

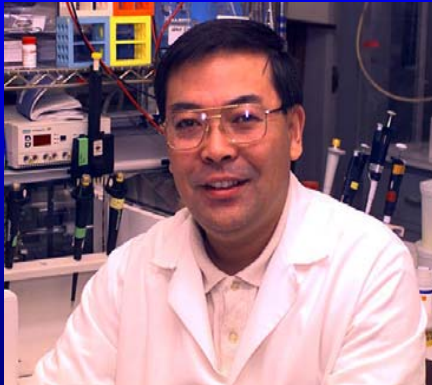


Dietary Energy Intake, Exercise and Energy Sensing In the Regulation of Carcinogenesis

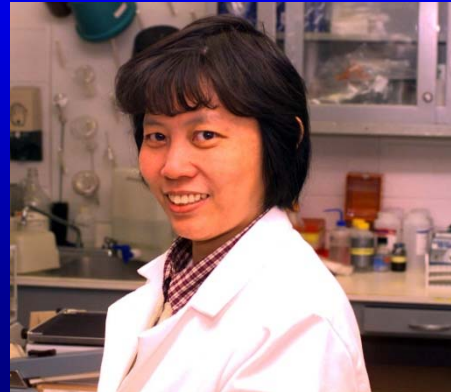
Henry J. Thompson
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Zongjian Zhu

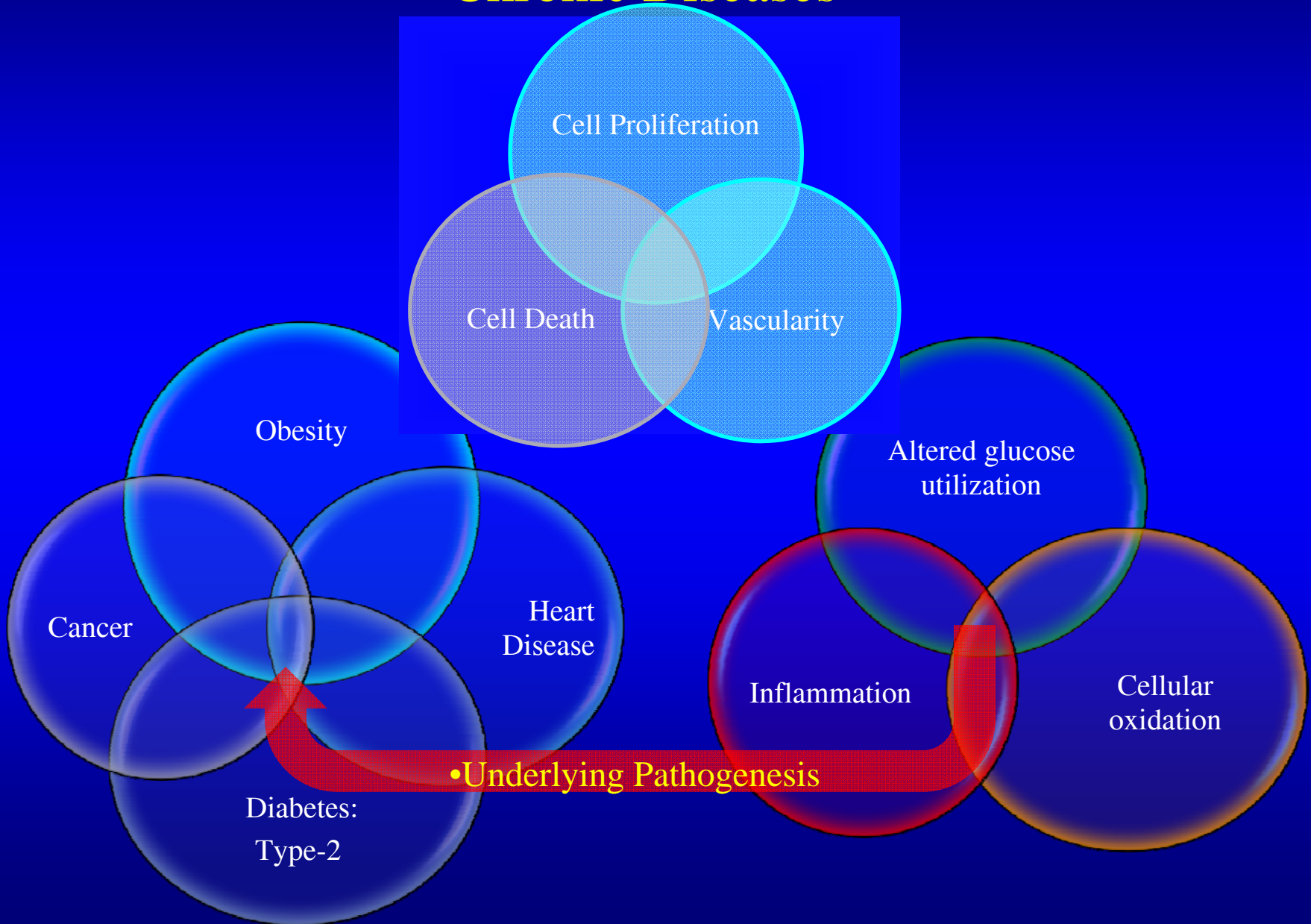


Weiqin Jiang

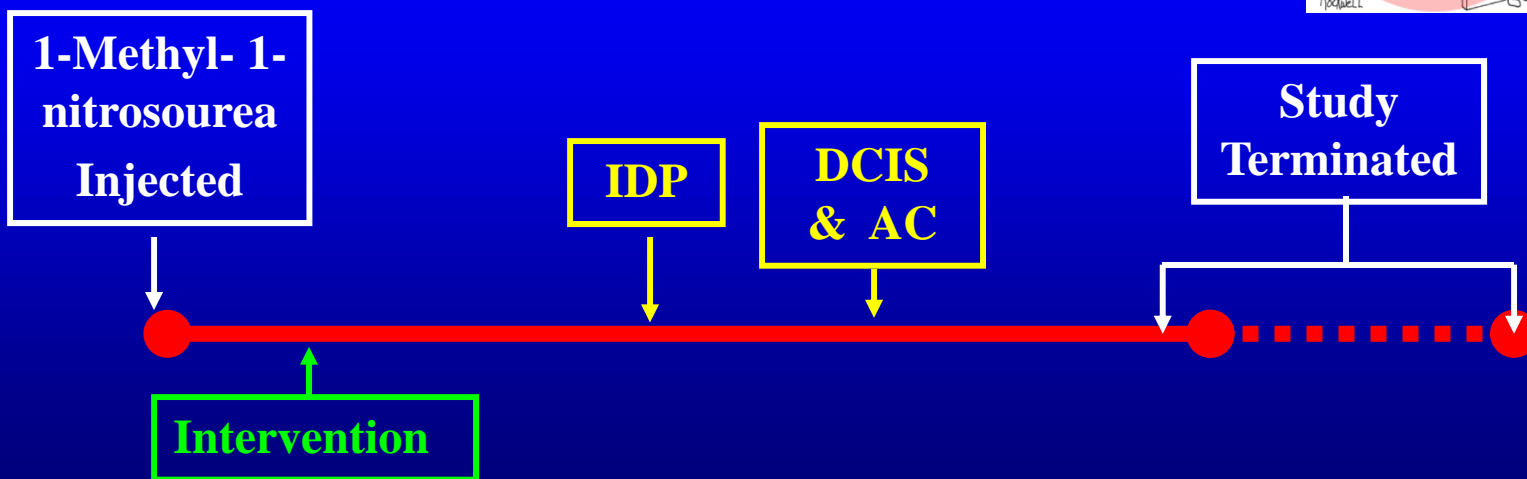
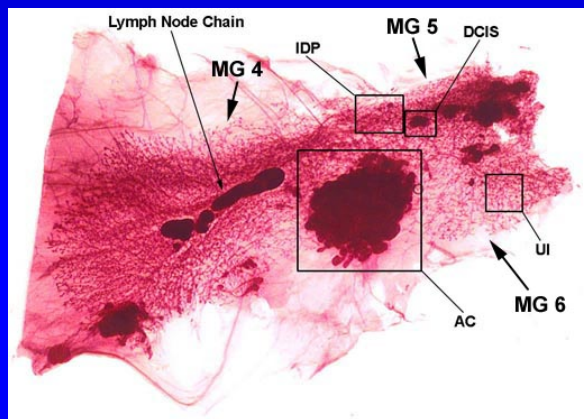
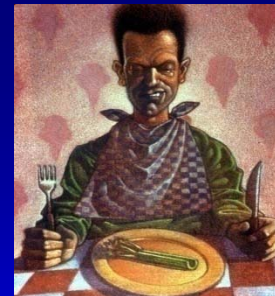


John McGinley

Common Alterations Underlying the Pathogenesis of Chronic Diseases

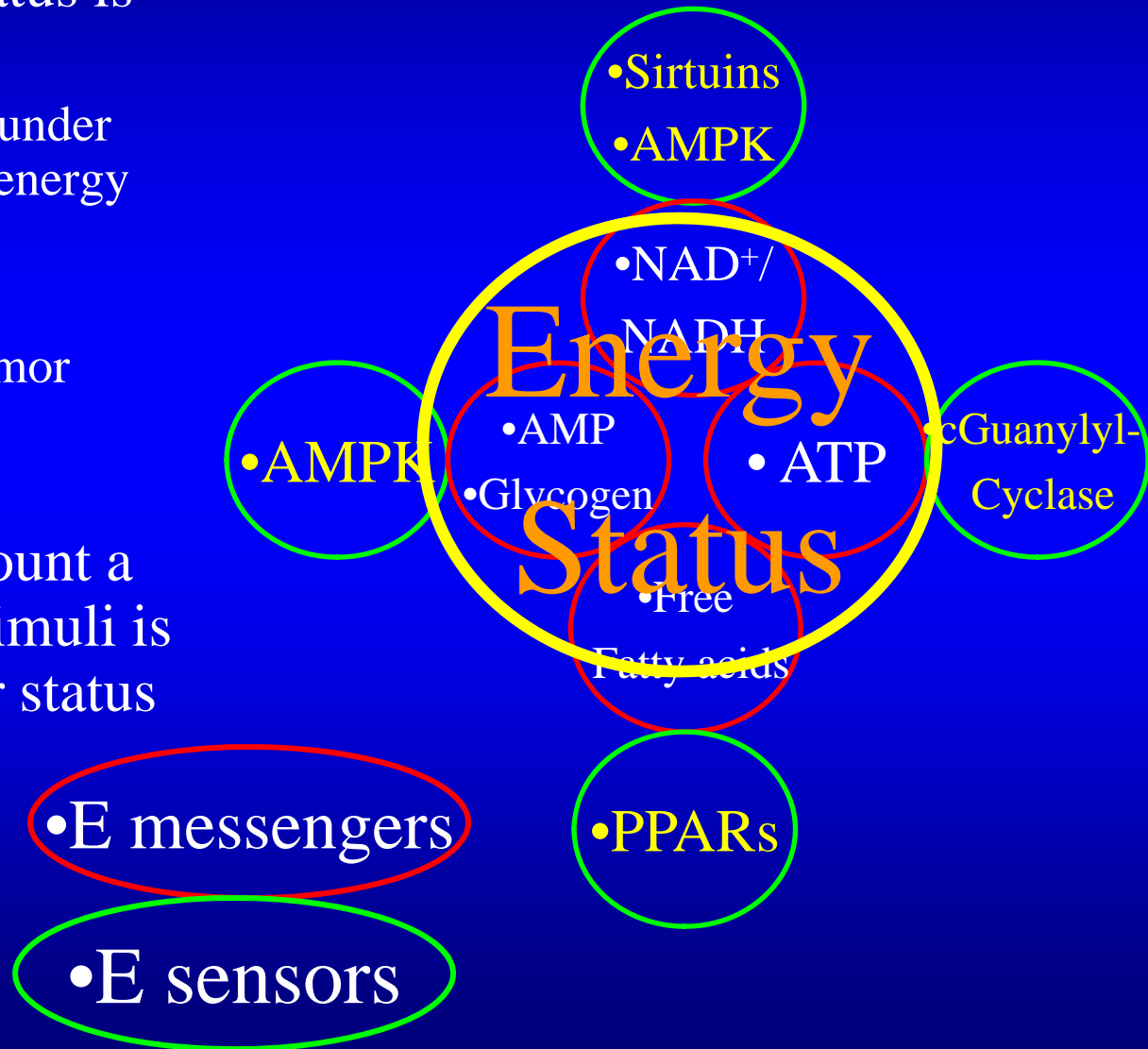


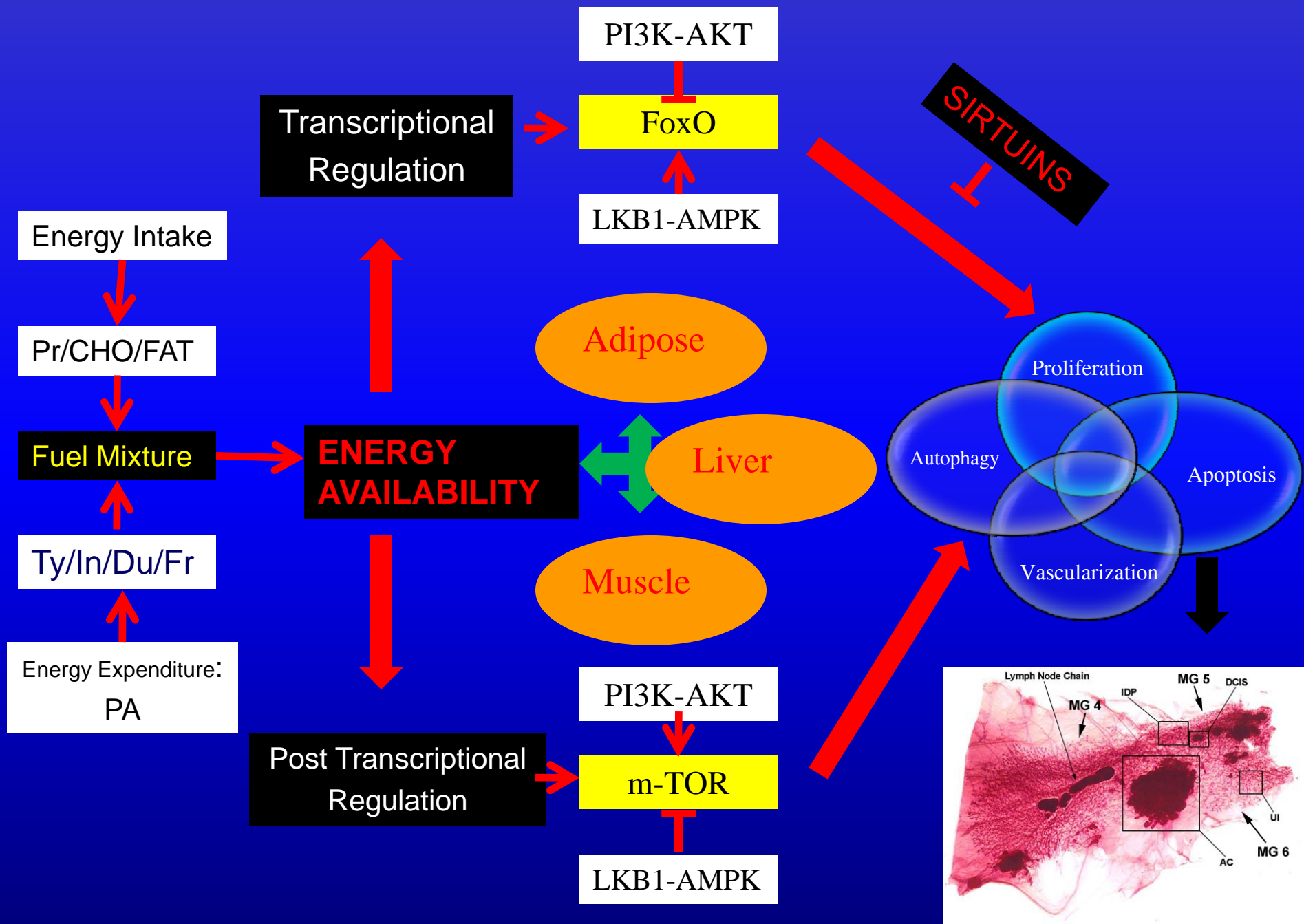
Pre-Clinical Model for Breast Carcinogenesis



Intracellular Energetics Paradigm

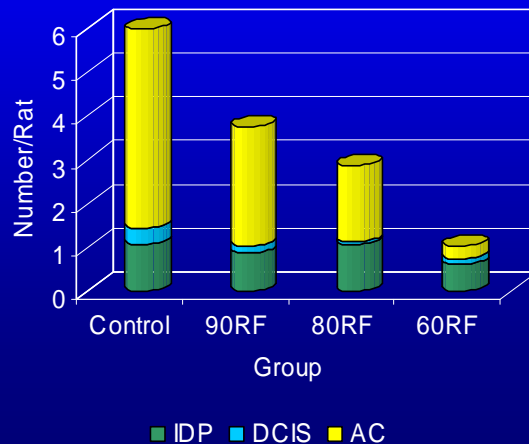
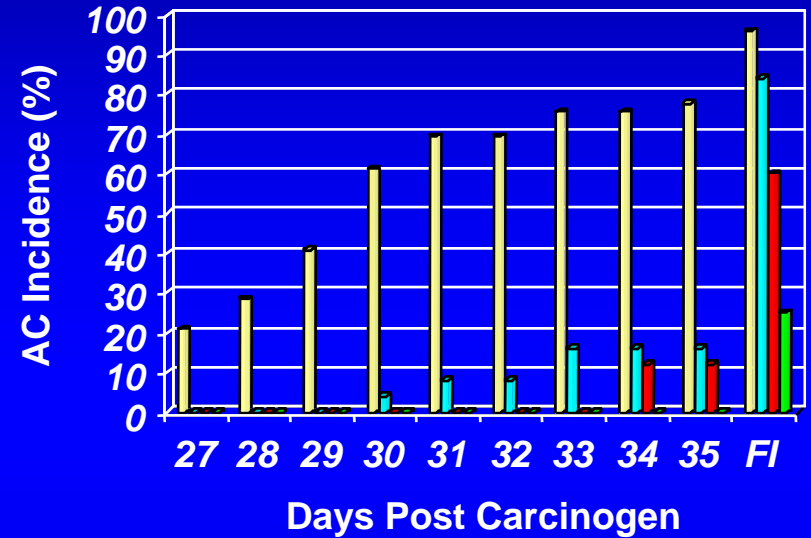
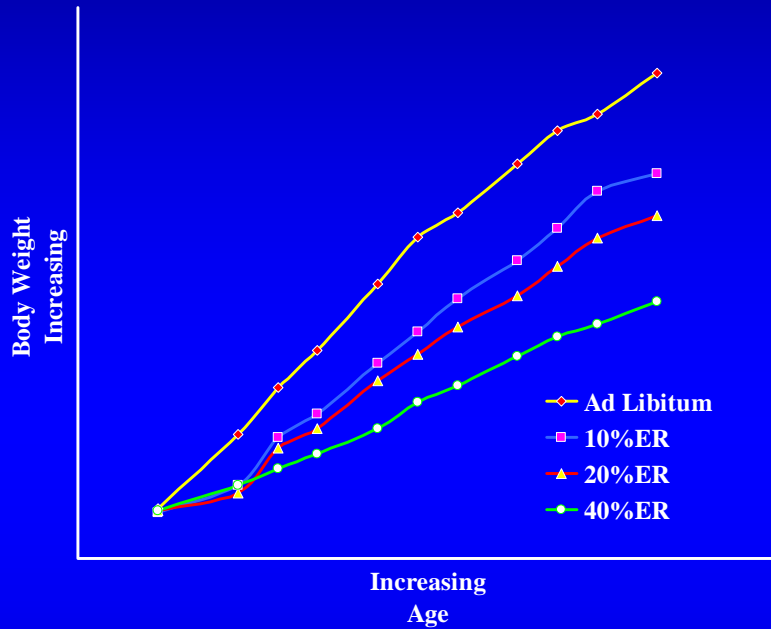
- Intracellular energy status is not constant
 - Differs in normal cells under different conditions of energy balance
 - Differs in normal vs tumor epithelial cells
- The cell's ability to mount a response to external stimuli is limited by intracellular status



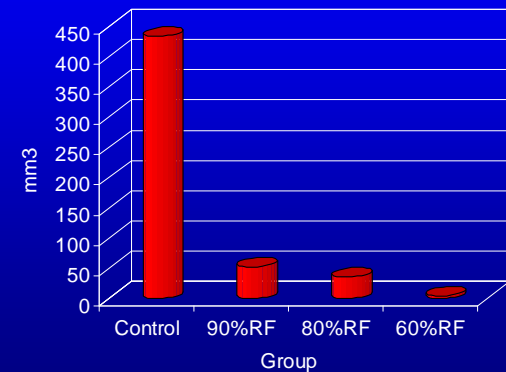


Pre-Clinical Model for Positive Energy Balance:

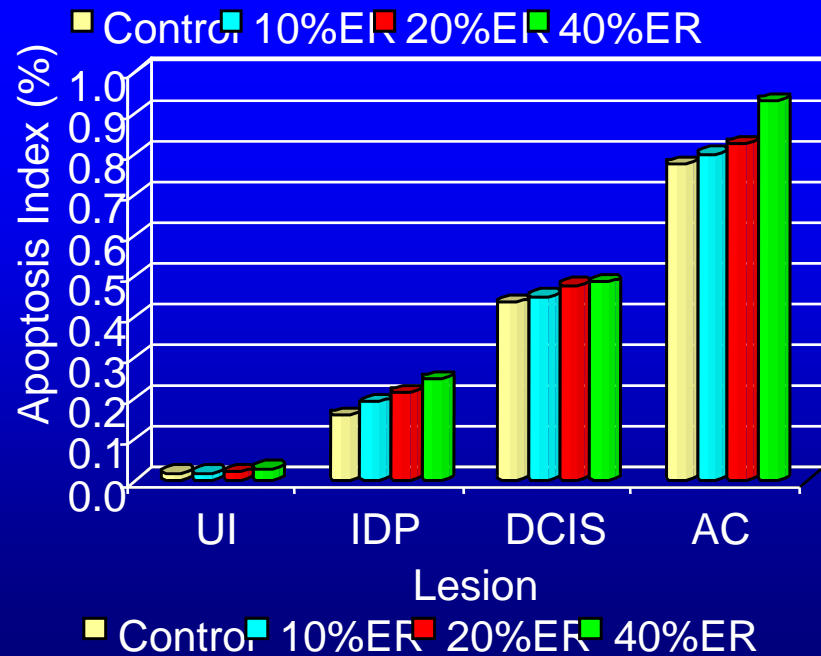
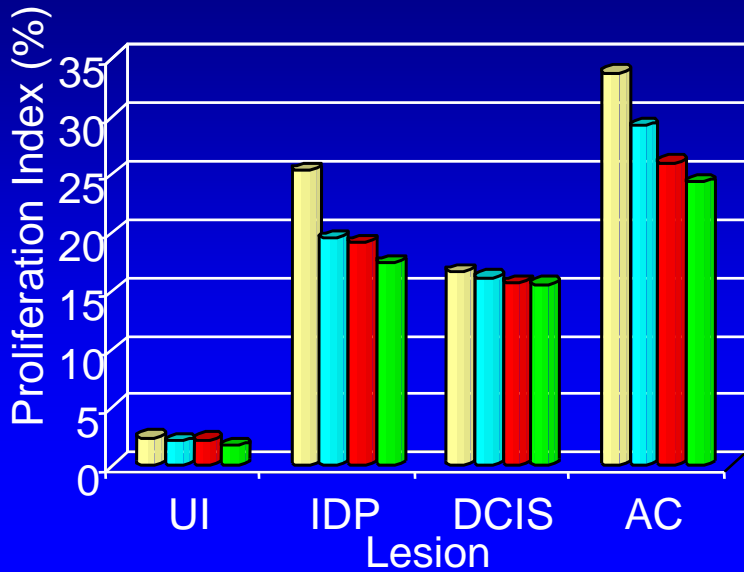
What is the effect of different planes of energy nutrition?



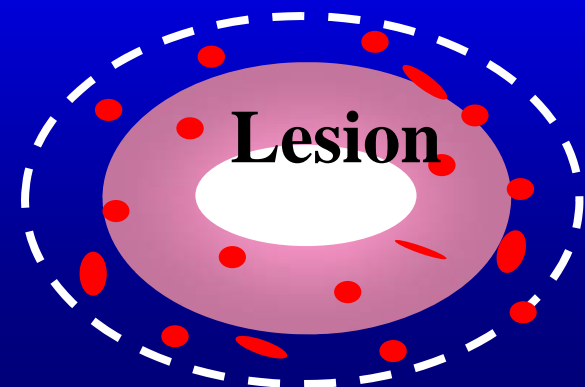
■ Control ■ 10%ER ■ 20%ER ■ 40%ER



Cellular Mechanisms



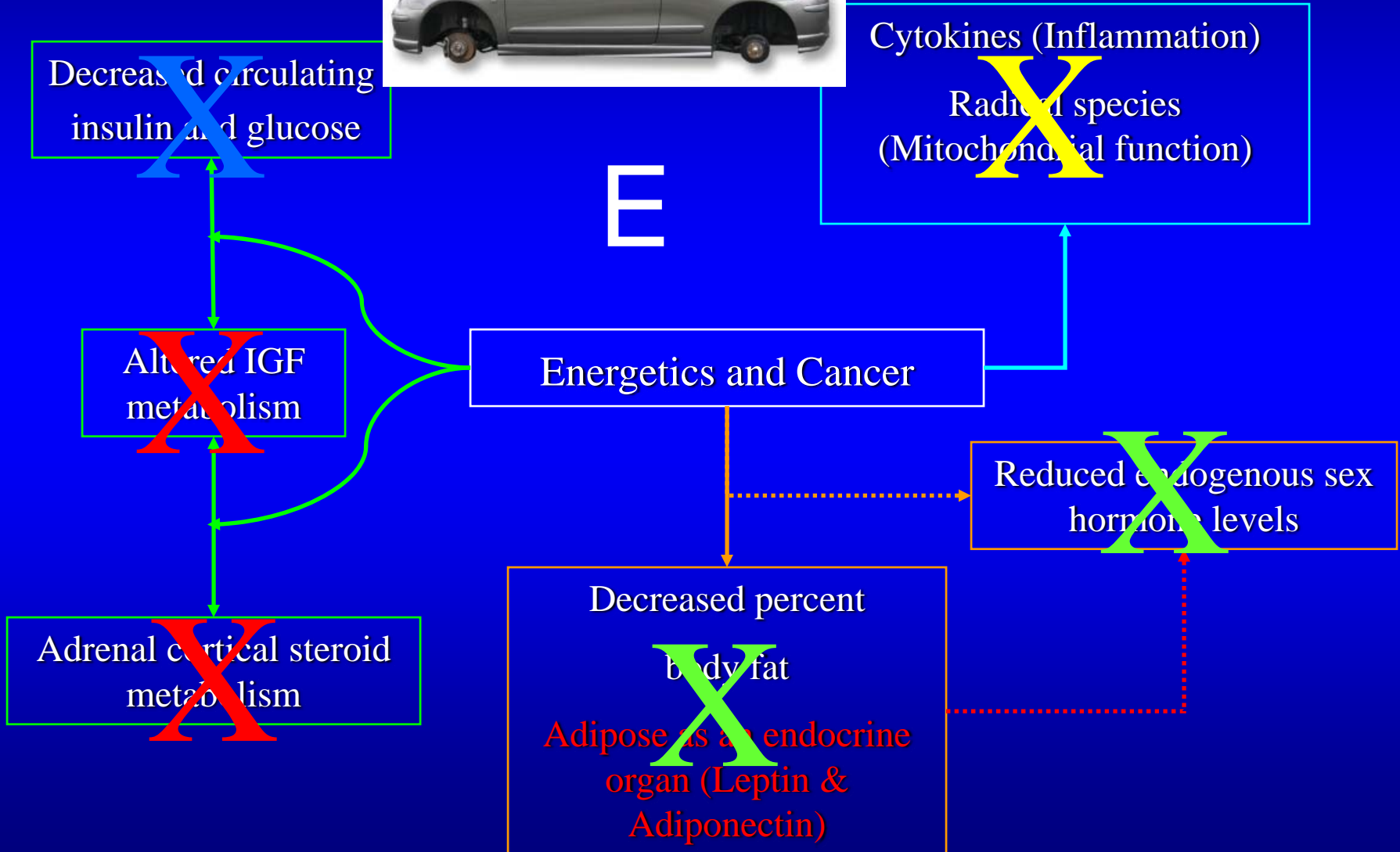
- Cell Proliferation
 - Jiang et al Cancer Res. 2003
- Apoptosis
 - Thompson et al. Cancer Res. 2004
- Vascularization
 - Thompson et al. Cancer Res. 2004



Which mechanisms are relevant to explore?

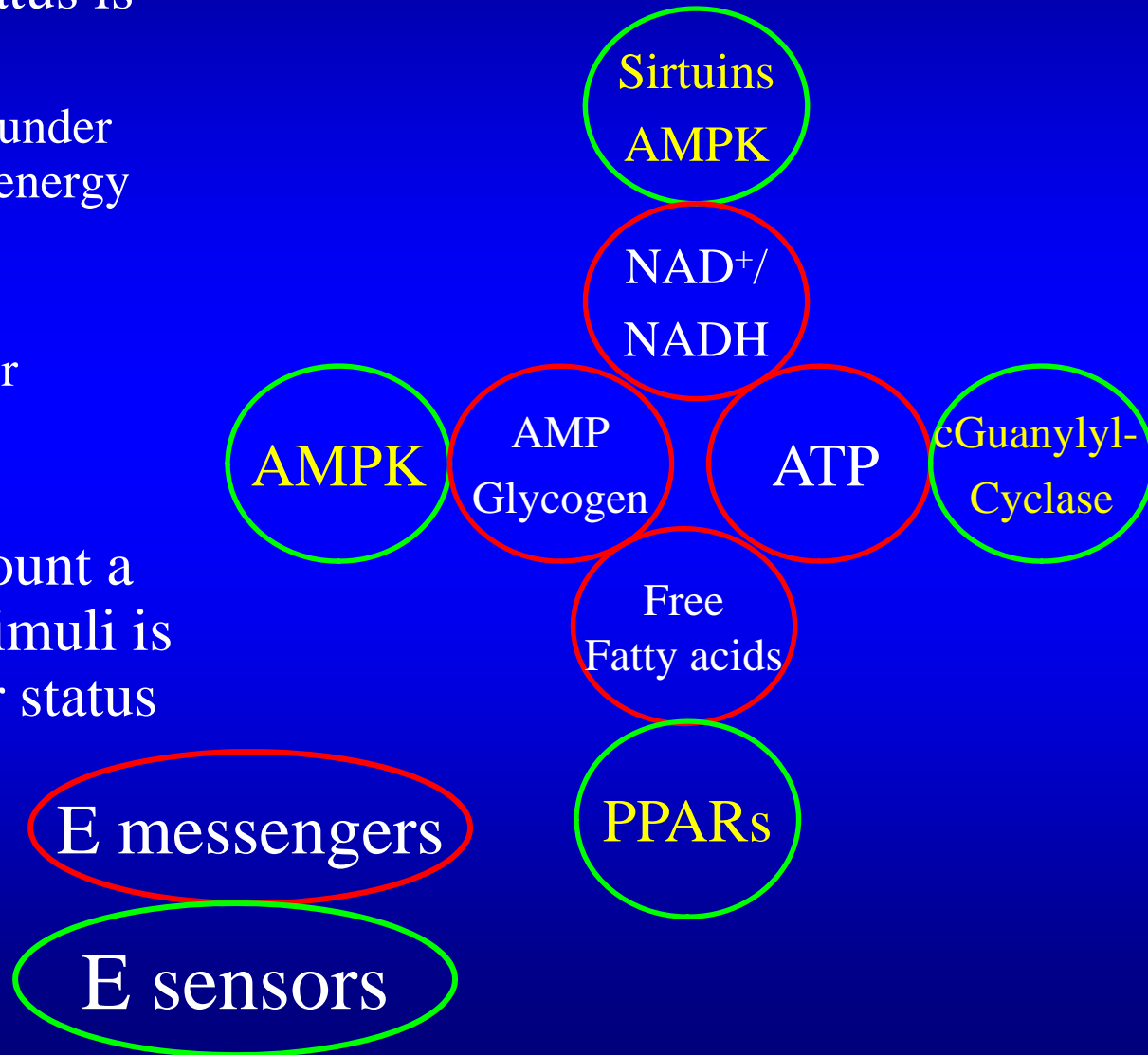


E

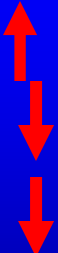


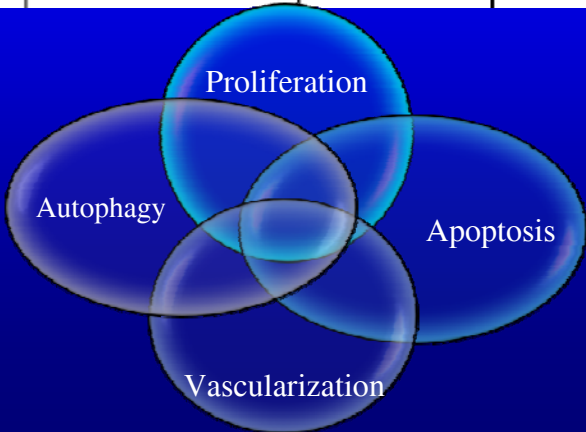
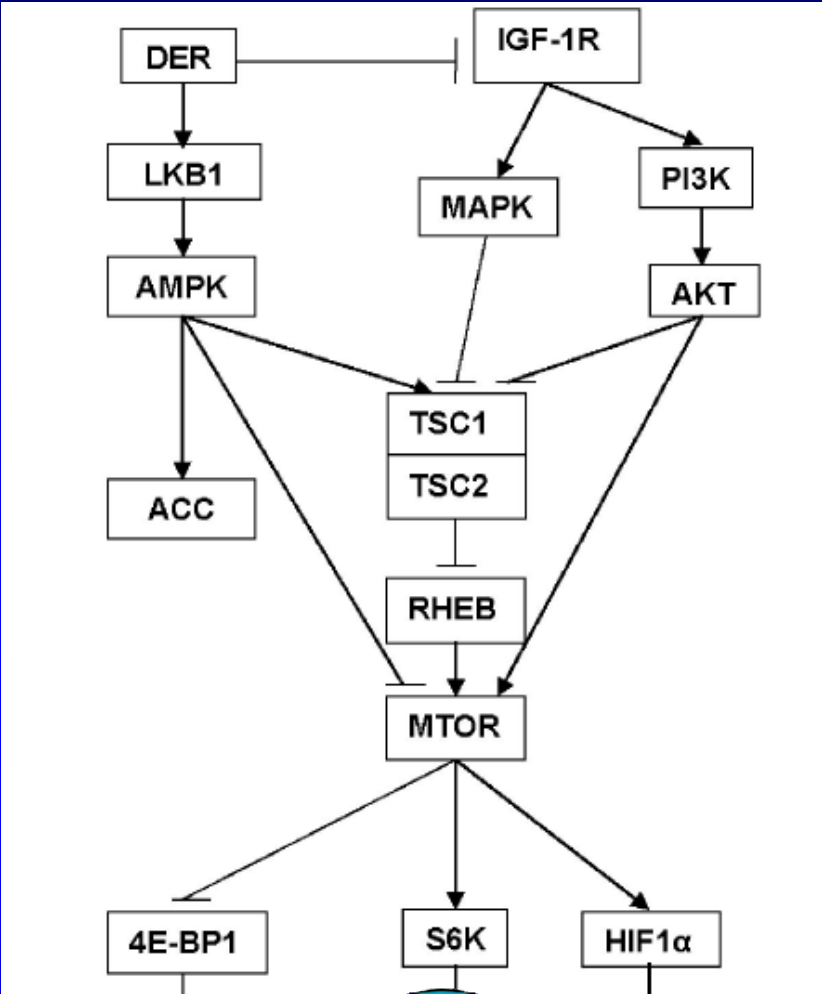
Energetics Paradigm

- Intracellular energy status is not constant
 - Differs in normal cells under different conditions of energy balance
 - Differs normal vs tumor epithelial cells
- The cell's ability to mount a response to external stimuli is limited by intracellular status



Ancient Energy Sensors

- AMP-Activated Protein Kinase
 - Activated by increased AMP/ATP, adiponectin
 - Phosphorylation of targets
 - Catabolism
 - Biosynthesis
 - Growth
 - Sirtuins: silent information regulators (Sir)
 - Class III histone/protein deacetylases
 - NAD⁺ –dependent (NAD/NADH)
 - P53 and FOXO
 - Death/survival/senescence
 - Cell Cycle Checkpoint arrest
 - Stress resistance
 - Energy metabolism
- 

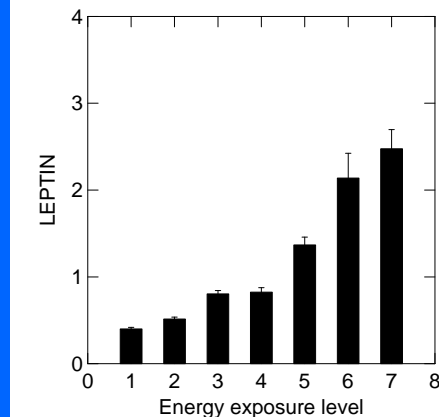
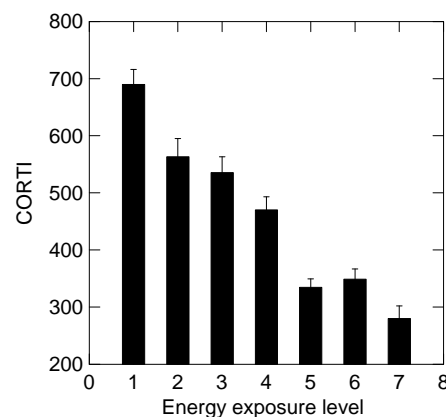
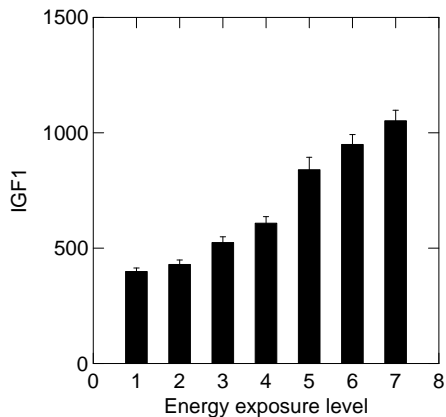


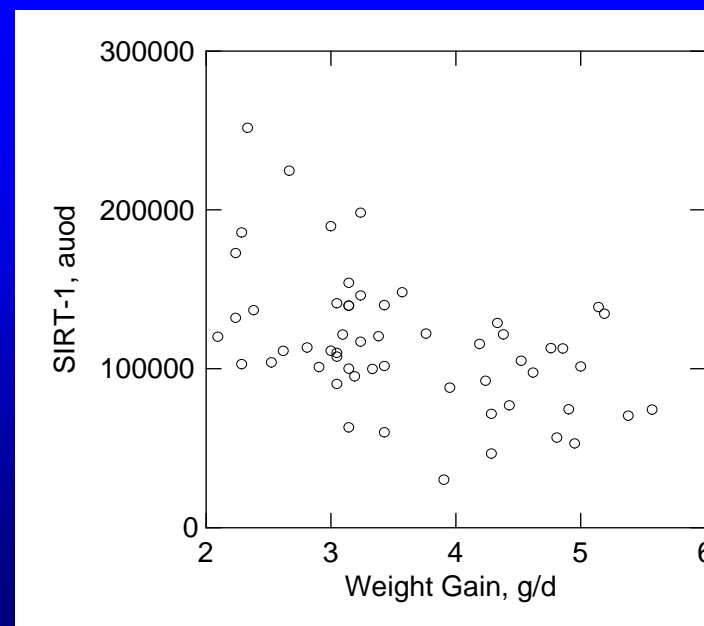
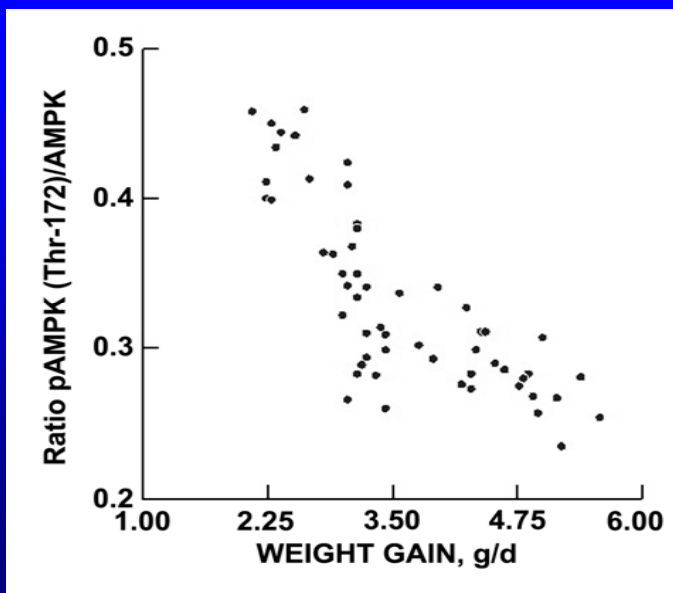
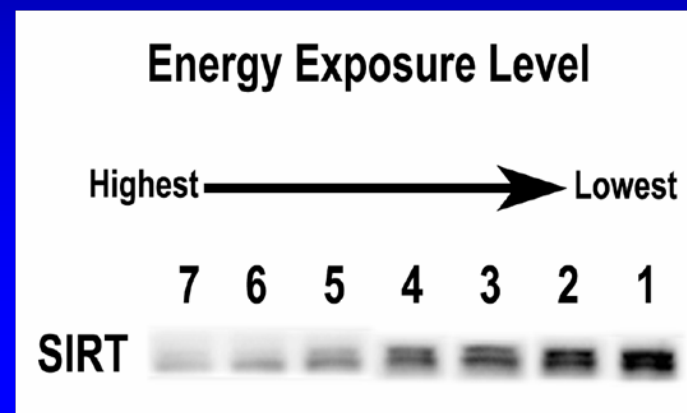
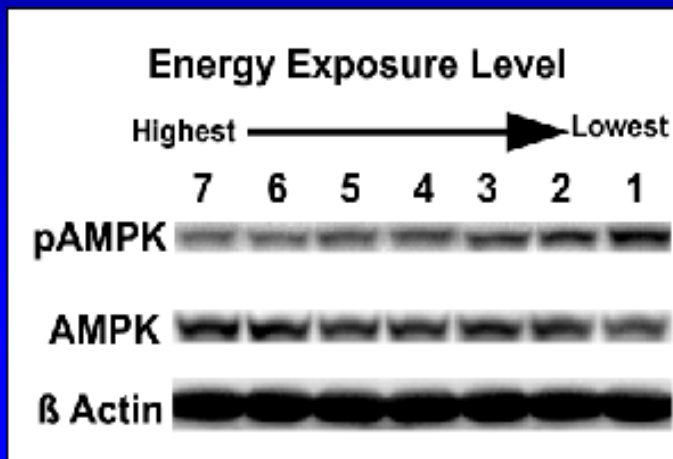
Dietary energy restriction (DER) vs Diet induced obesity (DIO)

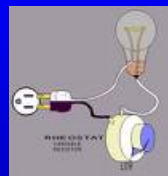
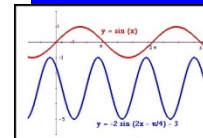
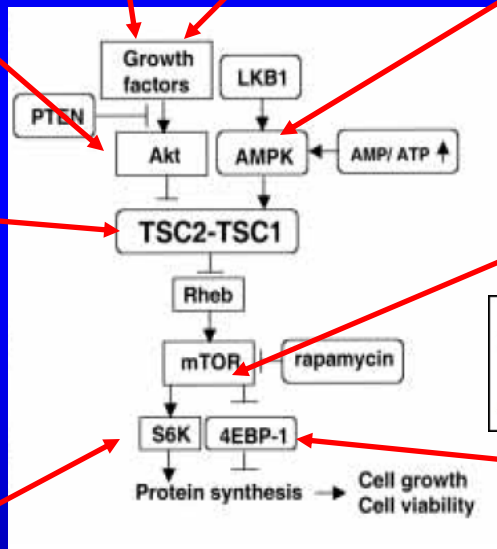
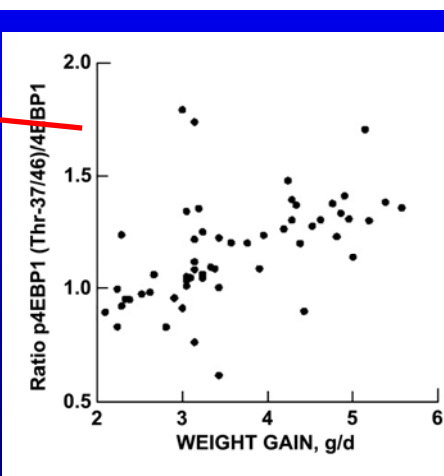
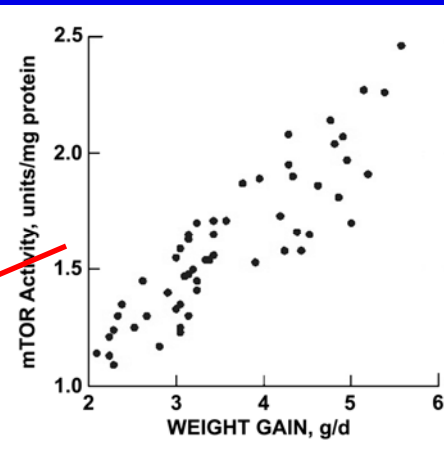
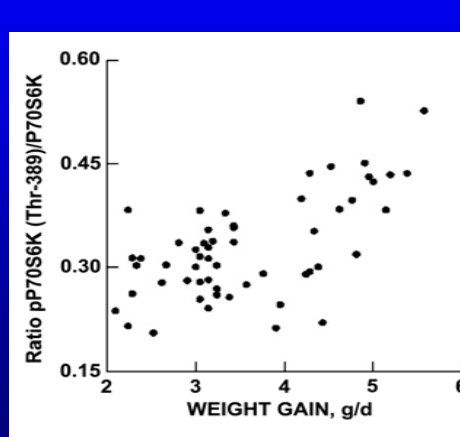
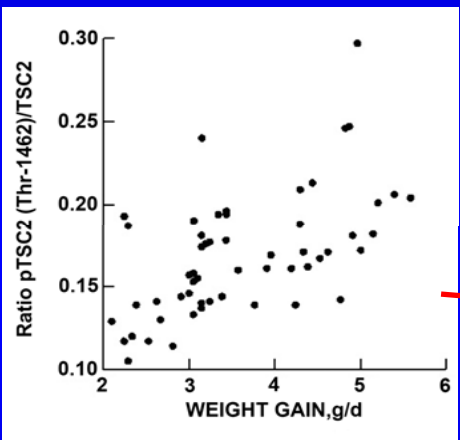
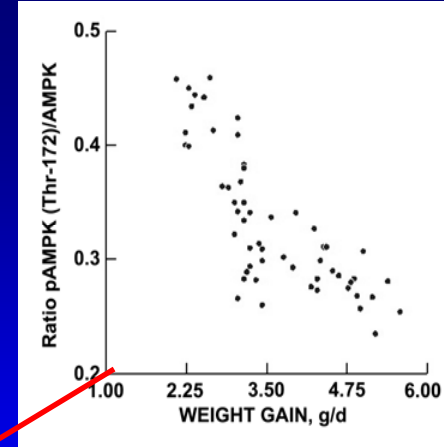
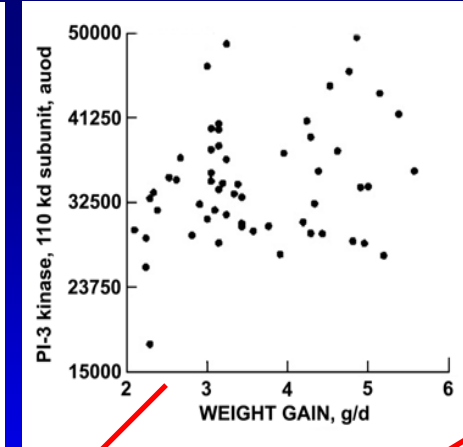
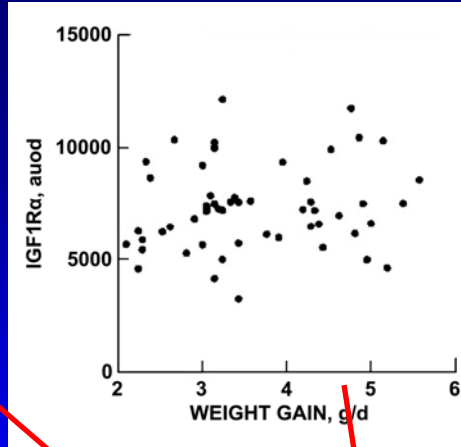
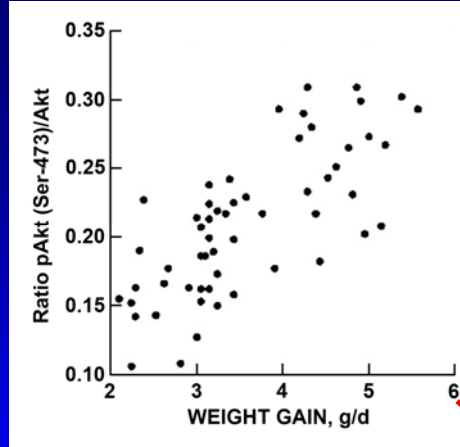
Discretely different or a **continuum**?



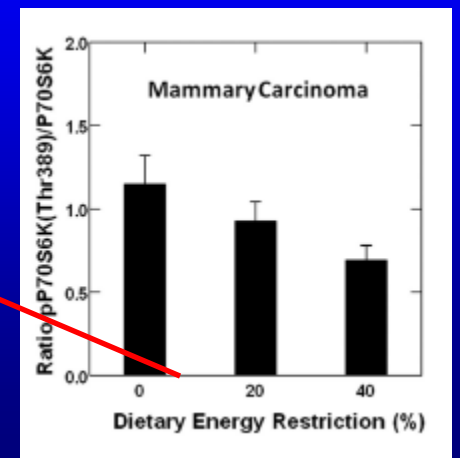
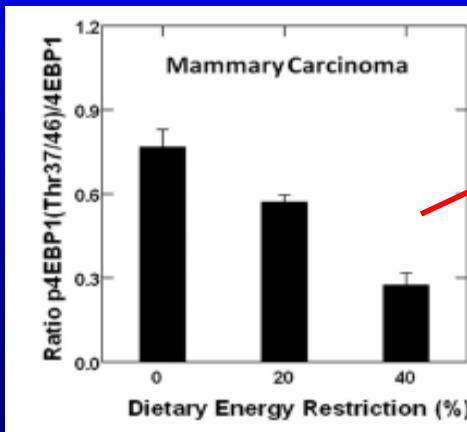
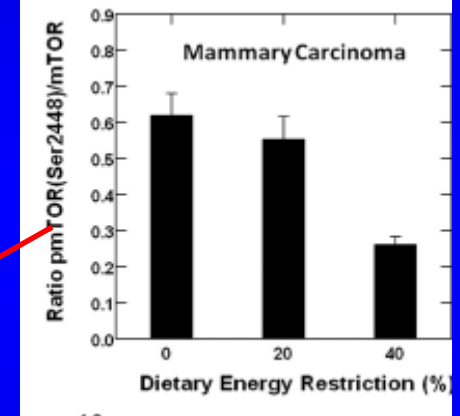
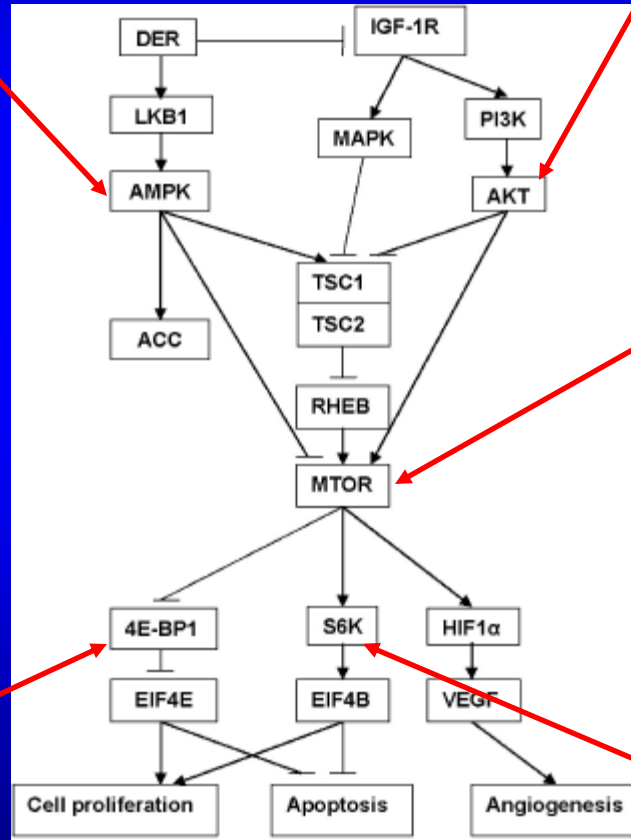
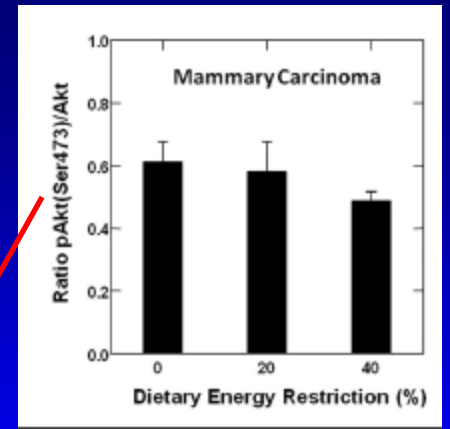
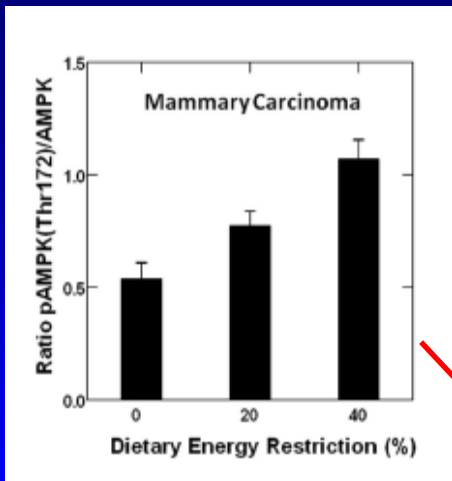
Body weight gained, total g	48.3 ± 2.6	61.0 ± 4.0	66.3 ± 2.8	68.4 ± 2.8	82.1 ± 6.9	94.9 ± 4.1	107.6 ± 5.2
Average daily weight gain, g/d	2.3 ± 0.1 *	2.9 ± 0.2 *	3.2 ± 0.1 *	3.3 ± 0.1 *	3.9 ± 0.3	4.5 ± 0.2	5.1 ± 0.3
Final body weight, g	93.9 ± 3.8	106.0 ± 3.3	111.4 ± 2.6	113.0 ± 3.6	127.4 ± 9.9	144.1 ± 11.1	156.2 ± 8.8

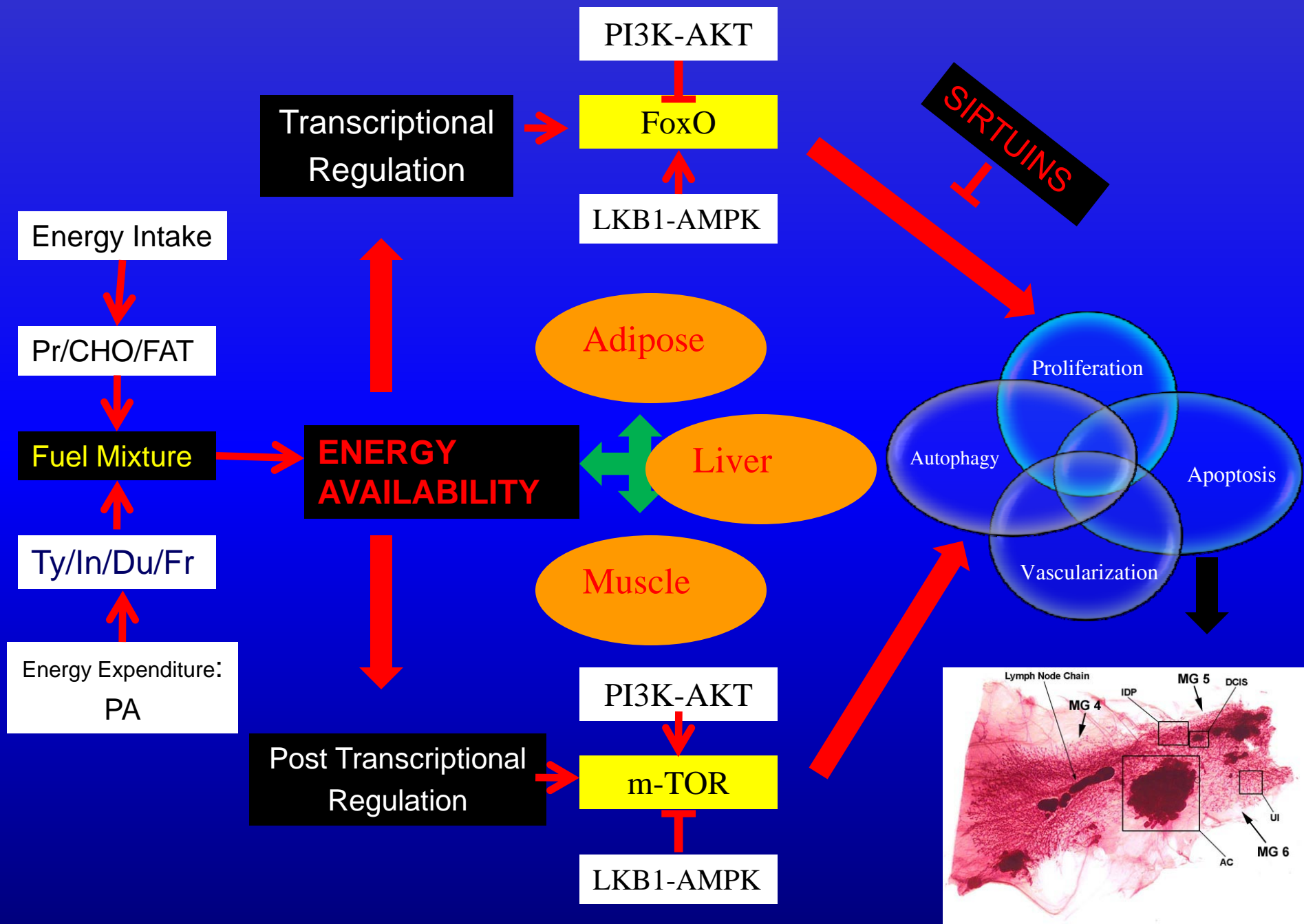






Regulated by phosphorylation/dephosphorylation



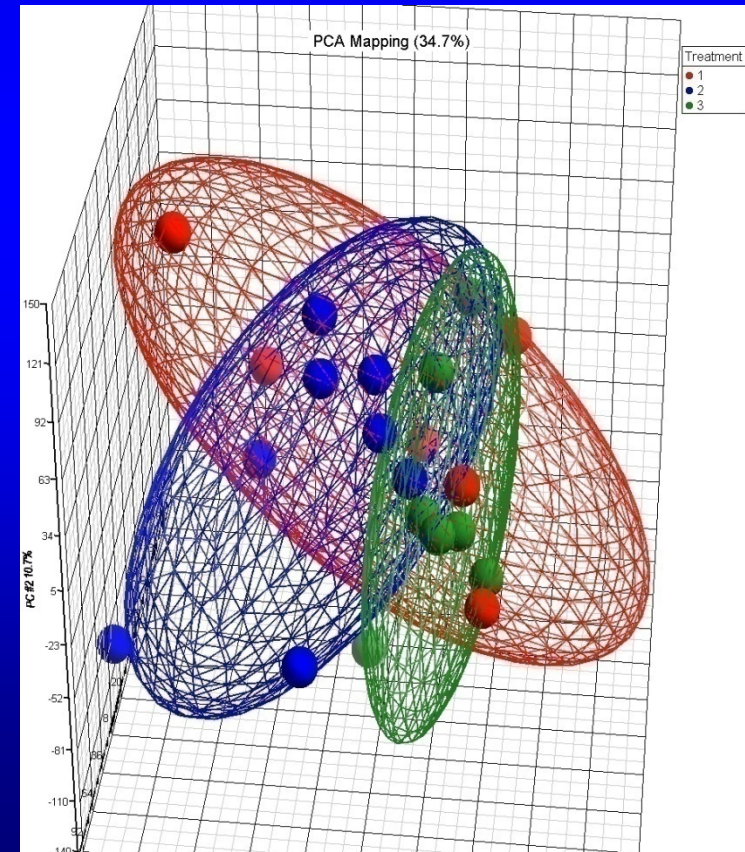
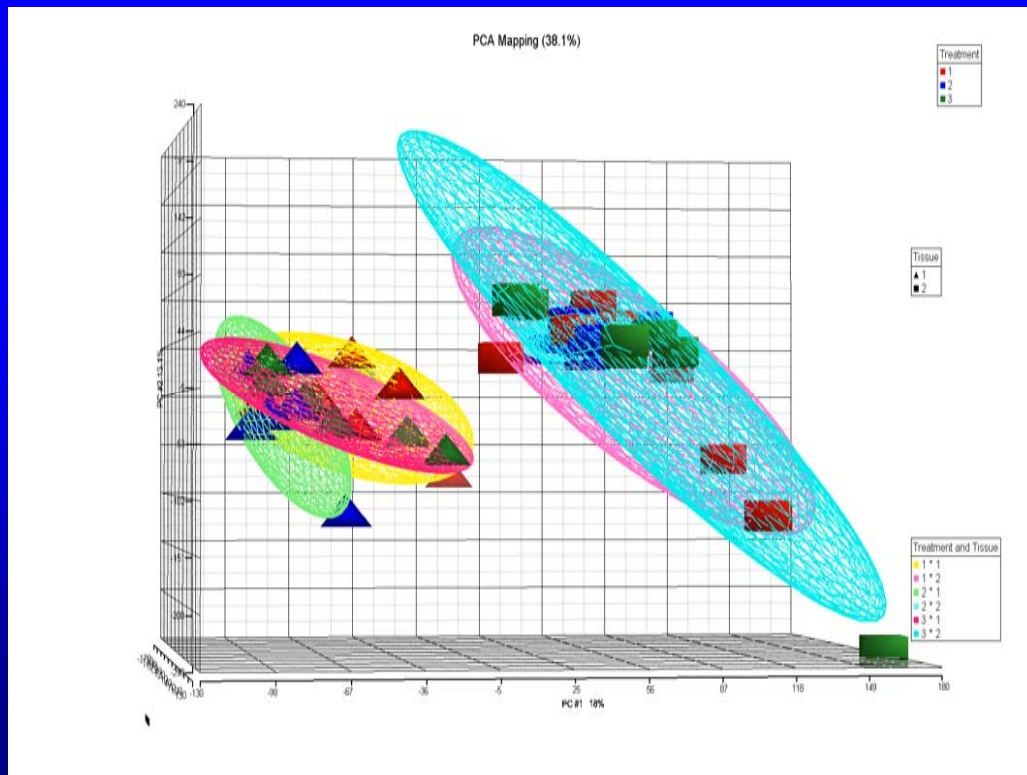


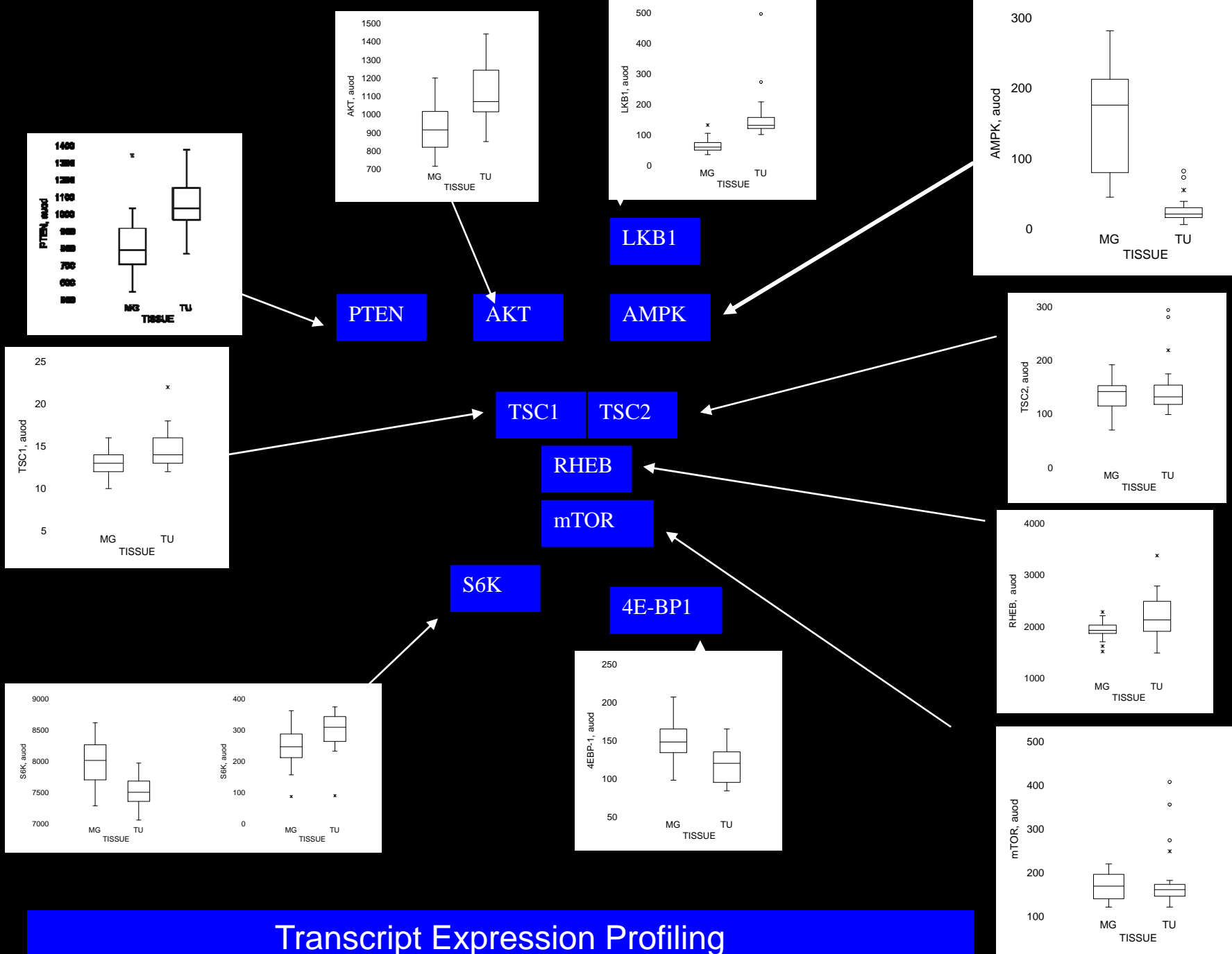
Effect of Dietary Energy Restriction on Gene Expression in LCM-Isolated MEC from Gland and AC

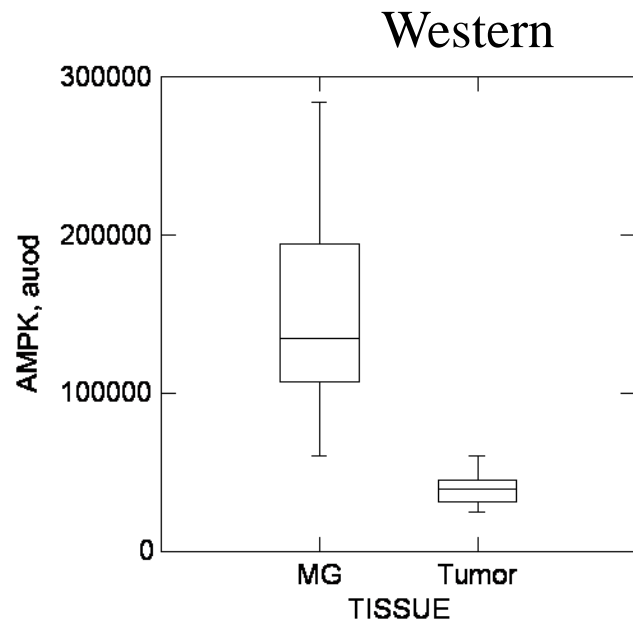
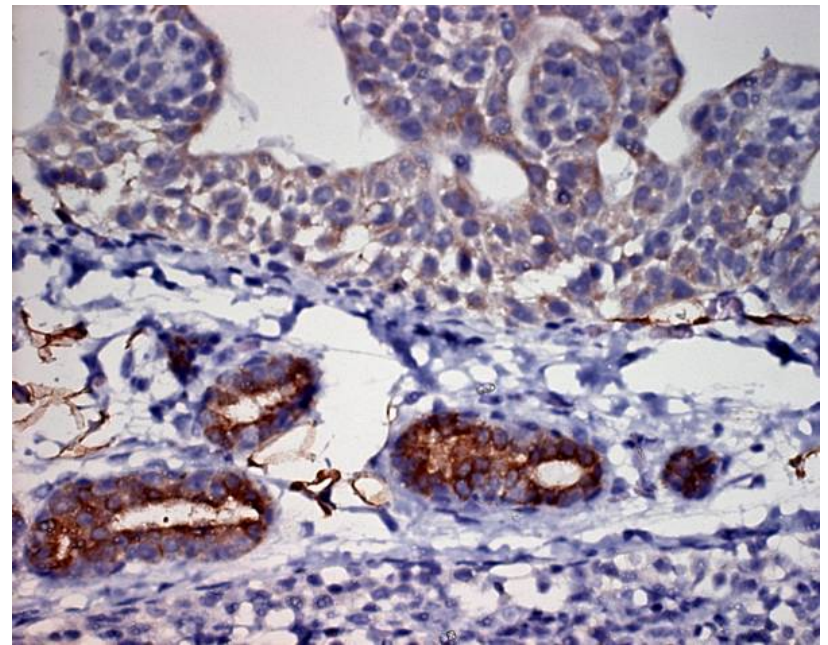
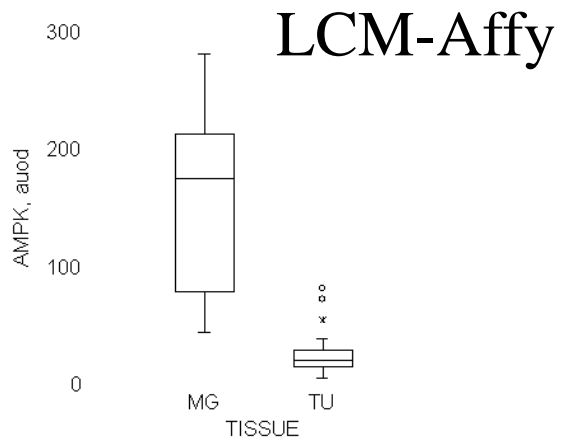
% Restricted	Number of Affymetrix Chips	
	Mammary gland	Mammary AC
0	9	9
20	9	9
40	9	9

27 animals, 9/gp

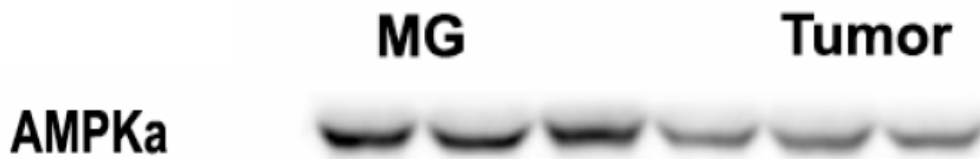
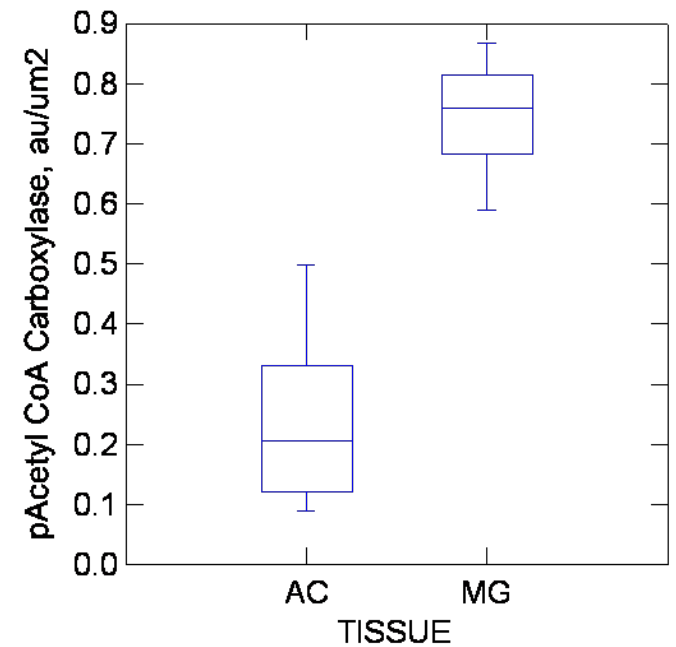
•RNA isolated from gland and AC (matching pair)





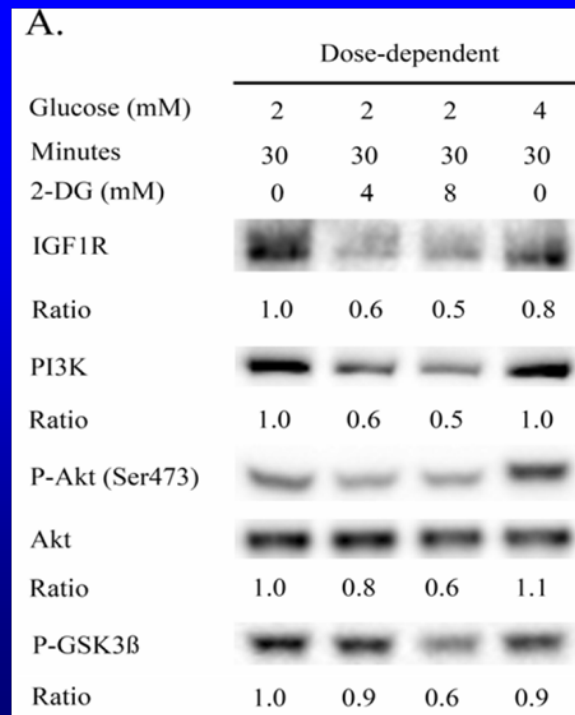
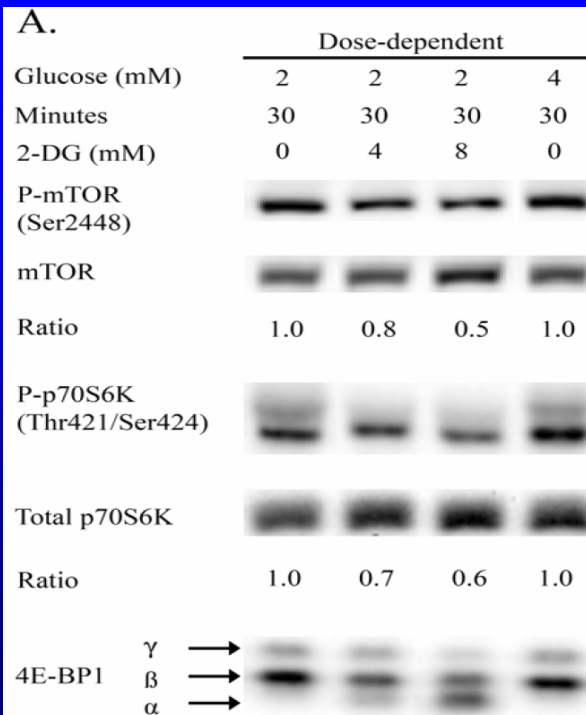
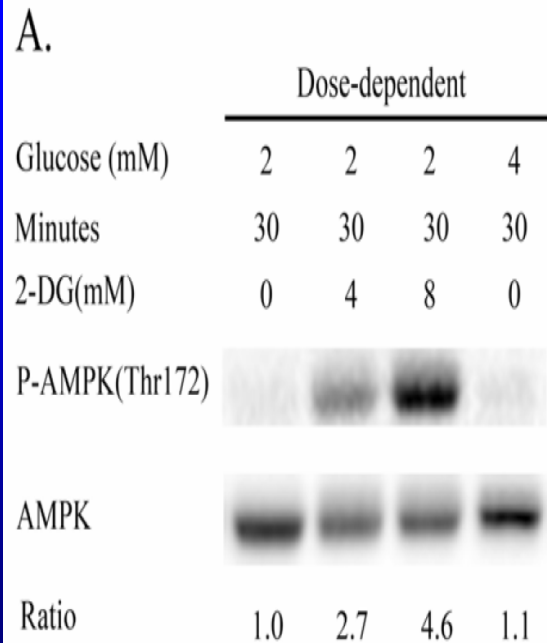
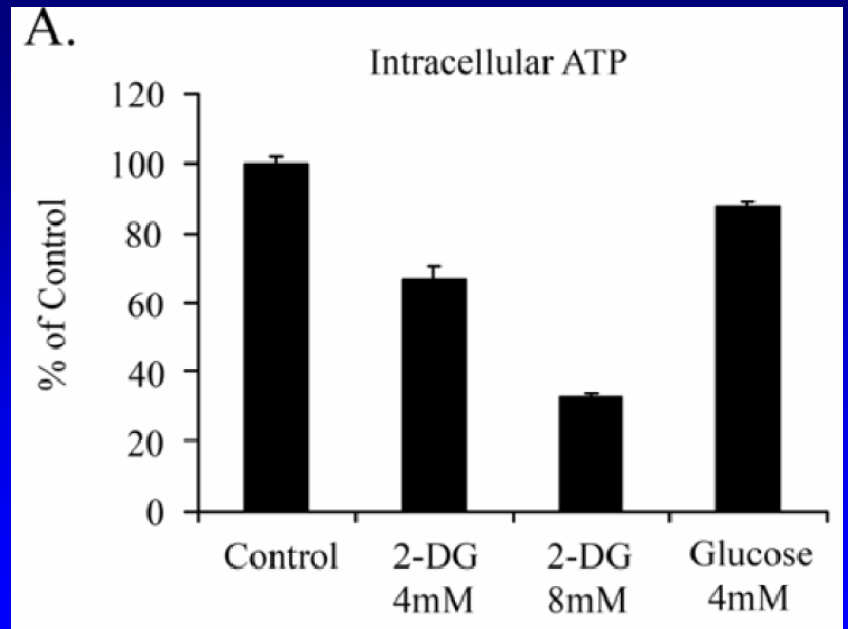


IHC-Activity-pACC



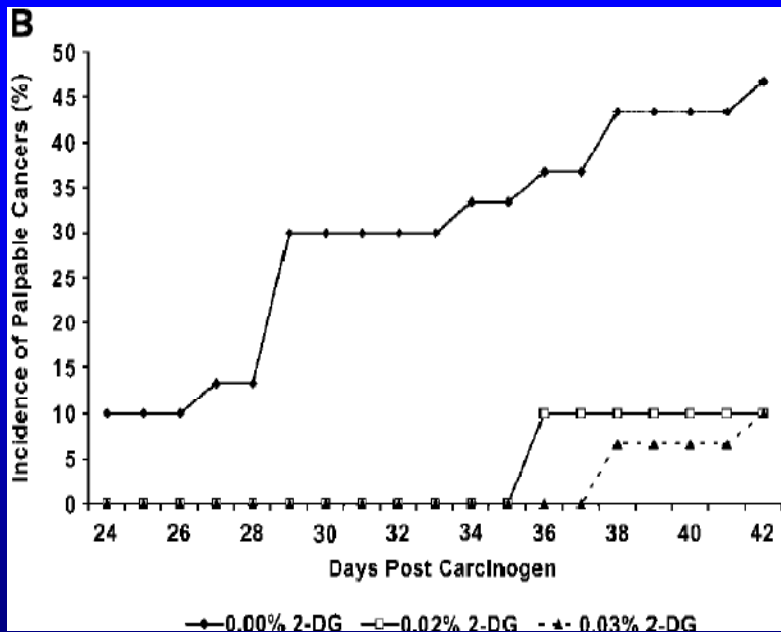
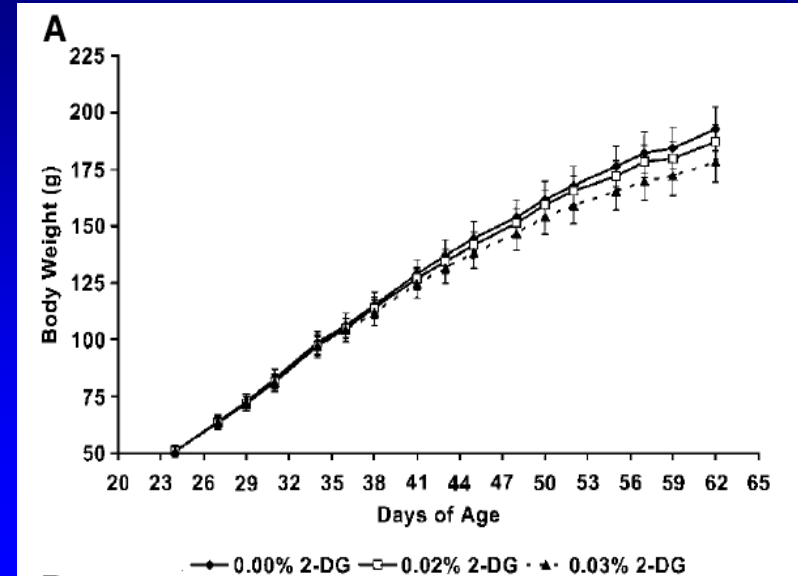
2-Deoxyglucose (2-DG)

- Glucose analogue
- Accumulates in tumor cells
- Blocks glycolysis
- Increases AMP/ATP



2-Deoxyglucose (2-DG)

- Glucose analogue
- Accumulates in tumor cells
- Blocks glycolysis
- Increases AMP/ATP



	Control	0.02% 2-DG
Serum insulin (ng/mL)	1.43 ± 0.07 ^a	1.27 ± 0.08 ^a
Serum corticosterone (ng/mL)	271 ± 16 ^a	327 ± 10 ^b
Serum leptin (ng/mL)	1.52 ± 0.06 ^a	1.50 ± 0.07 ^a
Plasma IGF-I (ng/mL)	697 ± 34 ^a	675 ± 55 ^a
Serum IGFBP-3 (intensity/mm ²)	2,851 ± 434 ^a	2,352 ± 408 ^a

Table 4. Effect of 2-DG on the Carcinogenic Response in the Mammary Gland*

	Control (N= 30)	0.03% 2-DG (N= 30)	P-value
Body weight (g)	177 ± 5 ^a	169 ± 6.03 ^a	0.324
Incidence (%)	86.7 (26) ^a	53.3 (16) ^b	<0.005
Multiplicity (no. of AC/rat)	2.03 ± 0.27 (61) ^a	1.37 ± 0.34 (41) ^b	0.018

2-Deoxyglucose

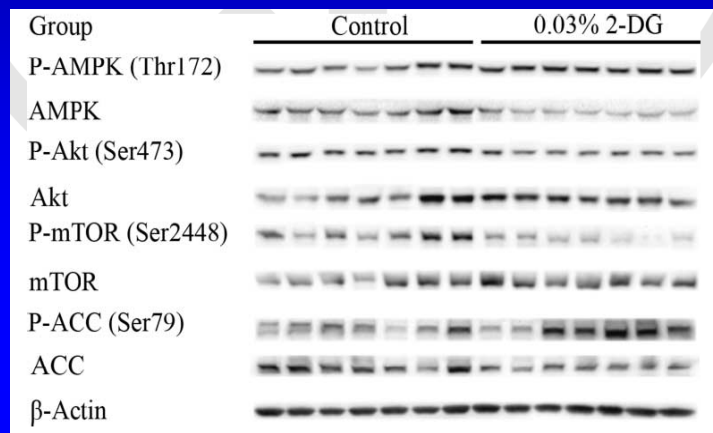
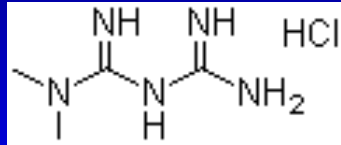


Table 5. Effect of 2-Deoxyglucose on Protein Expression in Mammary Carcinomas*

Protein name	Control [†]	0.03% 2-DG	P-value
P-AMPK (Thr172)	11335 ± 887 ^a	16244 ± 388 ^b	0.001
AMPK	12786 ± 1116 ^a	6600 ± 489 ^b	0.001
P-AMPK/AMPK	0.89 ± 0.04 ^a	2.52 ± 0.15 ^b	<0.0001
P-Akt (Ser473)	11709 ± 645 ^a	8304 ± 340 ^b	0.001
Akt	10228 ± 1401 ^a	12583 ± 868 ^a	0.183
P-Akt/Akt	1.23 ± 0.12 ^a	0.67 ± 0.04 ^b	0.003
P-mTOR (Ser2448)	11470 ± 1304 ^a	5041 ± 591 ^b	0.002
mTOR	11320 ± 1177 ^a	14815 ± 1139 ^b	0.054
P-mTOR/mTOR	1.01 ± 0.05 ^a	0.34 ± 0.03 ^b	<0.0001
P-ACC (Ser79)	8810 ± 943 ^a	20371 ± 2815 ^b	0.005
ACC	16530 ± 1352 ^a	12548 ± 396 ^b	0.025
P-ACC/ACC	0.54 ± 0.05 ^a	1.60 ± 0.21 ^b	0.002

Metformin



1,1-Dimethylbiguanide hydrochloride

- Inhibits OXPHOS-Complex 1

 - Owen et al BJ 200; El-Mir et al JBC 2000

- Alter cellular energy charge (AMP/ATP) ↑

- Activates AMPK

Metformin use:

>100 M worldwide

Cancer risk ↓

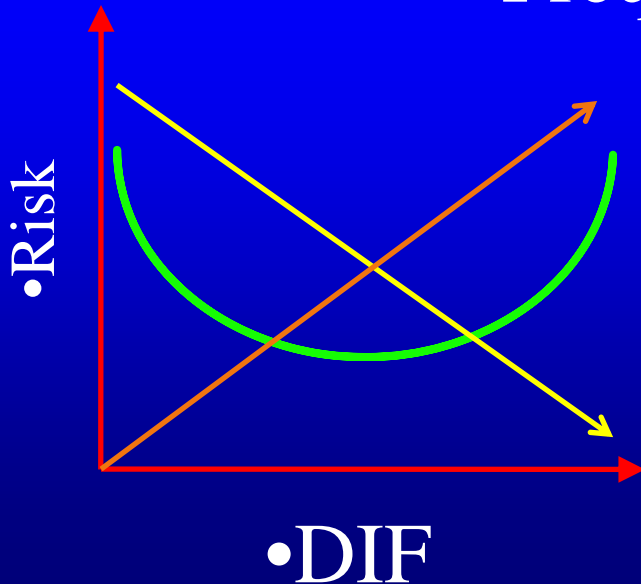
Evans et al BMJ
2005

Bowker et al
Diabetes Care 2006

*thiazolidinediones: reported to activate AMPK/ complex 1 & adiponectin

Thinking About Physical Activity

- Three primary components
 - Duration
 - Intensity
 - Frequency



• Which mechanisms are relevant to explore?



- Cytokines (Inflammation)
- Oxidative stress (Mitochondrial function)

- Decreased circulating insulin and glucose

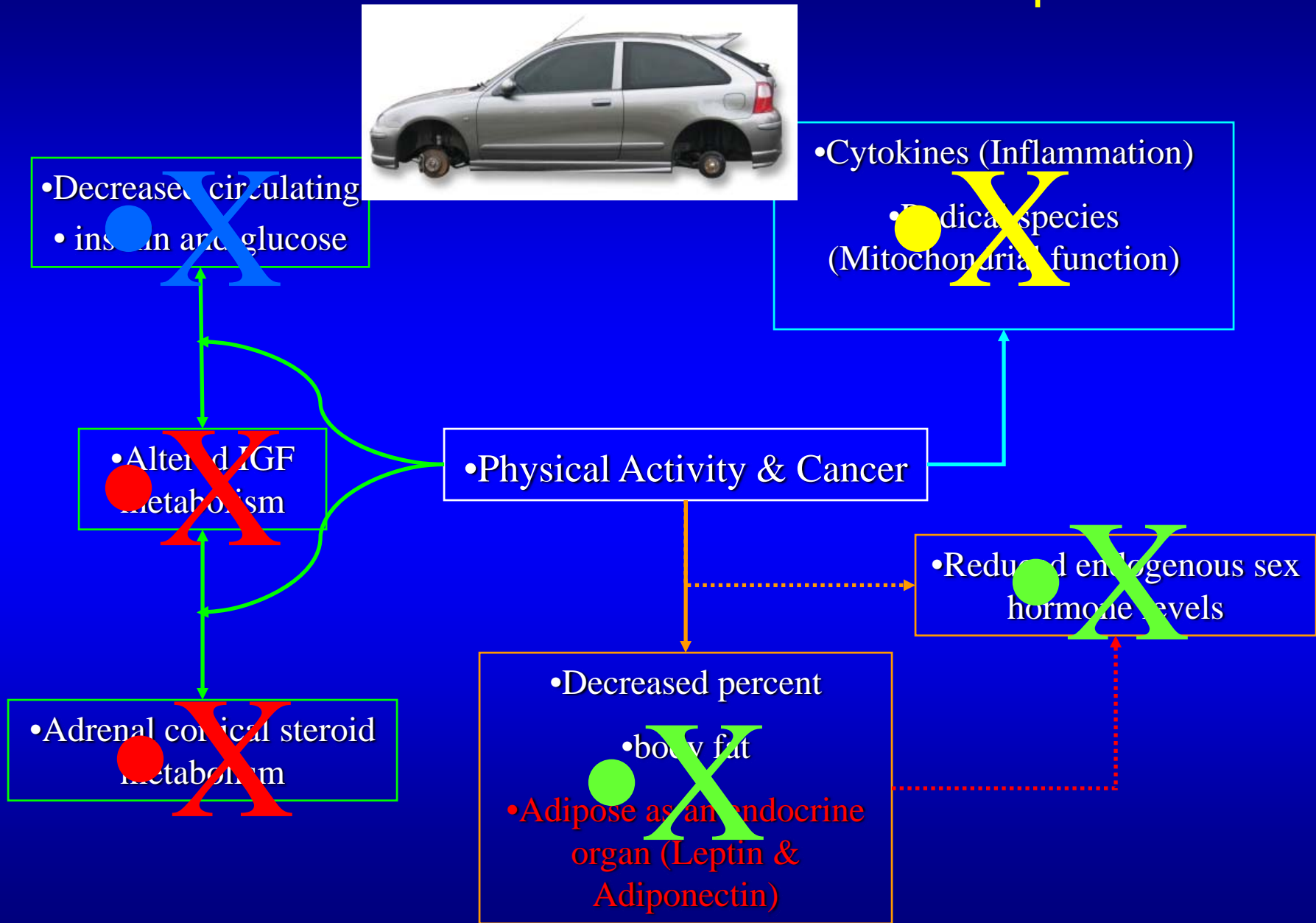
• Physical Activity & Cancer

- Altered IGF metabolism

- Reduced endogenous sex hormone levels

- Adrenal cortical steroid metabolism

- Decreased percent body fat
- Adipose as an endocrine organ (Leptin & Adiponectin)



•Complex Behaviors-Complex Biology

