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RESEARCH ARTICLE

Targeted proteomic scan identifies alteration of serum proteins among workers occupationally exposed to low levels of trichloroethylene

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Abstract

Occupational exposure to trichloroethylene (TCE) has been associated with alterations in B-cell activation factors and an increased risk of non-Hodgkin's lymphoma (NHL). Here, we aimed to examine the biological processes influenced by TCE exposure to understand the underlying molecular mechanisms. This cross-sectional molecular epidemiology study included data of 1317 targeted proteins in the serum from 42 TCE exposed and 34 unexposed factory workers in Guangdong, China. We used multivariable linear regressions to identify proteins associated with TCE exposure and examined their exposure-response relationship across categories of TCE exposure (unexposed, low exposed: <10 ppm, high exposed: ≥10 ppm). We further examined pathway enrichment of TCE-related proteins to understand their biological response. Occupational exposure to TCE was associated with lower levels of tumor necrosis factor receptor superfamily member 17 (TNFRSF17; $\beta = -.08$; p-value = .0003) and kynureninase (KYNU; $\beta = -.10$, p-value = .002). These proteins also showed a significant exposure-response relation across the unexposed, low exposed, and high exposed workers (all p-trends < .001, false discovery rate [FDR] < 0.20). Pathway analysis of TCE-related proteins showed significant enrichment (FDR < 0.05) for several inflammatory and immune pathways. TCE exposure was associated with TNFRSF17, a key B-cell maturation antigen that mediates B-cell survival and KYNU, an enzyme that plays a role in T-cell mediated immune response. Given that altered immunity is an established risk factor for NHL, our findings support the biological plausibility of linking TCE exposure with NHL.

KEYWORDS
carcinogenesis, KYNU, non-Hodgkin's lymphoma, proteomics, TNFRSF17, trichloroethylene

Abbreviations: KYNU, kynureninase; NAD, nicotinamide adenine dinucleotide; NHL, non-Hodgkin's lymphoma; RFU, relative fluorescent unit; TCE, trichloroethylene; TNF13B, tumor necrosis factor ligand superfamily member 13B; TNFRSF11A, tumor necrosis factor receptor superfamily member 11A; TNFRSF12A, tumor necrosis factor receptor superfamily member 12A; TNFRSF13B, tumor necrosis factor receptor superfamily member 13B; TNFRSF17, tumor necrosis factor receptor superfamily member 17.

H. Dean Hosgood, Mohammad L. Rahman, Deanna Blansky, and Qing Lan contributed equally to this work.

Luoping Zhang, Roel Vermeulen, Nathaniel Rothman, Bryan A. Bassig, and Qing Lan co-supervised this work.

1 | INTRODUCTION

Trichloroethylene (TCE) is a nonflammable, volatile organic solvent that is commonly used in manufacturing industries as a degreaser and refrigerant, as well as in the textile and dry-cleaning industries. Due to its volatility, TCE evaporates into ambient air from contaminated groundwater and soil. The global burden of disability associated with TCE exposure is among the greatest in Southeast and East Asia. While majority of the countries around the globe set the regulatory standard for occupational exposure of TCE at 10 ppm, biological effects in humans at a lower level of exposure is suspected (Lee et al., 2019). Occupational exposure to TCE has been associated with hematologic malignances, with evidence suggesting an increased risk of non-Hodgkin's lymphoma (NHL; Karami et al., 2013). While previous research among factory workers exposed to TCE found alterations in lymphoid cell types and B-cell activation factors (Bassig et al., 2016; Lan et al., 2010), limited data exist on proteome alterations associated with occupational exposure to TCE, especially at lower levels of exposure. In our current study, we applied an aptamer-based highly multiplexed and sensitive targeted proteomics platform in a well-established worker population to identify serum proteins associated with TCE exposure and characterize these proteins to understand the underlying molecular mechanisms of TCE-induced hematologic malignancies.

2 | METHODS

2.1 | Study design and exposure assessment

Full details of this cross-sectional study assessing effects of occupational TCE exposure have been previously described (Lan et al., 2010). Briefly, 80 workers exposed to TCE were selected from six factories in Guangdong, China. Factories with detectable benzene, styrene, ethylene oxide, formaldehyde, or epichlorohydrin levels were excluded during factory selection. Additionally, individuals with a history of cancer, chemotherapy, radiation, or prior occupational exposure to benzene, butadiene, or styrene were excluded during subject selection. Ninety-six unexposed controls were frequency matched by age (±5 years) and sex from separate factories in the same geographic region that did not use TCE in the manufacturing process, including two clothes manufacturing factories, one food production factory and a hospital. Peripheral blood samples were collected from all participants to assess the biological effects of occupational TCE exposure. For all TCE-exposed factory workers, we collected two to three personal air exposure measurements using a 3M organic vapor monitor 3500. These measurements were collected over the course of a full work shift during a 3-week period before blood collection in TCE exposed workers. Demographic information was collected by questionnaire.

The study was approved by Institutional Review Boards at the Guangdong National Poison Control Center, China, and the National Cancer Institute, United States. All participants have provided written informed consent prior to the study enrollment.

2.2 | Serum proteomic analysis

SOMAscan analysis (SomaLogic, Inc, Boulder, CO) using serum samples was performed on 34 unexposed controls and 42 exposed workers were randomly selected from the full study population at the Center for Human Immunology (CHI), National Institutes of Health. Following the recommended protocol from the manufacturer, 50-µl serum was run in the 1.3k HTS SOMAscan assay (Rohloff et al., 2014), which measures the levels of 1317 targeted proteins. Among the SOMAscan proteins, 47% are secreted proteins, 28% are extracellular domains, and 25% are intracellular proteins, which belong to a wide

TABLE 1 Demographic characteristics of workers exposed to occupational trichloroethylene (TCE) and unexposed controls

Characteristics	Controls ($n = 34$)	Total exposed ($n = 42$)	p-Value[a]
Age in years	22.24 (19.70–26.24)	24.55 (21.60–33.28)	.06
Body mass index	21.23 (19.23–23.05)	21.09 (19.15–23.92)	.81
TCE exposure (ppm)	<0.03 (<0.03–<0.03)	22.29 (11.46–39.58)	<.001
TCE exposure group, *N* (%)			
Low exposed, <10 ppm		9 (21.4)	
High exposed, ≥10 ppm		33 (78.6)	
Sex, *N* (%)			.06
Male	21 (61.8)	34 (81.0)	
Female	13 (38.2)	8 (19.0)	
Current smoker, *N* (%)	12 (35.3)	21 (50.0)	.2
Current alcohol use, *N* (%)	15 (44.1)	16 (38.1)	.6
Recent infection, *N* (%)	6 (17.6)	8 (19.0)	.88

Note: Values are median (interquartile range) except where indicated.
[a]*p*-Values were estimated between controls and exposed groups using either Fisher's exact test (categorical variable) or *t*-test (continuous variable).

range of biological subgroups including receptors, kinases, cytokines, proteases, growth factors, protease inhibitors, hormones, and structural proteins. Each target protein had a corresponding aptamer (SOMAmer) reagent that binds with high specificity. Aptamers were tagged with fluorescent DNA sequences to allow quantification of target proteins via custom hybridization and reported using relative fluorescent units (RFU).

SOMAscan has been validated in several studies that compared proteomic measurements across different platforms (Gold et al., 2010; Higgins et al., 2018) and have demonstrated usefulness for biomarker discovery in many different diseases, including cancers (Ganz et al., 2016; Ostroff et al., 2010; Qiao et al., 2017; Webber et al., 2014). The SOMAscan raw data were processed following the manufacturer's guidelines (Candia et al., 2017). In brief, to remove intra-array hybridization variation, we used hybridization normalization using control probes and to remove sample-to-sample differences within a group, we used median signal normalization within wells and SOMAmers of the same dilution group.

2.3 | Statistical analysis

The distribution of demographic characteristics between TCE exposed and unexposed participants were compared using *t*-test or ANOVA, when appropriate. SOMAscan data were logarithm to base 10 transformed to achieve normality. The intensity of each protein (RFU) was compared between the TCE exposed and unexposed participants in unmatched analysis using multivariable linear regression models, adjusted for age (continuous), sex (male, female), current smoking (yes, no), and batch (two batches). We also considered recent infection and current alcohol use as potential confounders. However, these variables were not associated with TCE exposure and additional adjustment for these variables did not materially change our results. Hence, our final models did not include recent infection and current alcohol use as covariates. Permutation *p*-value, which represents the probability of obtaining a result at least as extreme as the test statistics given the null hypothesis is true were calculated based on 100,000 iterations (Knijnenburg et al., 2009). To account for multiple testing, we applied Benjamini Hochberg's false discovery rate (FDR) (Benjamini et al., 2001). Associations were considered noteworthy for FDR <0.20.

To examine the exposure-response relationship between TCE exposure and serum proteins, we used linear trend tests across categories of TCE exposure, that is, controls, workers exposed to <10 ppm TCE (low exposed) and ≥10 ppm TCE (high exposed), adjusted for covariates mentioned above. This cut point was selected based on the common regulatory standard for occupational exposures limit of 10 ppm (8-h TWA) adopted by American Conference of Governmental Industrial Hygienists (ACGIH) and many countries across the globe (National Academies of Sciences, 2019). We also fit linear models comparing low exposed (<10 ppm TCE) and high exposed (≥10 ppm TCE) groups with controls. We also conducted a sensitivity analysis using a cut point of 12 ppm following our previous analysis in the same population (Lan et al., 2010). Mean differences of proteins across categories

TABLE 2 Mean (SD) serum levels (relative fluorescence unit) of selected SOMAscan proteins and their associations with TCE exposure

SOMAscan proteins	Annotation	TCE exposure (yes, no)					Categories of TCE exposure			
		Controls <0.03 ppm ($n = 34$), mean (SD)	Exposed ($n = 42$), mean (SD)	β	*p*-Value	FDR	Low exposed <10 ppm ($n = 9$), mean (SD)	High exposed ≥10 ppm ($n = 33$), mean (SD)	*p*-Trend	FDR
TNFRSF17	Tumor necrosis factor receptor superfamily, member 17	11,051.52 (2208.23)	9295.78 (2361.66)	−.08	.0003	0.34	11,022.47 (3463.88)	8824.86 (1754.78)	.0001	**0.15**
KYNU	Kynureninase	1495.03 (495.03)	1331.16 (453.71)	−.10	.002	0.34	1706.38 (304.25)	1228.83 (436.13)	.0002	**0.15**

Note: Models were adjusted for age, current smoking, and body mass index.
Abbreviations: SD, standard deviation; TCE, trichloroethylene.

of TCE exposure were tested using linear regression models and plotted using box and whisker plots. Finally, to understand the underlying molecular mechanisms of TCE health effects, we conducted pathway enrichment analysis with TCE-related proteins (p-value < .05, $n = 143$ proteins) using MetaCore, v20.3 (Thomson Reuters; https://portal.genego.com/) (Song & Lee, 2013). We used the pathway maps tool under "One-click Analysis" to identify the enriched pathways involving TCE-related proteins in terms of the hypergeometric distribution, and the p-values were calculated by using the default database as the background.

All computations were performed in R statistical programming environment (version 4.0.2).

3 | RESULTS

Of 42 exposed workers, 33 workers were exposed at or above the regulatory standard for occupational exposures limit of 10 ppm based on the ACGIH (8-h TWA) guideline (National Academies of Sciences, 2019). The distribution of age, sex, body mass index, current smoking, alcohol use, and recent infections were similar between the exposed and control workers (Table 1).

Serum levels of SOMAscan proteins between the controls and exposed workers are presented in Table S1. No proteins were associated with TCE exposure after adjusting for multiple testing. In multivariable adjusted models comparing controls with high exposure group, two SOMAscan proteins, tumor necrosis factor receptor superfamily member 17 (TNFRSF17; FDR = 0.12) and kynureninase (KYNU; FDR = 0.14)—showed a significant association after adjusting for multiple testing at FDR <0.20. These two proteins also showed a significant exposure-response relationship at FDR for trend test <0.20 (Table 2, Table S2). Specifically, the mean serum levels for TNFRSF17 among the controls, low exposed (<10 ppm), and high exposed (≥10 ppm) workers were 11.05×10^3, 11.02×10^3, and 8.82×10^3 RFUs, respectively (p-trend = .0001, FDR = 0.15) (Table 2, Figure 1). Similarly, the mean serum levels of KYNU among the controls, low exposed and high exposed workers were 1.50×10^3, 1.71×10^3, and 1.23×10^3 RFUs, respectively (p-trend = .0002, FDR = 0.15). Sensitivity analysis using the 12-ppm cut point for TCE exposure demonstrated similar findings (Table S3). When we compared controls with low exposed group (<10 ppm TCE), another member of the tumor necrosis factor receptor superfamily, TNFRSF1A showed the strongest association (p-value = .006) with TCE exposure, although the association was not significant after adjusting for multiple testing (FDR = 0.76). Pathway analysis of 143 TCE-related proteins (p-value < .05) showed significant enrichment for over 50 pathways—more than a third represented immune and inflammatory response pathways and a few pathways related to oxidative stress-induced signaling pathways (Table 2, complete results are presented in Table S4).

4 | DISCUSSION

In this cross-sectional study of 42 factory workers with well-characterized TCE exposure and 34 unexposed controls, we assessed 1317 serum proteins measured using a highly sensitive proteomics platform and identified several proteins associated TCE exposure in a dose-dependent manner. Specifically, occupational TCE exposure was associated with lower serum levels of TNFRSF17, a key B-cell maturation antigen that mediates B-cell survival and KYNU, an enzyme that plays an important role in immune response mediated through T-cell apoptosis. Pathway enrichment analysis identified that TCE-related proteins were enriched in immune and inflammatory pathways, suggesting that immune regulation and inflammation may play a role in biological response to TCE exposure.

The TNF superfamily of ligands and receptors are mediators of cell proliferation and hematopoiesis (Aggarwal, 2003), and are involved in the pathogenesis of hematologic malignancies (Younes & Aggarwall, 2003). TNFRSF17 is preferentially expressed in mature B lymphocytes and are thought to be important for B cell development and autoimmune response. TNFRSF17 acts as a B-cell maturation antigen and has been shown to specifically bind to the B-cell activating factor (TNFSF13B) to mediate B-cell survival and maturation. Interestingly, we found suggestion that TNFSF13B was also associated with TCE

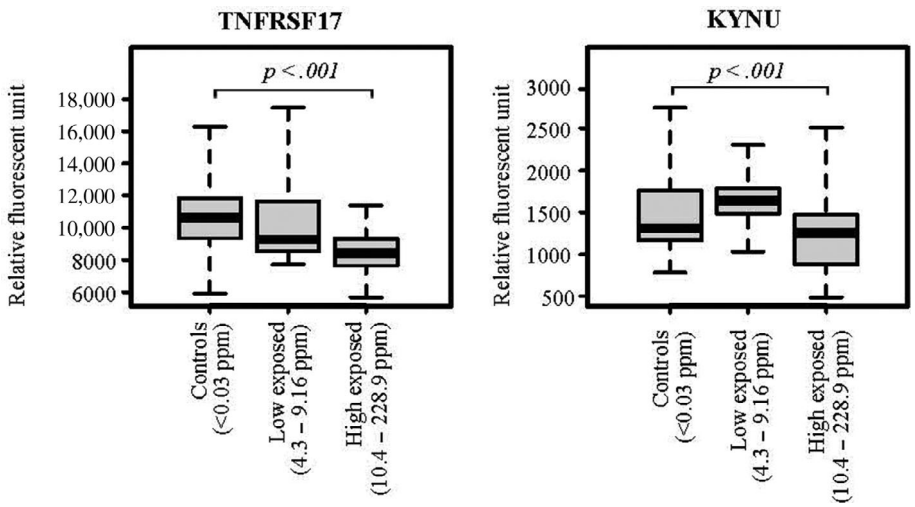

FIGURE 1 Box and whisker plots showing mean (95% confidence intervals) serum levels (relative fluorescence unit) of TNFRSF17 and KYNU across among 0 = unexposed controls; 1 = low exposed (<10 ppm); and 2 = high exposed (≥10 ppm) workers. Mean protein levels between trichloroethylene exposure categories were tested using linear regression models, adjusting for age, sex, smoking status, and analysis batch.

TABLE 3 Summary of enrichment analysis by top 10 pathway maps between the controls and TCE-exposure workers

Pathway maps	Proteins involved in the pathway[a]	FDR
Regulation of degradation of deltaF508-CFTR in CF	SUMO-2, SUMO-3, Ubiquitin, Sti1, HSC70, HSP70, UCHL1, E2I	2.8E-09
Immune response_TLR2 and TLR4 signaling pathways	MEK1/2, p38 MAPK, E2N(UBC13), Ubiquitin, IL-1 beta, IL-8, MSK1/2 (RPS6KA5/4), p90Rsk	3.0E-07
Immune response_HMGB1/RAGE signaling pathway	MEK1/2, p38 MAPK, IL-1 beta, IL-8, MIP-1-alpha, p90RSK2(RPS6KA3), FAK1	6.8E-07
Immune response_HSP60 and HSP70/TLR signaling pathway	MEK1/2, p38 MAPK, E2N(UBC13), Ubiquitin, IL-1 beta, IL-8, HSP70	7.8E-07
HSP70 and HSP40-dependent folding in Huntington's disease	Ubiquitin, Sti1, HSC70, HSP70, SGTA	3.4E-06
Release of pro-inflammatory mediators and elastolytic enzymes by alveolar macrophages in COPD	Leukocyte elastase, p38 MAPK, IL-1 beta, IL-8, MIP-1-alpha	6.2E-06
IL-17 and IL-17F-induced inflammatory signaling in normal and asthmatic airway epithelium	p38 MAPK, MSK1, MEK2(MAP2K2), IL-8, p90Rsk	6.2E-06
PDE4 regulation of cyto/chemokine expression in inflammatory skin diseases	MEK1/2, p38 MAPK, MSK1, IL-1 beta, IL-8, 14-3-3	7.8E-06
Oxidative stress_ROS-induced cellular signaling	GSTP1, p38 MAPK, Catalase, IL-1 beta, IL-8, E2I, KEAP1, Chk2	9.1E-06

Note: For complete results, please see Table S4.
[a]A total of 143 proteins that showed a significant trend (p-trend < .05) with TCE exposure were included in pathway analysis.

exposure at the level of p-trend = .02 (FDR = 0.31) (Table S3). Further, among many pathways enriched in TCE-related proteins, several TNF-related proteins, including TNFRSF17, TNFRSF11A, TNFRSF12A, and TNFRSF13B were involved in immune pathways, suggesting immune regulation playing a role in biological response to TCE exposure. Our findings suggest that TNFRSF17 may be involved in the underlying mechanism by which occupational TCE exposure influences immune response pathways. Furthermore, our findings shed light on how TCE may influence hematopoiesis, which is biologically plausible given that TNFRSF17, TNFRSF13B, and TNFSF13B were upregulated in NHL cases compared to healthy controls (He et al., 2004; Shen et al., 2016).

KYNU is a pyridoxal-5′-phosphate dependent enzyme that catalyzes the cleavage of L-kynurenine and L-3-hydroxykynurenine into anthranilic and 3-hydroxyanthranilic acids, respectively. KYNU is also involved in catabolism of tryptophan, leading to the biosynthesis of an important redox cofactor, nicotinamide adenine dinucleotide and several other biologically active metabolites. It has been reported that the KYNU pathway is often systematically up-regulated when the immune response is activated (Chen & Guillemin, 2009). The KYNU pathway also plays an important role in regulating immune response mediated via T-cell apoptosis (Fallarino et al., 2003; Mezrich et al., 2010; Munn et al., 1999). Understandably, prior studies have linked KYNU with lymphoid malignancies, including NHL (Masaki et al., 2018; Morita et al., 2021). In this study, TCE exposed workers had lower levels of KYNU compared to unexposed controls, suggesting a potential role of KYNU in the etiology of TCE-related lymphoid malignancy.

Our study has some limitations. We do not rule out the chance of false positive findings given the small sample size and the number of proteins assessed despite applying FDR to account for multiple testing. Hence, our results should be considered exploratory and ideally be replicated in a larger study. Our results may not be generalizable to non-occupational cohorts or occupational cohorts exposed to a different level of exposure to TCE. A key strength of our study was the utilization of an aptamer-based assay to quantify over 1300 plasma proteins in a well-established worker population with comprehensive data on TCE exposures.

In conclusion, our findings provide insight into the biological plausibility of the role of TCE exposure on disease pathophysiology. Given the role of TNFRSF17 in key B-cell maturation and survival pathways, and of KYNU in T-cell apoptosis and lymphoid malignancies, our findings support a biologic plausibility of the link between TCE and NHL. However, our results should be interpreted with caution given the limited sample size and confirmatory studies with larger sample size is warranted (Table 3).

AUTHOR CONTRIBUTIONS

Qing Lan and Nathaniel Rothman designed the study and supervised data collection. Mohammad L. Rahman prepared the analysis plan and analyzed the data. H. Dean Hosgood, Mohammad L. Rahman, and Deanna Blansky wrote the manuscript. All authors contributed to the interpretation of the results and revision of the manuscript for important intellectual content and approved the final version of the manuscript. H. Dean Hosgood, Mohammad L. Rahman, and Qing Lan are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data.

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CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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