Obesity and Energy Metabolism in Breast Cancer Progression Using Molecular Tools

Dorothy Teegarden, Ph.D.
Professor and Associate Dean for Research, Department of Nutrition Science, College of Health and Human Sciences
Obesity and Cancer

Prospective Study
900,000 men and women
Excess Weight Linked to
90,000 US Cancer Deaths
Annually!

Excess body fat may account for $\frac{1}{4}$ to $\frac{1}{2}$ of the occurrence of many frequent cancers


- Uterus
- Kidney
- Esophagus
- Gallbladder
- Colon and rectum
- Breast
- Liver
- Pancreas
- Prostate
- Cervix
- Ovary
- Stomach (men)
- Non-Hodgkin Lymphoma
- Multiple Myeloma
Postmenopausal Women
Obesity is Associated with
Increased Risk for Breast Cancer

- Smallest vs largest waist circumference reduces risk by 24%
- Reducing weight reduces risk

Premenopausal Women
Breast Cancer Risk

Reduced risk with increased weight

but

obesity in premenopausal is
associated with aggressive tumor
phenotype

Obesity and Breast Cancer: Global and Complex
Obesity and Energy Metabolism

Mechanistic Links

Breast Epithelial Cell

Proliferation
Evasion of apoptosis
Energy Metabolism
(Warburg+)

Metastasis

Taubes, Science 335, 2012; Prieto-Hontoria, et al., BBA, 2011;
Metabolic Reprogramming in Proliferating and Cancer Cells

Growth Factors

O$_2$

Glucose

Glycolysis

Lactate

TCA Cycle

ATP

Drug Inhibitors

Oncogenes

• Nucleotides
• Amino acids
• Lipids
• NADPH

Warburg Effect

Red: Decrease
Green: Increase
Obesity and Energy Metabolism
Mechanistic Links

Adipose
- Glucose/Glutamine
- Insulin/IGF
- ROS
- Mitochondrial Dysfunction

Adipokines

Sex hormones

Inflammatory Cytokines

Breast Epithelial Cell
- Proliferation
- Evasion of apoptosis
- Energy Metabolism (Warburg+)

Taubes, Science 335, 2012; Prieto-Hontoria, BBA, 2011
Breast Cancer Prevention and Energy Metabolism

Cell Model

MCF10A Human Breast Epithelial cells:

- MCF10A cells (untransformed)
- MCF10A-ras cells (Harvey-ras oncogene transfected, 30% of all cancer)
Approaches for Studying Cellular Glucose Metabolism

- Real-time trans-membrane glucose/oxygen flux measurement *(Dr. Marshall Porterfield, Bindley Bioscience Center, Purdue)*
  - Highly sensitive micro biosensor in self-referencing mode
  - Enzyme-based nanoprobe

- Metabolic profiling by nuclear magnetic resonance (NMR) analysis *(Dr. Daniel Raftery, University of Washington)*

- \[^{13}\text{C}_6\]glucose kinetics by gas chromatography-mass spectrometry (GC-MS) *(Dr. Brian Bequette, University of Maryland)*

- Biochemical methods: Enzyme assay, RT-PCR, protein expression, etc.

Alterations in Glucose Metabolism in MCF10A-ras cells

Need for higher glucose levels = ‘glucose addiction’

Enzyme Abbreviations:
- HK: Hexokinase
- PGK1: Phosphoglycerate kinase 1
- PKM: Pyruvate kinase
- LDH: Lactate dehydrogenase
- PDH: Pyruvate dehydrogenase
- PDK1: Pyruvate dehydrogenase kinase 1
- PC: Pyruvate carboxylase

Anticancer Effects of Vitamin D

- Inhibits proliferation
- Induces apoptosis
- Induces differentiation
- Inhibits angiogenesis
1,25(OH)$_2$D Reduces Oxygen Uptake in MCF10A-ras Cells

* Statistically significant relative to vehicle of the same cell type, P< 0.05.
** Significant difference between MCF10A-ras and MCF10A cells treated with vehicle (P < 0.05).

Zheng et al. 2013, JSBMB. 138C:81

1,25(OH)$_2$D Reduces Glucose Uptake in Response to Increasing Glucose in MCF10A-ras Cells
1,25(OH)₂D Reduces Glycolytic Flux in MCF10A-ras Cells

**[¹³C]glucose flux**

**Intracellular Level of PEP Relative to Vehicle**

- **MCF10A**
  - Vehicle: 0.8 ± 0.1
  - 1,25(OH)₂D: 1.2 ± 0.2

- **MCF10A-ras**
  - Vehicle: 1.0 ± 0.2
  - 1,25(OH)₂D: 1.5 ± 0.3

*Statistically significant relative to vehicle of the same cell type, P< 0.05.

Zheng et al. 2013, JSBMB. 138C:81
1,25(OH)\(_2\)D Reduces Lactate Production in MCF10A-ras Cells

* Statistically significant relative to vehicle of the same cell type, P< 0.05.

** Significant difference between MCF10A-ras and MCF10A cells treated with vehicle (P < 0.05).

Zheng et al. 2013, JSBMB. 138C:81
1,25(OH)₂D Regulates Glucose Metabolism in MCF10A-ras cells

Zheng et al. 2013, JSBMB. 138C:81
Critical Periods of Exposure and Risk of Breast Cancer

- **Birth**: Number of end-buds
- **Puberty**: Branching and Differentiation
- **Menopause**: Resting, differentiated mammary gland with cycles of proliferation (monthly), branching and differentiation followed by involution (pregnancy)

Genomic imprinting

Imprinting possible in small portion of the glandular epithelium
Imprinting in entire or large portions of ductal systems
Imprinting in whole gland or entire ductal systems

Maternal Exercise During Pregnancy Reduces Risk of Mammary Tumorigenesis in Rat Offspring

Wei Zheng¹, Ignacio G. Camarillo², Leon Clah², Xuanzhu Zhou¹, Brienna Larrick¹, Nicole Blaize³, Emily Breslin³, Shawn S. Donkin⁴, Timothy P. Gavin³, Sean Newcomer³ and Dorothy Teegarden¹

Departments of ¹Nutrition Science, ²Biological Sciences, ³Health and Kinesiology, ⁴Animal Sciences, Purdue University

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Maternal Exercise and Breast Cancer Risk

- Several developmental windows exist when mammary gland is more susceptible to tumorigenesis, including pregnancy and prenatal period (Friedenreich et al., 2001, Epidemiology).

- Dietary or behavioral modifications in pregnancy may impact embryonic environment thus the risk of breast cancer in generations of offspring (De Assis et al., 2012, Nat Commun; Cho et al., 2012, Carcinogenesis).
Maternal Exercise Impact on Mammary Tumorigenesis in Rat Offspring (pups) Experimental Design

Female Sprague-Dawley Rats

Pregnant ~21 days

Distance (km/day)

Birth

3 weeks

Weaning

6 weeks

15 weeks

MNU Injection

Pups

Pregnant pups

Dams

Locked running wheel

Unlocked running wheel

Housed individually

Sedentary (n=4)

Exercise (n=7)

3 weeks

Locked running wheel

Standard chow

Housed individually


- Exercised dams ran on average 2.0±0.2 km/d during pregnancy.
- No difference in body weight between sedentary and exercised dams during pregnancy.
Maternal exercise during pregnancy reduces the risk of carcinogen induced mammary tumorigenesis in the offspring, and may be an effective behavioral modification for cancer prevention.
Complex Problems

Interdisciplinary, Innovative, Global Solutions

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