Chloroethylaziridine-Induced Xenobiotic Metabolism Gene Expression in the Mouse Lung

Mackenzie Dickson
Chemotherapy: 
Cyclophosphamide (CPA)

- FDA approved in 1959

- Treats breast, ovarian, blood, lung, lymph, nerves, eye, bone marrow and skin cancers
  - Neuro- and retinoblastoma most common in kids
  - Also treats autoimmune disorders like lupus

- Administered via injection or orally
  - Length of treatment varies based on response, dose and stage of disease, e.g. weeks in cancer patients to years for those suffering from lupus
Bioactivation of CPA:

- Cyclophosphamide (CYPs 2B, 3A)
- Aldophosphamide
- 4-Hydroxycyclophosphamide (HOCP)
- Phosphoramide Mustard (PM)
- N-2-Chloroethylaziridine (CEZ)
5-Year Cancer Survival Rates Have Increased

- All cancers:
  - 68% compared to 50% in 1977

- Breast cancer:
  - 90% compared to 63% in the 1960s

- Childhood cancer:
  - 80% compared to less than 50% before the 1970s
Obesity Contributing to Cancer

- 34.9% of adults in America are obese
- 40% of cancer cases are due to obesity

Center for Disease Control, 2014
http://www.cdc.gov/obesity/data/adult.html
http://www.cancer.gov/cancertopics/factsheet/Risk/obesity
Hypothesis

PM exposure results in CEZ production and that lung tissue is being exposed to CEZ, which would activate a cellular protective response.
Study Design

Treatments:
LNCT = Lean control (DMSO:saline)
LNPM = Lean PM
OBCT = Obese control (DMSO:saline)
OBPM = Obese PM

Jackson Laboratories
No apparent impact of CEZ on lung morphology
Investigation of altered drug metabolism gene expression

RNA isolation

Convert to cDNA

Amplify the DNA
Genes investigated

- Microsomal epoxide hydrolase (mEH)
  - Action can increase or decrease toxicity of a drug

- Super Oxide Dismutase 1 (SOD1)
  - Detoxifies reactive oxygen species (free radicals)
  - SOD2 was investigated but did not amplify

- Glutathione S-Transferase isoforms mu & pi (GSTmu & GSTpi)
  - Add glutathione to compounds for detoxification
Obesity increases

Insulin

IRS-1

PI3K

Causes increase in drug metabolism genes

mEH

Hydrolysis allows for activation or excretion

GSTpi

GSTmu

Aides in excretion

PM and CEZ

GSH

Excretion

PM and CEZ
$mEH$ is increased by obesity and PM exposure
Obesity or PM do not impact lung Sod1 expression.
Lung *Gstmu* is unaffected by obesity or PM exposure
Lung *Gstpi* is not impacted by obesity or PM.
Result Summary

- mEH:
  - Obesity increased mRNA level, with additional increase in PM-treated obese mice

- SOD1, GSTmu and GSTpi:
  - No significant results, too much variation
  - Numerically obese control is higher than lean control suggesting potential effect of obesity on lung gene expression
Conclusions

- Lung metabolism activation suggests chemical exposure, likely CEZ

- Obesity impacts metabolism gene expression in the mouse lung

- Lung response to PM was accelerated with obesity
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Questions?