Military occupations with and without presumed jet fuel exposures and miRNA expression following military deployment

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Clinical Significance

Many military personnel are exposed to jet fuel, yet the long-term biological and health effects remain poorly understood. MicroRNAs, which regulate gene expression and shift in response to environmental stressors, are emerging as potential biological response indicators to extended jet-fuel exposure that can negatively impact health outcomes.

Introduction

- Military members have occupational exposures to airborne contaminants, such as jet fuel, that could increase the risk for negative health outcomes
- Select military occupations (aircraft maintenance, refuelers) are expected to have elevated exposures to jet fuel, compared with the general US population
- Health conditions can be influenced from a biological perspective based on changes in biological signaling molecules, including microRNAs (miRNAs)
- Research on miRNAs is relatively new, but past military and Veteran studies on miRNA have investigated cancers, ALS, and posttraumatic stress disorder

Methods

- Military exposure after deployment was estimated using military occupation specialty from Millennium Cohort Study (MCS) records and categorized according to the Veteran Affairs Long-Term Impact of Fuel Exposure (LIFE) study
- Post-deployment serum samples were obtained from the Department of Defense Serum Repository
- Serum miRNA was extracted (Qiagen) and processed with untargeted sequencing (Illumina)
- Optimized extraction methods for serum retrieved from 12–20 years of storage in non-RNA-specific tubes
- miRNA was extracted from 1,191 samples with, 1,039 high-quality samples retained after sequencing
- miRNA data were processed in CLC Genomics Workbench to generate reads, group similar sequences, and annotate to miRBase, followed by differential expression analysis
- Differentially abundant miRNAs and associated pathway changes were further analyzed using Qiagen Ingenuity Pathway Analysis (IPA)

Results

1. Eleven miRNAs showed significantly different abundance based on presumed exposure for both Navy and AF

- Observed shift in miRNAs for jet fuel exposure more prevalent in Navy personnel (n = 17), as compared to Air Force (AF) (n = 1)
- miRNA differential expressed between jet fuel exposed and control based on sex and race:
  - Navy: Black/Male (n=5), White/Male (n=21), Black/Female (n=13), White/Female (n=2)
  - AF: Black/Male (n=2), White/Female (n=2)
- In the jet fuel-exposed group, compared with the control, we observed:
  - Downregulation of miRNAs (miR-184, miR-133a-3p) associated with oxidative stress
  - Downregulation of miRNA (miR-184, miR-133a-3p) associated with DNA methylation indicates potential epigenetic modifications
  - Reduced miRNAs (miR-184, miR-133a-3p, miR-29a-5p) associated with neuronal survival and mitochondrial integrity

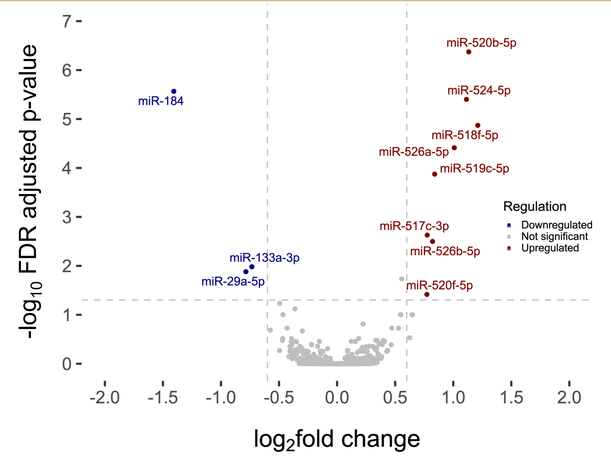

Figure 1. Up (red) and down (blue) regulation of significant miRNA, Air Force and Navy

2. miRNA linked to five biological processes and eight diseases and functions significantly altered in the exposure group

- All eight diseases and functions identified using the full miRNA data set were downregulated in the exposed group
- Three miRNA that were significantly downregulated targeted 29 experimentally observed human biological agents

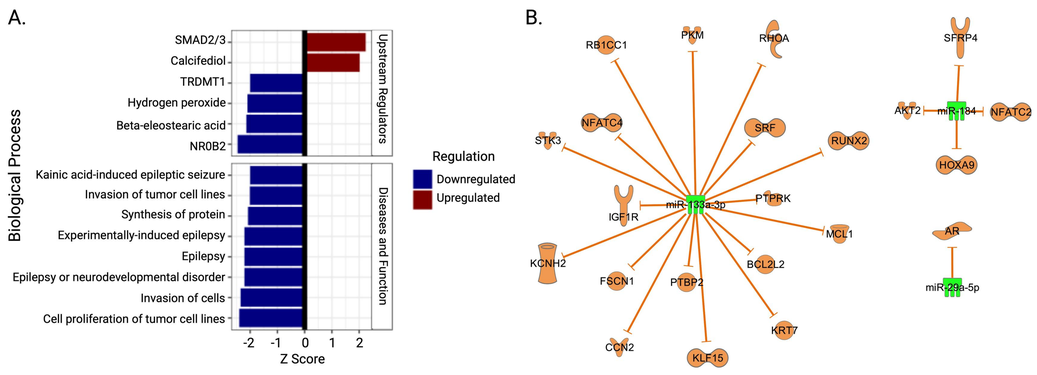

Figure 2. A. Biological processes associated with miRNAs in Air Force and Navy and B. Network diagram of three downregulated miRNAs.

Conclusions

Jet fuel exposure was associated with the dysregulation of key miRNAs related to neurotoxicity. Conceptually, our results are consistent with jet fuel exposure causing oxidative stress and mitochondrial dysfunction, resulting in miRNA dysregulation. Continued chronic exposure could lead to epigenetic remodeling and neuroinflammation, increasing the risk of chronic inflammation and negative health outcomes. These findings may facilitate clinical intervention trials that incorporate personalized approaches to mitigating exposure effects.

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