Proximity to uranium mine waste on the Navajo Nation increases serum ANA and IL17

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INTRODUCTION

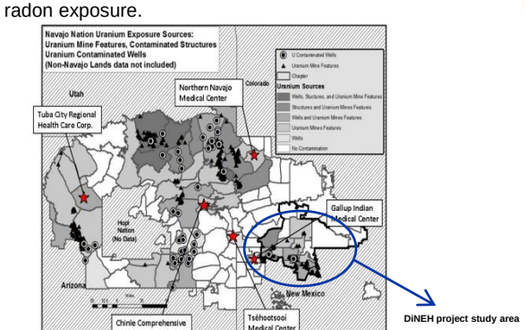
From 1948 to 1986, hundreds of uranium mining and milling operations were conducted on Navajo Nation lands. More than 1,000 un-remediated and abandoned uranium mines and associated waste sites remain, leaving a legacy of potential mining waste exposure through drinking water and soil contamination, and from living in homes built with materials containing mining waste. The adverse health outcomes that can be directly attributed to *chronic environmental exposure to legacy mine waste are not well established*.

On the Navajo Nation, uranium ore grade ranges from about 0.12 - 0.25% uranium (U) with concomitant high amounts of other potentially toxic metals such as arsenic (As) and cadmium (Cd), and locally high concentrations of selenium (Se), molybdenum (Mb) and manganese (Mn) (1,2). Prior studies conducted by the University of New Mexico (UNM) Diné Network for Environmental Health (DiNEH) team (J. Lewis, PI), and the New Mexico Department of Health, have consistently shown elevation of urine uranium with median, 75th and 95th percentiles elevated by several fold to nearly an order of magnitude above the NHANES cohort (3), The Navajo Nation Environmental Protection Agency in collaboration with CDC reported 42% of participants in one community study with urine uranium exceeding the NHANES 95th percentile, with elevations in arsenic over NHANES 95th percentiles reported for some participants as well (4).

STUDY COHORTS

1. The DiNEH project is a partnership formed between the UNM CEHP, Southwest Research and Information Center (SRIC), and Navajo Area Indian Health Services (NAIHS), in collaboration with 20 chapters of the Eastern Agency of Navajo Nation to investigate the contribution of chronic, low-level community exposures to uranium waste on kidney disease, hypertension and diabetes (NIEHS RO1 ES14565).

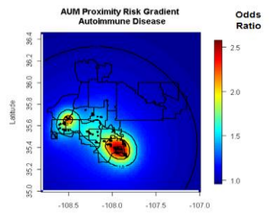
2. Navajo Birth Cohort Study (NBCS) is a collaborative effort between the UNM CEHP (J. Lewis, PI), NAIHS, the Navajo Nation and the CDC/ATSDR to examine the impact of uranium exposures on birth outcomes and early child development on Navajo Nation. Exposure assessments include quantification of 36 metals in blood and urine specimens, in-home assessments of metals in house dust and radon exposure.



DiNEH project study area

BACKGROUND DATA

Living in proximity to mine waste was associated with increases in reported autoimmune disease.



Gradient of increased odds ratio of autoimmune disease within the DiNEH project study area based on proximity to abandoned uranium mine (UAM) waste sources.

In the chapters with the highest number of mines (n=41), 20% of participants reported autoimmune disease, while only 0 to 2% reported autoimmune disease in chapters with less than 4 mines.

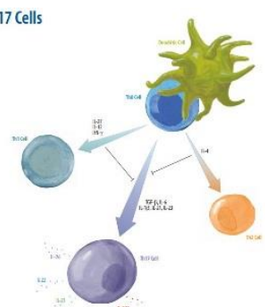
48% of individuals in the DiNEH cohort were positive for the presence of serum antinuclear antibodies (ANA) compared to an ANA prevalence of 13.8% for the US population as a whole.

ANA positivity in the DiNEH samples were statistically predicted by both the proximity and the participants' urine As levels (p=.0073), suggesting that environmental exposures increase risk for autoimmune biomarkers such as ANA.

HYPOTHESIS

***Our overall hypothesis is that environmental exposure to mixed metal legacy mine waste within the Navajo leads to alterations in immune responses or immune dysregulation resulting in increases in TH17 activity and autoimmunity*.**

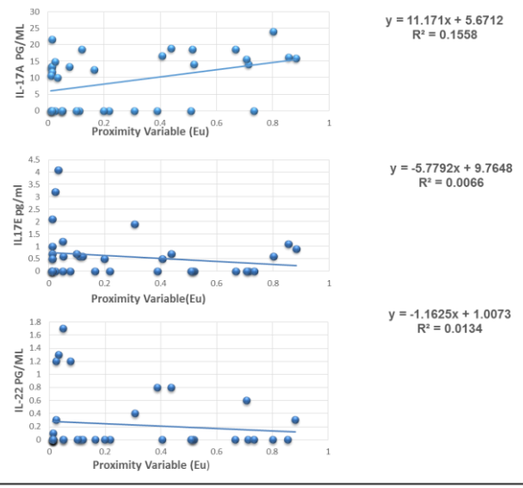
Th17 Cells



IL17-producing Th17 cells have been associated with the pathogenesis of autoimmune diseases and other inflammatory conditions such as multiple sclerosis, rheumatoid arthritis, psoriasis, and SLE.

RESULTS

IL17A, but not IL17E or IL22, increases with increasing proximity score



The proximity variable in the model (Eu) was calculated by the inverse distance of residence from each waste source in the study area, weighted by its surface area.

Using a reduced regression model:
IL-17A = (intercept) + A_M*M +A_{lEu}*log(Eu) + (error)

IL-17A increases were predicted by the proximity variable with a β= 1.77 and p=0.014

ANA in NBCS COHORT

# NBCS Samples Tested (20 Male/20 Female) Average Age=27	# Females positive/ # Males Positive	Overall Incidence of ANA
40	4/4	8/40 (20%)

Half of the ANA positives (4/8, 50%) had speckled patterns of staining. Serum from patients with diffuse systemic sclerosis may produce speckled nuclear staining or nucleolar staining. In patients with SLE, homogeneous, speckled, or nucleolar staining patterns may be observed.

CONCLUSIONS

Serum cytokine IL-17 analysis demonstrates a significant association between environmental uranium and legacy waste exposure and increased production of IL-17A (β= 1.77 and p= 0.014) which supports the hypothesis that exposure to a low, chronic level of mining waste can modify immune responses, potentially toward induction of autoimmune disease.

While the presence of ANA itself is not a diagnosis of disease this degree of positivity is a concern. Molecular markers of autoimmunity can precede clinical symptoms or any other signs of disease development years or even decades earlier.

Higher than expected prevalence of ANA is observed in the NBCS cohort (average age 27), with 20% of preliminary samples testing positive (n=40).

FUTURE STUDIES

Analyze all 268 serum samples from DiNEH project for Th17 family cytokines based on these preliminary results. We will also perform cytokine cluster analysis (all 268 samples have been analyzed for 13 key cytokines). With larger sample sizes, we can determine if increases in Th17 activity is associated with ANA, urinary As or U levels and other chronic disease conditions reported in this population.

Analyze NBCS samples for ANA and Th17 family of cytokines. With the NBCS study we have extensive biomonitoring data for 36 metals in blood and urine which will allow us to determine the effect of specific metal exposure on Th17 responses in an affected population.

ACKNOWLEDGEMENTS

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