Diet, metabolic disease and cancers in mouse models

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Cancer risk and metabolic disease

+ and =
Diet-induced obesity: Gene - diet interactions

- B6 on HFHS
- A/J on HFHS
- B6 on LFLS
- A/J on LFLS

Body Weight (grams)

Age (days)

N ~ 25, Error Bars = 1 SD

HF: 58% kcal coconut oil
LF: 11% kcal coconut oil
Calorically balanced

B6 - obese only with a HFHS diet
A/J - lean regardless of diet
Long-term effects of high fat diet

Mean Weight (grams)

Age (days)

HCC
20 of 34

No NASH
No HCC
Non-alcoholic steatohepatitis (NASH) in B6 but not A/J mice

- steatosis (40% of liver mass is lipid)

after 100 days on high fat, but not low fat diet

- hepatitis (inflammation)
- fibrosis
- limited cirrhosis

after 400 days
Diet-induced malignant transformation and hepatocellular carcinoma (HCC)

Cycles of cell damage, death and regeneration eventually lead to transformation, NASH - the 'fertile soil' in which transformation occurs.
Hepatocellular carcinoma (HCC)

• 3rd most common cause of cancer death worldwide
• Rapidly growing cause of cancer death in U.S.
• Risk factors:
  1. Hepatitis B or C
  2. Chronic alcohol use
     \[\text{\{~70\% of cases\}}\]
     (Ken Tanabe, MGH personal communication)

• Remaining 30\% of “unexplained” cases are frequently associated with obesity, diabetes, non-alcoholic steatohepatitis
HCCs in humans and mice

1. Biochemistry
2. Histology
3. mRNA profiles

1. Molecular pathways (Myc and NFkB)
2. miRNA profiles (X-linked cluster)
3. Predicted mRNA targets of miRNAs

Liver necrosis, cell death
Liver steatosis
Liver proliferation
Hepatocellular carcinoma
Cardiac degeneration, cell death

Similar features in humans and mice
Diet-switch prevents HCC

- No NASH
- No HCC
- No death
- Sudden death

- 135 days
- 35 days

Graph showing mean weight (grams) vs. age (days) with different lines representing different conditions.

Legend:
- HCC
- No NASH
- No HCC
- No death
## Metabolic Syndrome, NASH, HCC

### On High Fat, High Sucrose Diet:

<table>
<thead>
<tr>
<th></th>
<th>B6</th>
<th>A/J</th>
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</thead>
<tbody>
<tr>
<td><strong>Obesity</strong></td>
<td>√</td>
<td>X</td>
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<tr>
<td><strong>Hypertension</strong></td>
<td>√</td>
<td>X</td>
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<tr>
<td><strong>Insulin Resistance</strong></td>
<td>√</td>
<td>X</td>
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<tr>
<td><strong>Cardiovascular Disease Risk</strong></td>
<td>√</td>
<td>X</td>
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<tr>
<td><strong>Non-alcoholic steatohepatitis</strong></td>
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</tbody>
</table>

### Genetics of disease vs. Genetics of health

J. Nadeau and E. Topol, Nat. Genet. 2006; Shao et al. PNAS; JHN et al, in prep
HCC summary

Diet-induced, rather than genetically-engineered or carcinogen-induced

Similar pathology and molecular features

Two pathways in one strain on the same diet

Diet switch reverses outcome

A similar diet modification may have important implications for prevention of HCCs in humans
HCC questions

Genetic control of susceptibility
  chromosome substitution strains

Mechanisms of transformation
  engineered mutant genes and alternative fats

Diet switch effects
  physiological mechanisms

Interventions
  drugs and diets

Biomarkers
Eric Lander, Nate Berger, John Lambris, Mark Daly, Colleen Croniger, Aris Economides, Ken Tanabe, and Shankar Subramaniam