Obesity, Energy Balance and Cancer: Mechanistic Insights from Transdisciplinary Studies

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University of Texas at Austin

and

Professor, Department of Molecular Carcinogenesis
University of Texas MD Anderson Cancer Center
Today’s Presentation

• Lessons from mice: molecular targets and strategies for breaking obesity-cancer links
  - Growth factors and their signals
  - Adipokines and their signals
  - Inflammatory signals

• Translation of mechanistic insights through transdisciplinary, multilevel research
LOOMING QUESTION:
How to Decrease Cancer Risk in the ~700 Million Adults Worldwide Currently Obese?

Need a mechanistic approach to identify targets and strategies to break obesity-cancer links
Cancer: A Complex Foe

Obesity impacts the essential aberrations of cancer

Dysregulated growth signals and cellular energetics

Evading growth suppression, apoptosis and immune surveillance

Limitless replicative potential

Sustained angiogenesis

Inflammation

Genomic instability

Tissue invasion and metastasis

Adapted from: Hanahan & Weinberg, Cell (2000) and Cell (2011)
Modeling Energy Balance and Human Cancer in Mice by Altering Key Genes and Pathways

Hursting, et al., *Mutation Res*, 2005
Growth Factor Levels and MMTV-Wnt-1 Mammary Tumor Growth in Lean, Overweight and Obese Mice

<table>
<thead>
<tr>
<th></th>
<th>IGF-1 (ng/ml)</th>
<th>Insulin (pg/ml)</th>
<th>Leptin: Adiponectin</th>
<th>Tumor Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR (30%)</strong></td>
<td>390</td>
<td>380</td>
<td>0.2</td>
<td>120</td>
</tr>
<tr>
<td>(29% body fat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overweight</strong></td>
<td>526</td>
<td>398</td>
<td>0.6</td>
<td>510</td>
</tr>
<tr>
<td>(35% body fat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIO</strong></td>
<td>718</td>
<td>596</td>
<td>1.8</td>
<td>1485</td>
</tr>
<tr>
<td>(47% body fat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=12 mice/group


Dr. Nomeli Nunez
Transplanted Wnt-1 Tumor Growth in AZIP/F-1 (Fatless) Mice Versus Wild-Type Mice

Hursting et al., Cancer Res, 2007
Genetic Reduction of Systemic IGF-1

~75% of IGF-1 in serum is produced by liver

Ecuadorians with Laron Syndrome have very low IGF-1 and inflammatory cytokines, increased longevity, and virtually no cancer or diabetes. NY Times 2/16/11.
Energy Balance Effects on Transplanted Mammary Tumor Growth in Liver IGF-1 Deficient (LID) Mice

Diet Effects on Final Tumor Volume in LID Mice

Ford, et al. *Endocrine-Related Cancer*, 2013

Dr. Nikki Ford

Days after tumor cell injection

Tumor Vol (mm³)
IGF-1 Infusion or mTOR Activation Impacts Transplanted MMTV-Wnt-1 Mammary Tumor Growth in Calorie Restricted Mice

Nogueira et al. *Endocrine-Related Cancer*, 2012
Dietary Energy Balance Modulation of Akt/mTOR Signaling (normal and tumor tissue)

Skin
Liver
Prostate
Colon
Pancreas
Mammary

Hursting, et al., Cancer Res, 2007
Moore, et al., Cancer Prev Res, 2008;
Olivo-Marston, et al., Mol Carcinogenesis 2009
deAngel, et al., Mol Carcinogenesis, 2013
RAD001 (Afinitor®) Inhibits mTOR and Wnt-1 Mammary Tumor Growth in Lean, Control and Obese Mice

Cancer: A Complex Foe

Obesity, CR impact the essential aberrations of cancer

- Dysregulated growth signals and cellular energetics
- Evading growth suppression, apoptosis and immune surveillance
- Sustained angiogenesis
- Limitless replicative potential
- Inflammation
- Genomic instability
- Tissue invasion and metastasis

Dietary Energy Balance Modulates Epithelial-to-Mesenchymal Transition and Tumor Progression in Murine Claudin-Low and Basal-like Mammary Tumor Models

Sarah M. Dunlap¹, Lucia J. Chiao¹, Leticia Nogueira¹, Jerry Usary², Charles M. Perou²,³, Lyuba Varticovski⁴, and Stephen D. Hursting¹,⁵

(75% CD44⁺/24⁻/Aldefluor⁺) (2% CD44⁺/24⁺/Aldefluor⁺)

EMT® migration, invasion

Cells become ‘mesenchymal’ (invasive and migratory) and then differentiate to a new cell type in another location.

Dynamics of epithelial tissues: epithelial-mesenchymal transition (EMT)
Inflammation and Cancer

• Malignancies often arise from areas of chronic infection and inflammation

• Chronic inflammatory conditions linked to tumorigenesis include:
  - Gastritis (H. Pylori) – Gastric Cancer
  - Cystitis – Bladder Cancer
  - Bronchitis – Lung Cancer
  - Esophagitis – Esophageal Cancer
  - Dermatitis – Skin Cancer
  - Ulcerative colitis – Colon Cancer
  - Inflammatory bowel disease – Colon Cancer
  - Hepatitis (including NASH) – Liver Cancer
  - Pancreatitis – Pancreatic Cancer
  
  (up to 55-fold increased risk)
BK5.COX-2 Transgenic Mouse Model of Pancreatitis-Induced Pancreatic Tumors

- 100% pancreatitis by 3-4 months
- 20% spontaneous adenocarcinoma by 9 months in normoweight mice

Obesity increases (CR decreases):
- Pancreatic steatosis
- Pancreatitis
- Malignant conversion
- Serum insulin, IGF-1 levels
- Serum inflammatory cytokine levels
- IGF-1R/Akt/mTOR signaling
- NF-kB signaling

Multistep Pancreatic Cancer Progression Model


©2000 by American Association for Cancer Research
Effects of Dietary Energy Balance on PanIN and Pancreatic Adenocarcinoma Development in Kras Ink4a<sup>+</sup>/<sup>-</sup> Mice

<table>
<thead>
<tr>
<th>Diet Groups</th>
<th>Interim Timepoint (10wks)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% Calorie Restriction (CR)</td>
<td>n=15</td>
<td>n=25</td>
</tr>
<tr>
<td>Control (CON)</td>
<td>n=15</td>
<td>n=25</td>
</tr>
<tr>
<td>Diet-induced Obesity (DIO)</td>
<td>n=15</td>
<td>n=25</td>
</tr>
<tr>
<td><strong>Total Mice:</strong></td>
<td><strong>45</strong></td>
<td><strong>75</strong></td>
</tr>
</tbody>
</table>

**Primary Endpoints:** Prevalence of PanIN/PDACs, fibrosis, inflammation, and atypia; tumor-free survival

**Pathological Assessment at 10-Week Time Point**

### A. Incidence of pancreatic lesions

<table>
<thead>
<tr>
<th></th>
<th>No lesion</th>
<th>PanIN-1</th>
<th>PanIN-2</th>
<th>PanIN-3</th>
<th>PDAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DIO</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

n=15

**CR**
mostly normal; some PanINs

**Control**
mix of normal, PanINs, PDAC

**DIO**
mix of PanINs, PDAC

---

### B. Prevalence of pathological indices

**Incidence of fibrotic lesions (%)**

**Incidence of atypia (%)**

**Level of metaplasia (%)**

**Infiltration of inflammatory cell (%)**

Dietary Energy Balance Affects Pancreatic Tumor-Free Survival in Kras Ink4a⁺/- Mice

% Survival

Kras^{G12D}/Ink4a⁺/-

DIO increases, CR decreases:
- Pancreatic steatosis
- Serum INS, IGF-1 levels
- Serum Leptin:Adpn
- Serum cytokine levels
- IGF-1R/Akt/mTOR signaling
- NF-kB signaling

Lashinger, et al., Cancer Prev Res 2013
IGF-1 and Leptin Modulate NF-κB Signaling in Pancreatic and Colon Tumor Models

Translational Example: CR and Exercise Pilot Trial in Obese Postmenopausal Women

28 High Risk Women:
BMI >30 kg/m²
No HRT

RPFNA

6-month NHLBI Step 1 Diet/Exercise

Repeat RPFNA

Response Biomarkers

FNA Tissue Markers
RPPA; qRT-PCR; insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

Proliferation (Ki-67)

Mammographic Breast Density

Serum
insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3
Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10% weight loss in postmenopausal women

Carol J. Fabian · Bruce F. Kimler · Joseph E. Donnelly · Debra K. Sullivan · Jennifer R. Klemp · Brian K. Petroff · Teresa A. Phillips · Trina Metheny · Sonya Aversman · Hung-wen Yeh · Carola M. Zalles · Gordon B. Mills · Stephen D. Hursting

Change in Serum Biomarkers by Weight Loss Group

- Adiponectin
- Leptin Ratio
- IGF1:IGFBP3 Ratio
- SHBG
- CRP
- HGF
- PAI-1
- Free E2 & Test

* * Significant change within group
Changes in Benign Breast Tissue (FNA) Biomarkers After 6-Month Diet and Exercise Intervention in Obese Women

Table 7 Summary of favorable adipocytokine, mRNA, and proteomics changes in benign breast tissue, showing number of paired specimens exhibiting either a decrease or an increase in value

<table>
<thead>
<tr>
<th>Biomarker (assay method)</th>
<th>Total cohort</th>
<th>Weight loss &lt;10 %</th>
<th>Weight loss &gt;10 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Dec</td>
<td>No. Inc</td>
<td>Change over time, $P$ value $^b$</td>
</tr>
<tr>
<td>Adiponectin:Leptin Ratio (Luminex)</td>
<td>3 21</td>
<td>0.003</td>
<td>2 9</td>
</tr>
<tr>
<td>pS2 (RT-qPCR)</td>
<td>12 5</td>
<td>0.035</td>
<td>2 5</td>
</tr>
<tr>
<td>CyclinB1 (RPPA; Epitomics 1495-1$^a$)</td>
<td>16 2</td>
<td>0.001</td>
<td>8 1</td>
</tr>
<tr>
<td>Rb pS807-S811 (RPPA; CST 9308$^a$)</td>
<td>14 4</td>
<td>0.005</td>
<td>6 3</td>
</tr>
<tr>
<td>S6 pS235-S236 (RPPA; CST 2211$^a$)</td>
<td>14 4</td>
<td>0.004</td>
<td>7 2</td>
</tr>
</tbody>
</table>

Bold denotes statistically significant results

$^a$ Antibody source and catalog number: CST Cell Signaling Technology

$^b$ Wilcoxon signed rank test (2-tailed) assessment of change in values over time (Pre-study to Post-Study)

Mechanisms Underlying the Obesity-Cancer Link: 2013?

Microenvironment (EMT, CSCs)

Obesity and Cancer: Emerging Mechanistic Targets

S. Hursting and M. Hursting.
Arterioscler Thromb Vasc Biol, 2012
Acknowledgements

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Can the Adverse Effects of Obesity on MMTV-Wnt-1 Mammary Tumor Progression be Reversed by Modest Weight Loss?

Figure 1. Wnt tumor transplant

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Lean</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Weight</td>
<td>a</td>
<td>b</td>
</tr>
</tbody>
</table>

Wnt tumor transplant

DeAngel, et al., in preparation
The Effects of Obesity on MMTV-Wnt-1 Mammary Tumor Progression Are Not Reversed by Restoring Weight to Overweight Control Levels

Potential mechanism: persistent mTOR activation (mTOR inhibitors decrease tumor progression in obese and former obese mice)

DeAngel, et al., in preparation