The Effects of Whole Life, Low Dose Cadmium Exposure on Mouse Lung Histology and DNA Damage Repair

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A One Environmental Health Approach

We pursue a One Environmental Health approach, focusing on genomic stability.

We minimize occupational and environmental heavy metal exposure, which requires long-term administration of low doses. We use chemical carcinogen tests and "Omics" technologies combined with the One Environmental Health Approach (i.e. using wildlife and ecosystems to inform about human health) to gain insight into the function, persistence, and cellular heritability of metal-induced genetic instability and changes in DNA damage repair and their role in lung cancer. We translate discoveries in our cell culture models to responses in animal models. The integration of our models, from cells and rats to human and whole is key to answering our research questions about the molecular mechanisms for metal-induced lung cancer.

We perform a thorough characterization of the overall effects of cadmium on the lung, performing histological analysis of formalin-fixed paraffin-embedded lungs. This analysis will reveal any changes in the amount of collagen present, indicating progression towards inflammation or other disease states.

One of the major events leading to heavy metal carcinogenesis is DNA damage. Changes in the ability to repair DNA damage have been associated with carcinogenic mechanisms. To determine if cadmium exposure leads changes in DNA damage repair, protein levels of Rad51 were measured in lung tissue from mice exposed to cadmium.

Aim 1: Characterize Cadmium-Induced Changes in Cellular Structure and Morphological Assays

As an initial characterization of the overall effects of cadmium on the lung, we performed histological analysis of formalin-fixed paraffin-embedded lungs. This analysis will reveal any changes in the amount of collagen present, indicating progression towards inflammation or other disease states.

What we did:

- Sections from mice lungs treated with 0, 0.5, or 1 ppm cadmium were H&E stained to look at cellular morphology. No changes in self proliferation or morphology were seen at 0.5 ppm cadmium. At 1 ppm, small changes in cell morphology were seen. These changes were seen throughout the lung sections and showed mesenchymal consistent with the development of adenomas.

What we found:

- Structural changes were seen in the 5 ppm high dose cadmium exposure group compared to that of the control group. Alterations include several differences seen in multiple slices of the lung. These data suggest the development of adenomas. Structural changes in lung tissue consistent with a carcinogenic outcome.

Future work aims at continuing the analysis of expression levels of various proteins involved in the repair of DNA damage. Any proteins showing changes in expression will be analyzed for changes in mRNA levels. Changes in chromosome instability will also be assessed. Results will lead to the first reports of the impact of cadmium on DNA damage and repair in the lung.

Aim 2: Effect of Cadmium-Induced Tissue Remodeling and Repair

Analysis of cohort and case-control studies among general and occupational populations.

Why we did it:

- As part of the characterization of the overall effects of cadmium on the lung, we performed fibrosis analysis of formalin-fixed paraffin-embedded lungs. This analysis will reveal any changes in the amount of collagen present, indicating progression towards inflammation or other disease states.

What we did:

- Sections from mice lungs treated with 0, 0.5, or 1 ppm cadmium were PSR stained to look increases in the presence of collagen. No changes in the levels of collagen were seen at 0.5 ppm cadmium. At 1 ppm, small increases in collagen were seen. These changes were seen throughout the lung sections and showed mesenchymal consistent with the development of adenomas.

What we found:

- Collagen staining analyses between the control groups and the cadmium exposed groups showed no significant difference in the amount of collagen present in the lung tissue. These data indicate that cadmium exposure did not induce fibrosis or inflammation to cause tissue remodeling.

Future work aims at continuing the analysis of expression levels of various proteins involved in the repair of DNA damage. Any proteins showing changes in expression will be analyzed for changes in mRNA levels. Changes in chromosome instability will also be assessed. Results will lead to the first reports of the impact of cadmium on DNA damage and repair in the lung.

Aim 3: Measure Cadmium-Induced DNA Damage

Testing increasing concentrations of cell-type from cultured mouse cells showed that the Rad51 antibody used reacts to the active antigen and signals increases in protein expression levels.

How we did it:

- Western blot analysis was then performed for the DNA damage marker Rad51.

What we did:

- Western blot of paraffin tissue extract from lungs of cadmium-exposed mice shows an increase in Rad51 protein expression with increasing amounts of cadmium exposure.

What we found:

- Increasing amounts of Rad51 in higher doses of cadmium suggest that DNA Damage occurs and is linked to repair in lung tissue if exposed to cadmium. Low, low dose cadmium and increases with higher cadmium exposure.

Further Reading


Project Overview

Aim 1: Characterize Cadmium-Induced Changes in Cellular Structure and Morphological Assays

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