Obesity, Energy Balance and Cancer Prevention

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Aim: Inhibit the development of cancer through pharmacological intervention before the appearance of a clinically detectable tumor.

From Greenwald, et. al., Cancer, 1990
The US Obesity Epidemic (JAMA 10/9/02)

- 64.5% of US Adults Overweight – body mass index (BMI) >25.0 kg/m²
- 30.5% US Adults Obese – BMI > 30.0 kg/m²
- ~5% US Adults Extremely Obese – BMI > 40.0 kg/m²
• A nation out of energy balance: the scope of the obesity problem in the US
• Energy balance and cancer studies in transgenic mouse models: IGF-1 as a molecular target
• Effect of energy balance modulation on gene expression
Prevalence of *Obesity Among U.S. Adults
BRFSS, 1987

*Obesity defined as  BMI > 30

Mokdad, et al., 1999
Prevalence of *Obesity Among U.S. Adults
BRFSS, 1991

*Obesity defined as BMI > 30

Mokdad, et al., 1999
Prevalence of *Obesity Among U.S. Adults
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Prevalence of *Obesity Among U.S. Adults
BRFSS, 2000

*Obesity defined as BMI > 30
### Cancers Associated with Obesity

#### In Women
- Breast (postmenopausal)
- Endometrium
- Cervical
- Ovarian
- Colorectal
- Kidney
- Liver/Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

#### In Men
- Prostate
- Colorectal
- Kidney
- Liver/Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

ACS, 2002
Nutrition and Molecular Carcinogenesis Section, NCI Laboratory of Biosystems and Cancer
The Multi-Disciplinary Approach to Cancer Prevention Research

Animal Model Studies

Basic Molecular/Cellular Studies

Identify Risk Factors & Mechanisms

Clinical/Epidemiologic Studies

Behavioral Studies

Effective Human Interventions
Central Question

Can we offset increased cancer risk due to a genetic lesion (e.g., loss of p53 tumor suppressor function) by preventive approaches?

(Focus: diet, energy balance)
The Accumulation of Genetic Alterations in Human Colon Carcinogenesis
Energy Balance and Cancer Prevention

Energy in
- Amount
- Type
- Pattern

Energy Balance

Energy out
- Physical Activity
- Growth
- Storage
- Routine Metabolism
- Thermoregulation
p53-/- Mice

Attractive tumorigenesis model since tumor development is:

- spontaneous
- rapid
- relevant to human cancer
- responsive to interventions?
The Effect of 40% Calorie Restriction on Body Size in p53-/- Mice

p53-knockout (p53-/-) mice fed ad libitum (AL) or calorie restricted (CR) for 4 weeks.
The Effect of 40% Calorie Restriction on Survival in p53-/- and p53+/+ Mice


IGF-1 (ng/ml) : 648 373 660 365
Calorie Restriction Extends Lifespan and Delays Neoplasia in Multiple Species

- p53-/- Mouse: 44%
- p53+/+ Mouse: 37%
- C3B10RF1 Mouse: 56%
- Sprague-Dawley Rat: 32%
- F344 Rat: 39%
- Labrador Retriever: 16%
- Hereford Cow: 35%

The Effect of Dietary Restriction on Spontaneous Tumorigenesis in Aged Male p53+/- Mice

Study start: all mice 9-10 months of age

## Treatment Effects on Serum IGF-1 and Leptin Levels in p53+/− Mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IGF-1 (ng/ml)</th>
<th>Leptin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>514 ± 14</td>
<td>15.9 ± 1.9</td>
</tr>
<tr>
<td>Calorie Restriction</td>
<td>387* ± 30</td>
<td>4.9* ± 1.1</td>
</tr>
<tr>
<td>1-Day/Week Fast</td>
<td>463* ± 17</td>
<td>19.6 ± 1.5</td>
</tr>
</tbody>
</table>

* p (versus control) < 0.05

Summary: Models Responsive to Anti-Obesity Interventions

- **p53-/-, p53+/-, p53+/+** (spontaneous HN’s, sarcomas)
- **p53+/-:** \( p \)-cresidine (6-month bladder model)
- **BK5.IGF-1 TG:** \( p \)-cresidine (6-month bladder model)
- **p53+/- x MMTV-\( Wnt-1 \) TG** (spont. mammary tumors)
- **C3(1) -Large T Antigen TG** (spont. mammary tumors)
- **p53+/-:** AOM (chemically-induced intestinal tumors)
- **APC^{Min}** mice (spontaneous intestinal tumors)
Insulin-like Growth Factor (IGF)-1 and Cancer

• IGF-1 regulates mitogenic and apoptotic rates of epithelial cells

• High serum levels of IGF-1 are significantly associated with risk of several cancers: prostate (Chan, et al., Science 1998); premenopausal breast (Hankinson, et al., Lancet, 1998); lung (Wu, et al., JNCI, 1999); leukemia (Petridou, et al. Int J Cancer, 1999); bladder (acromegaly; Higuchi, et al., Endocr J, 2000)

Approach: Low-dose carcinogen induction in p53+-/- mice

- \( p \)-cresidine, 4-aminobiphenyl (bladder)
- azoxymethane (colon)
- PhIP (colon, prostate)
- MNU (mammary; lymphoma)
p-Cresidine

- 2-methoxy-5-methylbenzeneamine
- intermediate in azo dyes
- dye industry: high bladder cancer rate
The Effect of Diet Restriction (+/- IGF-1) in p-Cresidine-Treated p53-Deficient Mice

A. Graph showing IGF-1 levels in AL, DR, and DR +/- IGF-1 treatments.

B. Graph showing incidence of transition cell carcinoma in AL, DR, and DR +/- IGF-1 treatments.

C. Graph showing average % BrdU positive nuclei/500 cells counted per mouse.

D. Graph showing ratio of apoptotic cells/total cells counted in hyperplasia.
NCI Nutrition and Molecular Carcinogenesis Section

Breaking Open the Black Box

Microarrays

Ad Lib v. CR v. CR + IGF-1
### Effects of CR + IGF-1 on Gene Expression

<table>
<thead>
<tr>
<th>IGF-I (µg/day)</th>
<th>% Calorie Restriction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>×</td>
</tr>
<tr>
<td>2</td>
<td>×</td>
</tr>
<tr>
<td>0</td>
<td>×</td>
</tr>
<tr>
<td>40</td>
<td>×</td>
</tr>
<tr>
<td>80</td>
<td>×</td>
</tr>
</tbody>
</table>

5 mice per group, all females, 5 wks old at surgery
### Number of Genes Changed with Increasing CR

<table>
<thead>
<tr>
<th>Percent Calorie Restriction</th>
<th>Mean of number of genes changed &gt;2-fold and statistically significantly different</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>955</td>
</tr>
<tr>
<td>30%</td>
<td>1092</td>
</tr>
<tr>
<td>40%</td>
<td>1222</td>
</tr>
<tr>
<td>Increased by CR:</td>
<td>Sultn</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>Sth2</td>
</tr>
<tr>
<td></td>
<td>Mgst3</td>
</tr>
<tr>
<td></td>
<td>Gstt2</td>
</tr>
<tr>
<td></td>
<td>Gsta2</td>
</tr>
<tr>
<td></td>
<td>Amd1</td>
</tr>
<tr>
<td></td>
<td>Mt1/2</td>
</tr>
<tr>
<td></td>
<td>Gadd45</td>
</tr>
<tr>
<td></td>
<td>Igfbp1</td>
</tr>
</tbody>
</table>

| Decreased by CR:         | Hsd3b5 | Hydroxysteroid dehydrogenase 3b5 |
|                         | Hsd17b2| 17b Hydroxysteroid dehydrogenase |
|                         | EGFR   | Epidermal growth factor        |
|                         | COMT   | Catechol O-Methyltrasferase    |
|                         | CycD1  | Cyclin D1                     |
IGF-1-Dependent Gene Expression Changes (30% CR versus 30% CR + IGF-I)

- 58 genes differentially expressed
- 27 restored to ~AL control level

Examples of IGF-I-Dependent Changes
- promote cell survival (Gadd45a; CycD1)
- promote gene transcription (Onecut1, Foxa2)
- decreased cell adhesion (dsc2)
- IGF pathway (IGF BP1)
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QuickTime™ and a Photo - JPEG decompressor are needed to see this picture.
Summary: Interventions

- Calorie restriction (chronic) + IGF, leptin
- 1-day/week fast (cyclical restriction)
- Treadmill/ running wheel exercise
- Chemopreventive steroids (DHEA, fluasterone)
- Chemopreventive nutrients/agents (soy, 4-HPR, Se, NSAIDs/COX inhibitors)
- Combinations? (CR + exercise; CR + chemopreventives; chemopreventives + vaccines)
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