Fetal alcohol exposures promote the development of aggressive tumors in the endocrine glands

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Alcohol and Cancer Risk

1. A large number of reports now show that alcohol consumption in adult increases the chance of developing certain cancers (e.g., Head and Neck, Esophageal, Liver, Breast, Colorectal). The more alcohol a person consumes, the higher their risk of developing some kinds of cancers.

Alcohol exposure *in utero* increases susceptibility to mammary tumorigenesis in rat offspring?

**Study-I**
- Sacrificed at 1 month of age
- Induction of Mammary Cancer by NMU (50 days of age)
- Sacrifice after 4 months

**Study-II**
- Sacrificed at 1 month of age
- Induction of Mammary Cancer by NMU (50 days of age)
- Sacrifice after 4 months
Animals exposed to alcohol *in utero* exhibit increased mammary gland proliferation.

Polanco et al., ACER (2010)
Alcohol exposure in utero increases the risk of developing mammary cancer

Alcohol exposure *in utero* results in more ER negative mammary tumors following MNU treatment

Polanco et al., ACER (2010)
Alcohol exposure *in utero* results in more lung metastasis of mammary tumors cells (MAD B106)

Zhang et al., ACER, 2016
Alcohol exposure *in utero* increases susceptibility to prostate tumorigenesis in rat offspring.

Alcohol-Fed (AF) or Pair-Fed (PF) or Rat chow-Fed (AD)

- Study-I
  - Induction of Prostate Cancer by NMU +T4 (3 months of age)
  - Sacrifice after 6 months of age

- Study-II
  - Induction of Prostate Cancer by ER-45 +T4 (4 months of age)
  - Sacrifice after 6 months
Effect of fetal alcohol exposure on prostate histopathology of offspring

Study-I

Histopathology

Cell proliferation

Murugan et al. ACER, 2014
Fetal alcohol exposure and prostate tumorigenesis of rat offspring

Study-II

Histopathological Changes

Expression of cell proliferation marker (ki-67)

Murugan et al. ACER, 2014
Fetal alcohol exposure and prostate tumorigenesis of rat offspring

Study-III - ER-45 (3.4 mg/kg) + T4 (2 mg/kg)

Tumor growth

H&E showing hyperchromatic cells

Increased fatty acid synthase

Jabbar et al., unpublished
Alcohol exposure *in utero* increases susceptibility to pituitary tumorigenesis in rat offspring.

**Alcohol-Fed (AF) or Pair-Fed (PF) or Rat chow-Fed (AD)**

Alcohol (6.7% v/v) or pair-fed liquid diet between ED7-21

**Female offspring (F1)**

Treated with estradiol at 3 months of age

Induction of pituitary adenoma

Tumor study at 1-4 months of age
Alcohol exposure *in utero* increases susceptibility to pituitary tumorgenesis in rat offspring

MRI of Pituitary Glands showing volume differences

Wynne and Sarkar, Unpublished
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring.

Jabbar and Sarkar, unpublished
Alcohol exposure \textit{in utero} increases susceptibility to form aggressive pituitary tumors in rat offspring.

Jabbar and Sarkar, unpublished
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring.

Jabbar et al., Sci Report, 2017
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring

Jabbar et al., Sci Report, 2017
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring.

Fetal alcohol exposure increases master transcription factors which control epithelial-to-mesenchymal transition.

Jabbar and Sarkar, unpublished
Quantitative real-time PCR (qRT-PCR) of rats pituitary tumor tissues demonstrate the activation of Frizzled2/Wnt signaling.
Summary and Conclusion

1. These results show that endocrine cells of mammary gland, prostate gland or pituitary gland of fetal alcohol-exposed rats develop hyperplasia (a marker for preneoplasia) during aging and form aggressive tumors following carcinogens challenge.

2. Tumor cells of alcohol-fed rats often acquire aggressive and metastatic tumorigenic behaviors, express multipotency stem cell regulators and Wnt signaling genes.

3. Together the data suggest that fetal alcohol exposure programs the endocrine cells to develop aggressive tumors possibly due to increase in stem cell niche within the tumor microenvironment.
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