQ) created by the University of California, Los Angeles' Center for Advanced Longitudinal Drug Abuse Research. Data was used as covariates in statistical models.

Participants with central nervous system (CNS) confounds (e.g., HIV-associated opportunistic infections or neurosyphilis), Hepatitis C coinfection, (confirmed by serology), major head injury (loss of consciousness >30 min), or contraindication to the safe use of magnetic resonance imaging, were also excluded.

The HIV+ participants in the current substudy were a chronically-infected (average years with known HIV infection = 18.5, range = 12 to 20), and clinically-stable population, with self- reported continuous anti-retroviral therapy (ART) for at least 3 months, plasma HIV RNA viral loads below virologic failure (< 5000 copies/mL) (Alvarez-Uria et al., 2012; WHO 2010) or undetectable (< 20 copies/mL), and current CD4+ T cell counts averaging above 600 cells/mm. All participants provided informed consent prior to study procedures (see Table 1 for demographic and clinical characteristics of substudy sample).

2.2 Materials and Methods

2.2.1 Perceived Discrimination—

The Brief Perceived Ethnic Discrimination Questionnaire – Community Version PED-Q- CV (Brondolo et al., 2005) is a 17-item questionnaire assessing the frequency and intensity of instances when the participant felt discriminated against based upon his or her race/ethnicity. The respondent is instructed to rate on a Likert scale (1–5) how often the instances have occurred. Examples of PED-Q-CV items include: (1) "*Have others thought that you couldn't do things or handle a job*?" (2) "*Have others threatened to hurt you*?". The questionnaire includes four subscales: social exclusion, stigmatization, workplace discrimination, and threat/harassment. The PED-Q-CV has demonstrated high reliability (Cronbach's $\alpha = 0.87$) and is considered a valid measure of perceived discrimination (Brondolo et al., 2005). For statistical analyses, we used the PED-Q-CV total score, which is a sum of all items as well as the subscales. Higher scores represent greater experiences with discrimination.

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2.2.2 Socioeconomic Status—The Hollingshead Index of Social Status (i.e., a weighted average of years of education, current or longest held occupation, and total household income of the participant) was used to assess current personal socioeconomic status. Years of education were based upon self-report from the participant and occupation was coded using the Hollingshead Index (Hollingshead, 1975). For married participants, the spouse's education and occupation were also used to compute the score. The Hollingshead Index is a reliable and valid measure of social status (Cirino et al., 2002), and it has been used in a racially diverse sample of HIV+ adults (Arentoft et al., 2015). Hollingshead scores range from 0 to 4, with higher scores representing higher levels of SES

2.2.3 Perceived Stress—Participants' levels of stress were measured using a shortened version of the Perceived Stress Scale (Cohen, Kamarck, and Mermelstein, 1983). The shortened version of the Perceived Stress scale (a = .82) consists of 12 items that ask how often in the last month the participants experienced symptoms of stress. Sample items include: "felt stressed," "felt in control" (reverse coded), and "had problems dealing with responsibilities." Participants used a 5-point response scale (1 = never to 5 = very often). Higher scores indicate greater stress levels over the past month.

2.2.4 Gene expression profiling and analysis—Total leukocyte RNA was extracted from whole blood samples drawn into PAXgene RNA tubes (Qiagen RNeasy) and checked for suitable mass (> 500 ng by NanoDrop 1000) and integrity (RNA integrity number > 8 by Agilent TapeStation capillary electrophoresis). All samples meeting quality criteria were assayed by RNA sequencing (RNAseq) in the UCLA Neuroscience Genomics Core Laboratory using Illumina TruSeq cDNA library synthesis and multiplex DNA sequencing on an Illumina HiSeq 4000 instrument with single strand 65 nt sequence reads (all following the manufacturer's standard protocol). Samples yielded >30 million sequence reads, each of which was mapped to the RefSeq human genome sequence using HISAT2 [Kim, Langmead, & Salzberg, SL, 2015] and quantified as transcript counts per million total transcripts (TPM) using StringTie [Pertea et al., 2016]. The following steps were performed to test study hypotheses:

1. TPM values were floored at .1 and $\log_2$-transformed for analysis by a standard linear statistical models to estimate the magnitude of difference in transcript abundance for African Americans vs. European Americans while controlling for age, gender, body mass index (kg/m^2), smoking history, alcohol consumption history, SES, years of education, ($\log_{10}$) HIV-1 viral load (0 for HIV- and floored at the 19 copy/mL lower limit of assay detection for HIV+ individuals with undetectable viral load), and duration of HIV infection (0 for HIV-).
2. The next set of analyses additionally controlled for individual differences in experienced discrimination to determine the extent to which they contribute to the overall differences observed in African Americans vs. European Americans.
3. In each analysis, all genes showing a point estimate of differential expression > 1.5- fold served as input into higher-order bioinformatics analyses using TELiS promoter sequence analysis (Cole, Yan, Galic, et al., 2005). This analysis tests a priori- specified hypotheses regarding activity of transcription control pathways

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relevant to CTRA biology, including sympathetic neurotransmitter signaling (CREB, measured with TRANSFAC position-specific weight matrix V $CREB_01); the positive CTRA component of inflammation (NF-κB, V $NFKAPPAB_01; AP-1, V$AP1_C); the inverse CTRA component of innate antiviral responses (interferon response factors, IRFs, V$ISRE_01); and the glucocorticoid receptor (GR, V$GRE_C), which is involved in cortisol signaling from the hypothalamus-pituitary-adrenal axis and is sometimes desensitized in association with the CTRA.

4. Each TELiS analysis was conducted using 9 different parametric combinations of promoter DNA sequence length (−300, −600, and −1000 to +200 nucleotides surrounding the RefSeq-designated transcription start site) and transcription factor- binding motif (TFBM) detection stringency (TRANSFAC mat_sim values of .80, .90, and .95) (Cole et al., 2005). Log2-transformed TFBM ratios (comparing prevalence in promoters of up- vs. down-regulated genes) were averaged across the 9 parametric combinations and tested for statistical significance using standard errors derived from bootstrap resampling of linear model residual vectors (controlling for potential correlation across genes).

Individual genes were not tested for statistically significant difference in expression because the goal of this study was solely to assess differences in average expression of sets of genes that reflect common transcription factor influences; for this application statistical significance screening at the individual gene level results in prevalent false negative errors and biases results from the subsequent set-based statistical analyses of transcription factor activity (see analytic results presented in Supporting Information for (Fredrickson et al., 2013)).

3. Results

3.1 Demographic comparisons

Results of demographic and clinical comparisons between African Americans and European Americans are reported in Table 1. African Americans reported fewer years of education than European Americans ($p = .02$), and greater incidences of racial discrimination (higher PED-Q scores) than European Americans ($p = .04$). There was a trend towards higher body mass index among African Americans relative to European Americans ($p = .07$) as well as a trend towards greater prevalence of tobacco use among African Americans compared to European Americans ($p = .07$). Among HIV+ participants, European Americans had a longer duration of known HIV infection than African Americans ($p = .01$).

3.2 Race-related differences in gene regulation (Hypothesis 1: Supported)

To determine whether African Americans showed differential activity of CTRA-related transcription control pathways relative to European Americans, we conducted RNA-sequencing- based transcriptome profiling of circulating white blood cell samples to serve as input into TELiS promoter-based bioinformatics analyses. CTRA-related analyses assess the relative activity of pro-inflammatory transcription factors (NF-κB, AP-1), innate antiviral response transcription factors (IRFs), and transcription factors involved in stress-related

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neuroendocrine signaling pathways (CREB, which mediates beta-adrenergic signaling from sympathetic nervous system catecholamines, and the GR, which mediates cortisol signaling from the hypothalamic- pituitary-adrenal axis). Analyses of differential gene expression controlled for age, gender, body mass index, smoking history, alcohol consumption history, and HIV-1 viral load. Results of these analyses (Figure 1a) indicated significantly greater activity of both pro-inflammatory transcription control pathways in African Americans relative to European Americans (NF-κB: mean +0.63 ± 0.21 log2 TFBM ratio in promoters of up- vs. down-regulated genes, $p = .003$; AP-1: +0.43 ± 0.22, $p = .049$). Results also indicated greater activity of IRF factors involved in Type I interferon antiviral signaling (+0.97 ± 0.47, $p = .041$). Analyses of the two neuroendocrine-related pathways indicated greater activity of GR (+0.84 ± 0.35, $p = .018$) but no significant difference in CREB activity (−0.09 ± 0.42, $p = .813$) in circulating leukocytes from African Americans compared to European Americans.

3.3 *Effect of HIV infection* (Hypothesis 2: Supported)

TELiS analyses were also performed comparing subjects by HIV status. Two transcription control pathways showed increased activity in HIV+ individuals relative to HIV-: NF- κ B (+0.61 ± 0.22, $p = .006$) and IRF factors (+1.25 ± 0.43, $p = .004$).

3.4 *Role of racial discrimination* (Hypothesis 3: Partially supported)

As noted above, African Americans reported experiencing greater levels of racial discrimination than did European Americans (PED-Q-CV mean = 34.3 ± standard deviation 13.2 for African Americans vs. 27.6 ± 10.0 for European Americans; difference, $p = .03$). To determine whether these differences might contribute to race-related difference in CTRA-related transcription factor activity, we conducted a second set of analyses that additionally controlled for PED-Q-CV scores. Results (Figure 1b) indicated that a substantial portion of the total race- related difference in pro-inflammatory signaling may potentially stem from correlated variations in experienced discrimination. Control for PED-Q-CV scores attenuated race-related differences in NF- κ B activity by 34% (+0.42 ± 0.21, $p = .042$), race-related differences in AP-1 activity by 58% (+0.18 ± 0.24, $p = .45$), and race-related differences in IRF activity by 16% (+0.82 ± 0.49, $p = .099$). In analyses of the two neuroendocrine-related pathways, control for PED-Q-CV scores attenuated race-related differences in GR activity by 31% (+0.58 ± 0.39, $p = .140$), whereas CREB continued to show no significant race-related difference in activity (+0.23 ± 0.39, $p = .561$).

3.5. *Interactive effects of HIV and race* (Exploratory Hypothesis; Not supported)

Among the transcription factors that showed significant race-related differences in activity (NF- κ B, AP-1, and GR), the magnitude of those effects did not differ significantly as a function of HIV infection (HIV x Race interaction terms all $p > .10$).

4. Discussion

In the present analyses of leukocyte transcriptome profiles, 1.) African Americans showed higher levels of inflammatory signaling and higher levels of stress-related neuroendocrine signaling than did European Americans, and, 2.) a substantial fraction of the elevated

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inflammatory signaling activity in African Americans may be associated with increased experiences of racial discrimination. These effects were not modified by HIV status. The profile of transcriptional/gene expression differences observed here is consistent with patterns previously observed in studies exploring the relationship between perceptions of the social environment and CTRA gene expression (Fredrickson et al. 2013; Miller et al. 2008, 2009, 2014; Powell et al. 2013). These results are also consistent with previous data linking chronic exposure to environmental stressors, such as perceived racism, to physiological processes such as chronic inflammation (Cunningham et al., 2012; Lewis et al, 2010; Moody et al., 2014). Considering that chronic SNS activation is a major driver of CTRA gene expression, and that SNS activation can result from perceptions of social threat, our findings are consistent with the idea that discrimination is a form of chronic stress. Given that the proportion of gene regulatory variation accounted for by discrimination was substantial in magnitude, it is important to think comprehensively about the various psychosocial factors that track with perceived discrimination such as lack of economic opportunity, personal safety concerns, and maladaptive forms of coping (e.g., drug/alcohol use) that may explain why discrimination effects on health outcomes are robust throughout the literature.

Contrary to our exploratory hypothesis, we did not find that racial differences in transcriptional/gene expression of NF- κ B, AP-1, CREB, and GR was greater in our HIV+ group. These results may be due, in part, to differences in transcription response pathways involved in threat/stress vs. infection, or the shorter duration of known HIV-infection in African Americans relative to European Americans, but they may also stem from a lack of statistical power to determine interactive effects of race and HIV infection given the limited sample size available in this study. Such interactions may exist but simply not be detectable in the present study, which is why the primary focus of this study was not on the interactive effects. Larger samples of HIV+ and HIV- individuals would be necessary for a well-powered analysis of the effects of HIV infection on gene expression overall, and the extent to which infection modifies the impact of race and discrimination on gene expression.

The biological profile of the current findings differs somewhat from another recent transcriptome profiling study that compared leukocyte transcriptome profiles from African Americans and European Americans (McDade et al., 2016). That study of healthy community- dwelling adults from the Chicago metropolitan area found elevated levels of Type I interferon signaling in leukocytes from African Americans but no difference in inflammatory signaling activity. Similar observations emerged from another ancillary analysis of racial differences in leukocyte gene expression profiles (Kohrt et al. 2016). The contrasting pattern observed here may stem from differences in infectious disease background (this study containing a substantial number of clinically-stable but HIV-seropositive individuals) or differences in socio-economic conditions or other environmental conditions that remain to be identified in future research. This report also differs from those analyses in identifying one mediating psychosocial pathway (i.e., the stress of experienced discrimination) for such racial differences in gene expression, whereas the previous studies were solely descriptive of race differences and did not seek to identify their etiology.

Limitations of this study include the cross-sectional study design (which precludes drawing causal conclusions), and the limited sample size, which was sufficient to test this study's a

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priori hypotheses regarding gene set-based bioinformatic assessments of CTRA-related transcription factor activity but was not powered for hypothesis-free discovery of statistically significant race-related differences at the level of individual genes, nor for extensive examination of HIV/race interactions. Future research in larger samples would be required to discover reliable associations of specific gene transcripts with race, and will also be required to evaluate the generalizability of the present findings in other settings. Further, larger samples are needed to examine the role of how intersecting stigmatized identities play a role in discrimination experiences. Discrimination in healthcare settings (particularly in the context of HIV) is not only potentially stressful, but may impact the quality of healthcare that patients receive. It is possible that discrimination due to HIV-status may be more salient for our HIV+ participants. We did not ask about discrimination as a function of HIV status, therefore, this is an area that needs further exploration. Finally, no direct measures of health outcomes are available in this study, so the health significance of the observed transcriptomic differences also remain to be determined in future research. The magnitude of the race-related TFBM ratio signals observed here is relatively large in comparison to other types of psychosocial risk factors (corresponding to 30% or greater asymmetries in TF binding-site prevalence in up- vs. down-regulated genes), but it remains unclear how these biological signaling metrics would translate quantitatively into an increased risk of disease. This study recruited a targeted sub-population of community-dwelling adults and the generalizability of these results to other socio-demographic contexts also remains to be determined in future studies.

These limitations aside, our study findings contribute to the extant literature on racial discrimination and health by demonstrating a potential biological mechanism (i.e., leukocyte gene profiles) through which racial discrimination influences health outcomes, and may partially explain racial disparities in health. With this knowledge, efforts can be directed towards better understanding racial disparities in health, particularly in diseases such as hypertension and cardiovascular disease, which have demonstrated clear racial disparities in prevalence and progression. If racial discrimination is perceived by the larger society as a social “health risk factor” similar to that of smoking, obesity, high blood pressure, and substance abuse, this may promote greater interest in reducing behaviors that may unintentionally disadvantage or discriminate against racial and ethnic minority groups.

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Highlights

- We examined race and HIV differences in transcription activity in pathways relevant to the conserved transcriptional response to adversity
- Relative to European Americans, African Americans showed greater activity of pro-inflammatory transcription control and stress-signaling pathways
- Experienced discrimination accounted for more than 50% of total race-related difference in pro-inflammatory transcription factor activity
- HIV group differences were found in pro-inflammatory and antiviral transcription pathways

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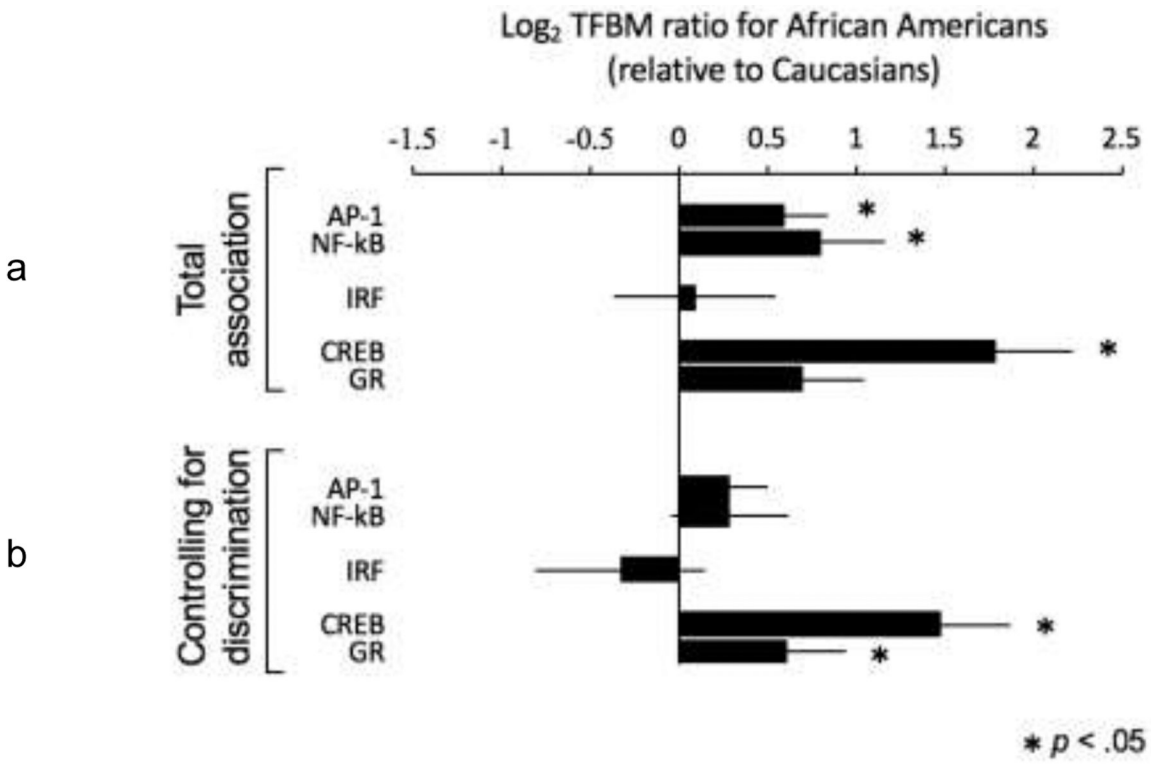

Figure 1.

Relationships between CTRA-related transcription factor activity and race. a: Total association using Log_2 transcription factor-binding motifs ratio. b: Association between CTRA-related transcription factor activity and race/ethnicity after controlling for discrimination.

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Table 1.

Participant demographics (overall and by race) and group statistics for African American compared to European American participants

	Overall sample (n = 71) Mean (SD) or %	African American (*n* = 48) Mean (SD) or %	European American (*n* = 23) Mean (SD) or %	Effect Size	Racial difference *p*-value
Age, years	52.9 (9.9)	52.8 (8.5)	53.2 (12.7)	η^2 = 0.00	.96
Education, years	13.8 (2.3)	13.3 (1.9)	15.0 (2.5)	η^2 =.13	**.02**
Gender				φ =0.34	.08
Male	68%	63%	82%	-	-
Female	29%	33%	18%		
Trans (Male-to-Female)	3%	4%	0		
HIV Status					
% positive	52%	54%	48%	φ =0.08	.50
****Nadir CD4 count, cells/mm^3***	266 (159)	282 (173)	226 (117)	η^2 = .02	.44
****Current CD4 count, cells/mm^3***	645 (271)	608 (285)	737 (220)	η^2 = .05	.20
****Viral load, % undetectable***	66%	64%	80%	φ =0.15	.65
****Self-reported length of HIV infection, years***		14.27 (6.80)	21.20 (8.77)	η^2 = .16	**.01**
BMI, kg/M^2	27.5 (6.4)	28.5 (7.15)	25.4 (3.5)	η^2 =0.05	.07
Tobacco use					
% endorsed use (past 12 months)	29%	35%	14%	φ = 0.27	.07
Alcohol use					.
% endorsed use (past 12 months)	62%	58%	71%	φ =0.12	.30
Socioeconomic Status					
Hollingshead Index Score	2.8 (1.8)	2.1 (1.0)	2.4 (1.2)	η^2 = 0.03	.45
Perceived Stress Score	23.3 (6.7)	23.9 (6.9)	22.0 (6.2)	η^2 = 0.02	.29
Perceived Discrimination Score (PED-Q)	32.2 (29.0)	34.3 (13.2)	27.6 (10.3)	η^2 = 0.06	**.04**

* HIV+ group only