Nutrition and Age-Associated Inflammation :Role of Nutritional Intervention

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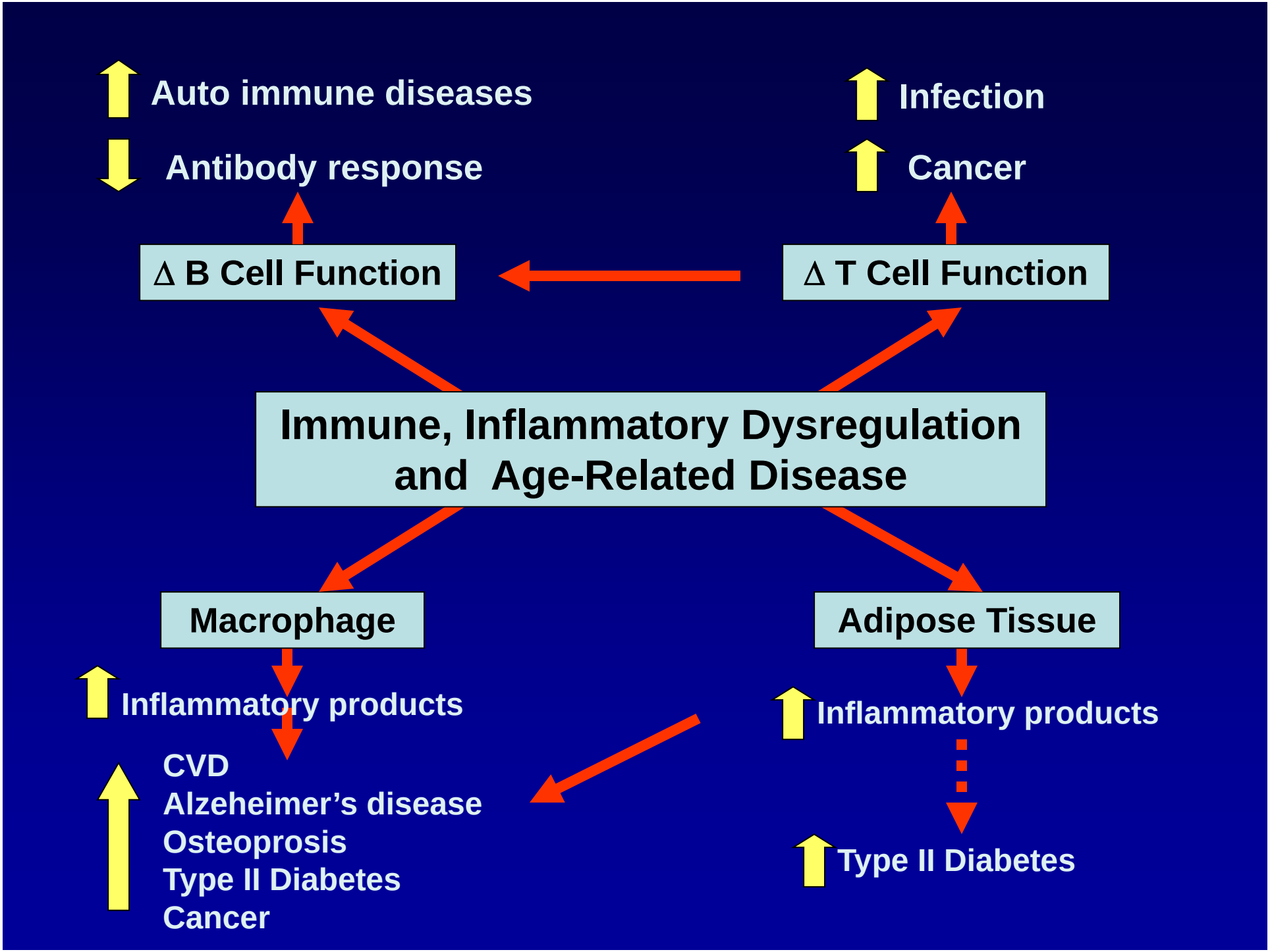
Outline

1) Role of immune and inflammatory responses in age-related diseases

2) Brief description of mechanism of age-related increase in macrophage inflammatory products and its contribution to age-associated decline in T cell function and increase susceptibility to infectious diseases.

3) Age-associated adipose tissue inflammation and its implication for type 2 diabetes

4) Use of nutritional strategies to reverse macrophage inflammation and its impact for reducing the risk of infectious diseases.


Auto immune diseases
Antibody response
Infection
Cancer
Δ B Cell Function
Δ T Cell Function
Immune, Inflammatory Dysregulation and Age-Related Disease
Macrophage
Adipose Tissue
Inflammatory products
CVD
Alzeheimer's disease
Osteoprosis
Type II Diabetes
Cancer
Inflammatory products
Type II Diabetes

Cytokine and PGE2 Production by LPS-stimulated Mϕ of Young and Old Mice (pg/μg protein)

	Young	Old
IL-1β	4 ± 1	20 ± 4*
IL-6	60 ± 24	82 ± 22*
TNF-α	5 ± 1	5 ± 1
IL-10	1.8 ± 0.4	20 ± 7*
PGE_2	85 ± 17	242 ± 50*

Mean ± SE, n=11-13/group *Significant age effect

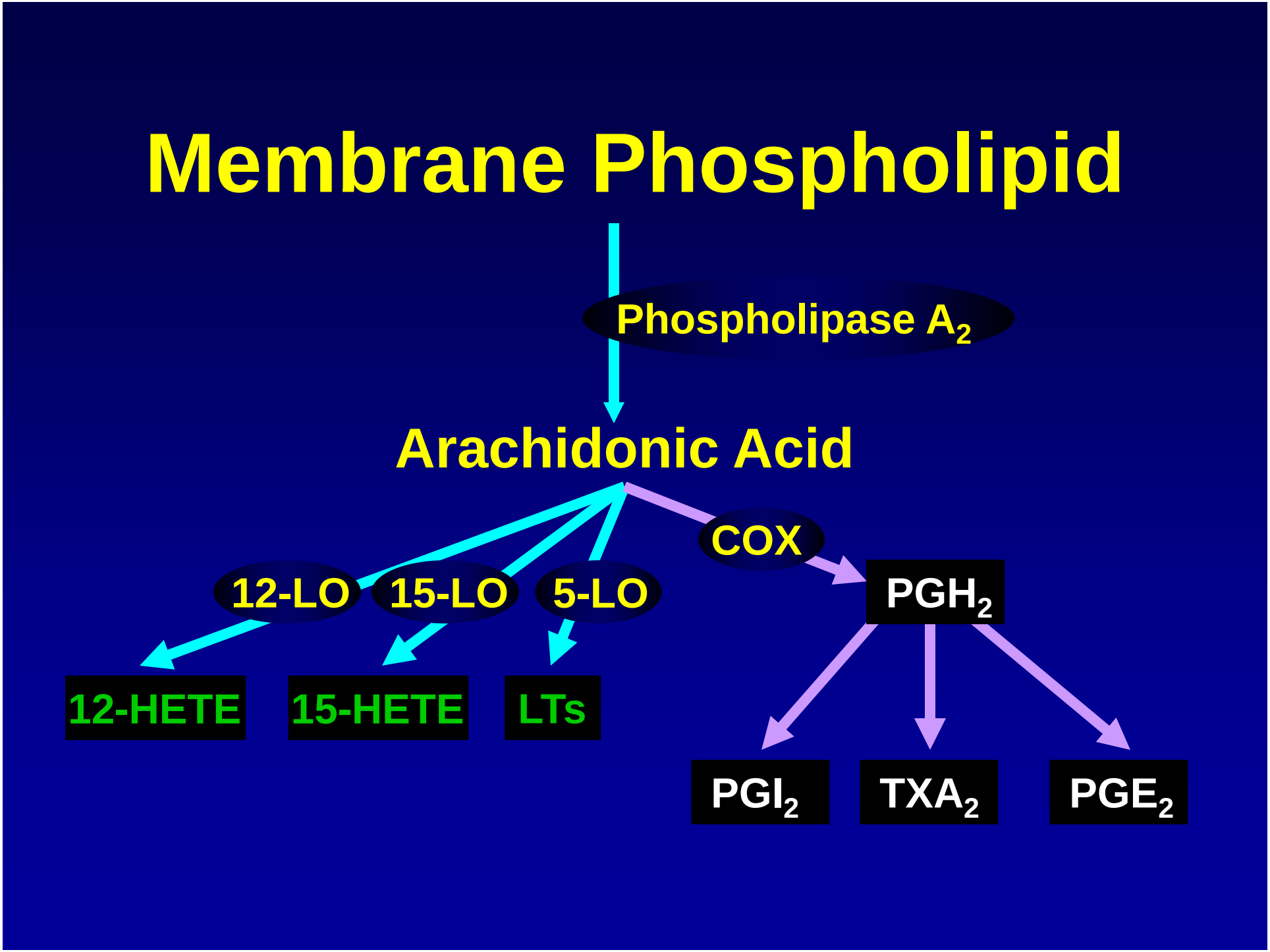
Ren et al., Unpublished data

PGE_2 and Immune Function in the Aged

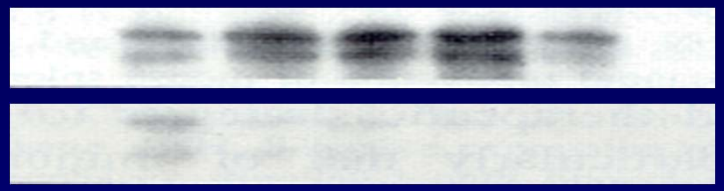
- T cell function declines with aging in both animals and humans
- Increased PGE_2 production contributes to the age- associated suppression in T cell function

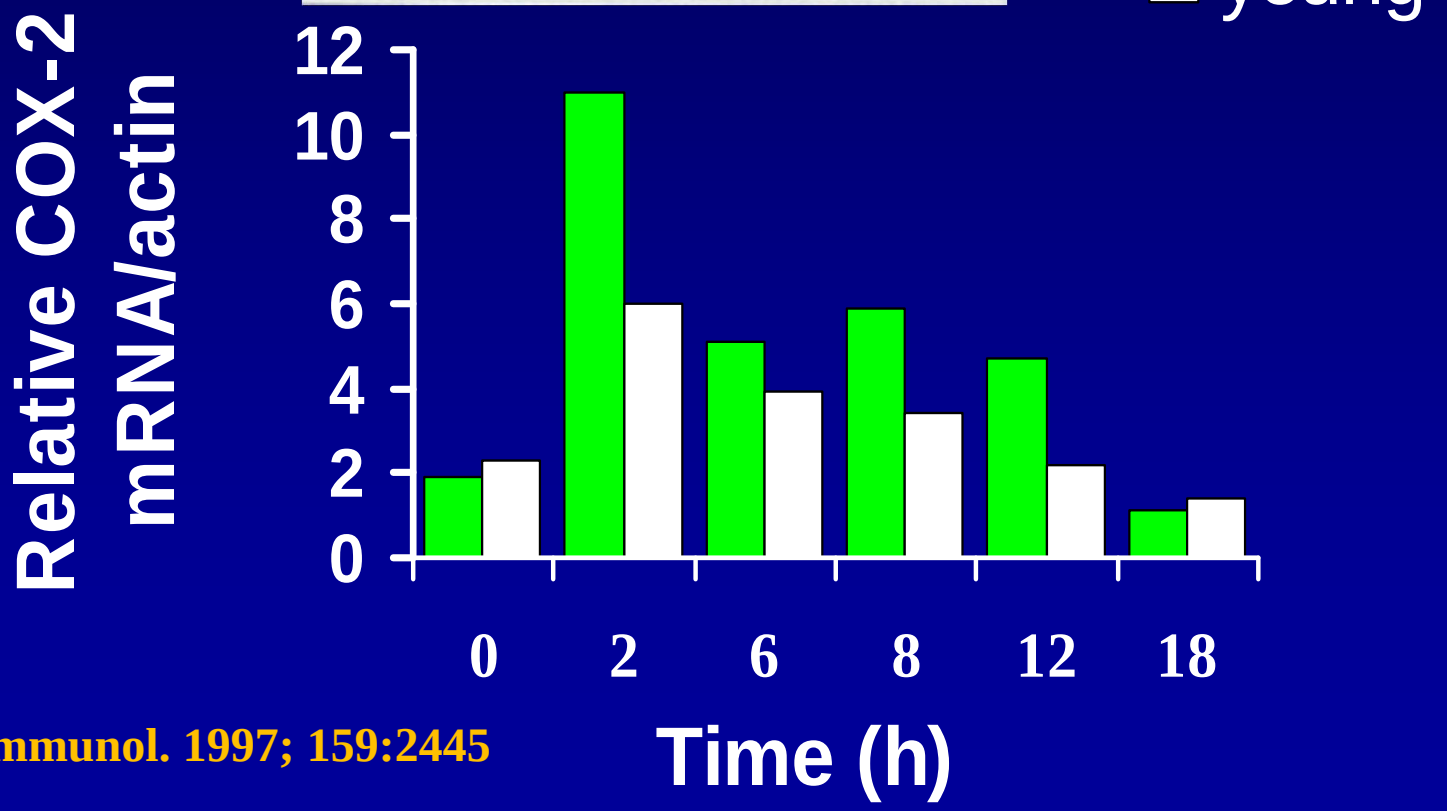
  (Beharka et al., Mech. Aging Devel. 93:59-77, 1997)

- PGE_2 is also implicated in pathogenesis of inflammatory, cardiovascular, and neoplastic diseases, incidence of which increases with age


Membrane Phospholipid
Phospholipase A2
Arachidonic Acid
COX
12-LO
15-LO
5-LO
PGH2
12-HETE
15-HETE
LTs
PGI2
TXA2
PGE2

Age-associated Increase in COX-2 mRNA Expression





Hayek et al. J. Immunol. 1997; 159:2445

What Is the Mechanism of Age-associated Increase in COX-2 Expression?

Regulators of COX-2 Gene Expression

	COX-2 expression
IL-1β	⬆
TNF-α	⬆
IL–6	⬆
ceramide	⬆
IL-10	⬇
glucocorticoid	⬇
GSH	⬇

Mediators of Age-associated COX-2 Expression

young

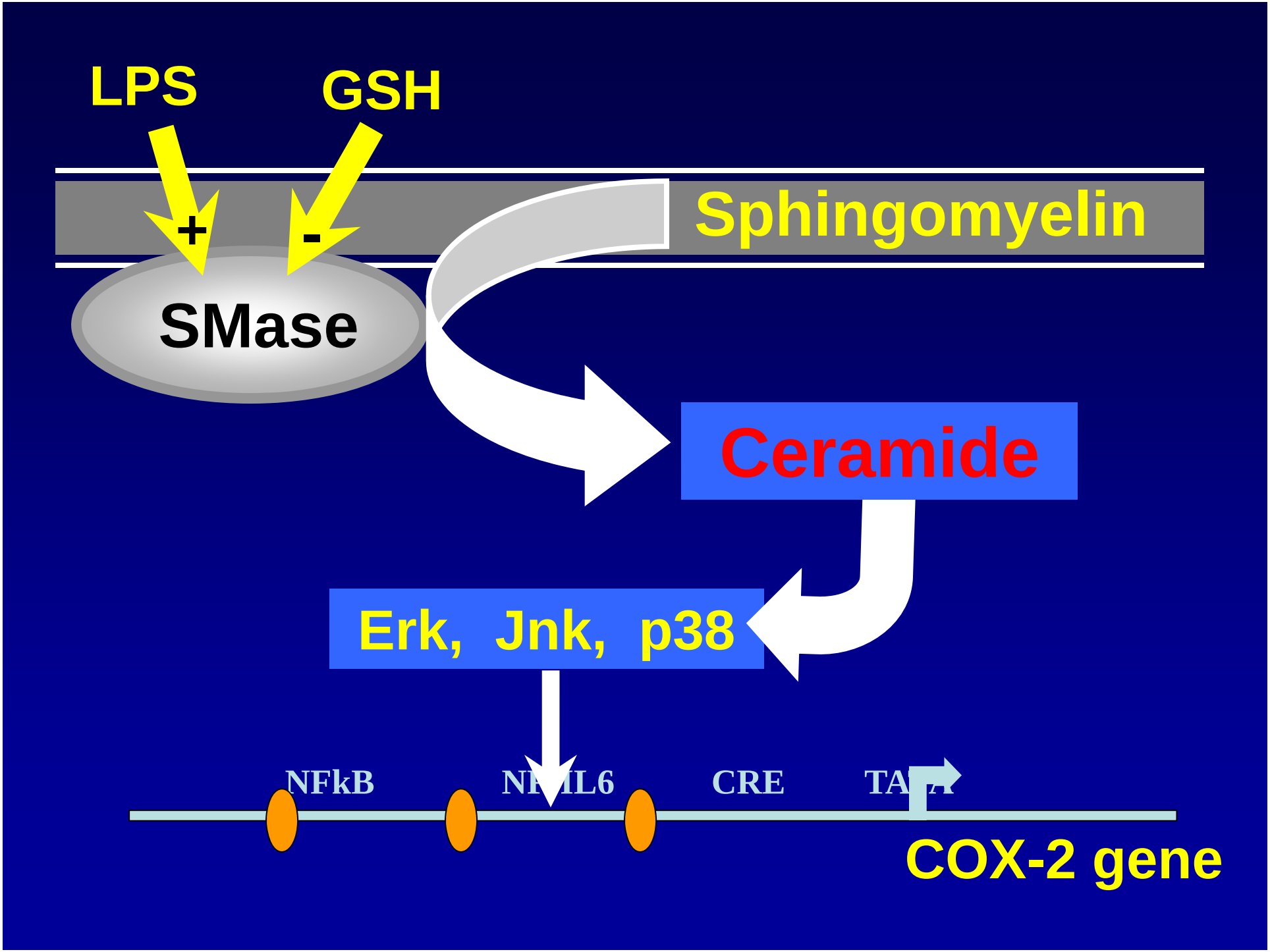
IL-1β
IL-6
TNF- α
IL-10
glucocorticoid

GSH
ceramide

old

IL-1β
IL-6
TNF- α
IL-10
glucocorticoid

↓ GSH
↑ ceramide


LPS
GSH
+
-
Sphingomyelin
SMase
Ceramide
Erk, Jnk, p38
NFkB
CRE
COX-2 gene

Age-associated Increase in COX-2 Expression is Due to Ceramide-induced Upregulating of NFκB Activation

- Old Mϕ have higher ceramide levels and NFκB activity than young Mϕ.
- Addition of Ceramide increases NFκB and COX-2 expression in young Mϕ.
- NFκB inhibitors decrease COX-2 expression in old Mϕ.

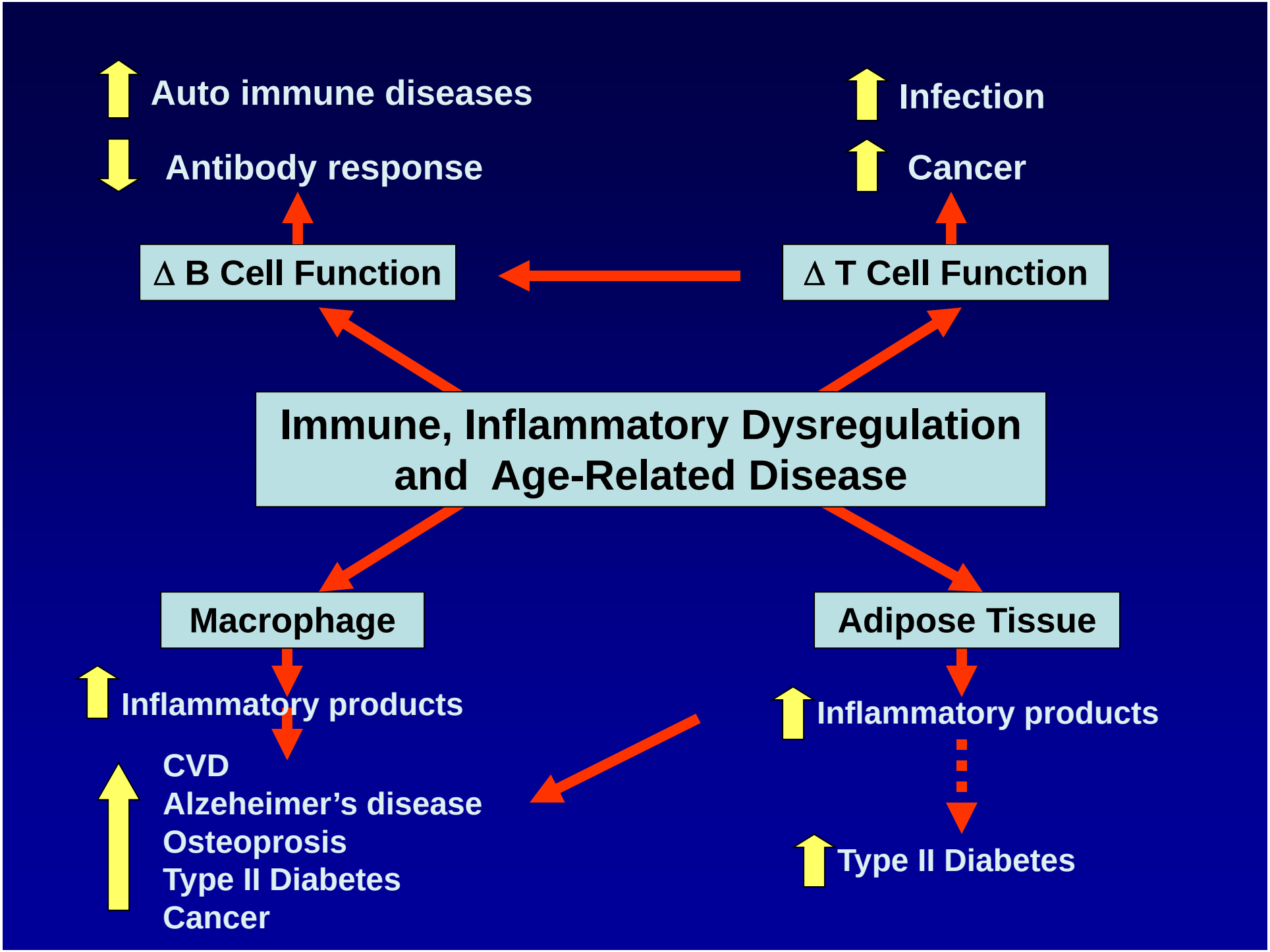
Claycombe et al., JBC 277:30784, 2002

Wu et al., JBC; 278: 10983, 2003

Mechanism for age-associated increase in COX-2 transcription

Claycombe et al., JBC 277:30784, 2002

Wu et al., JBC; 278: 10983, 2003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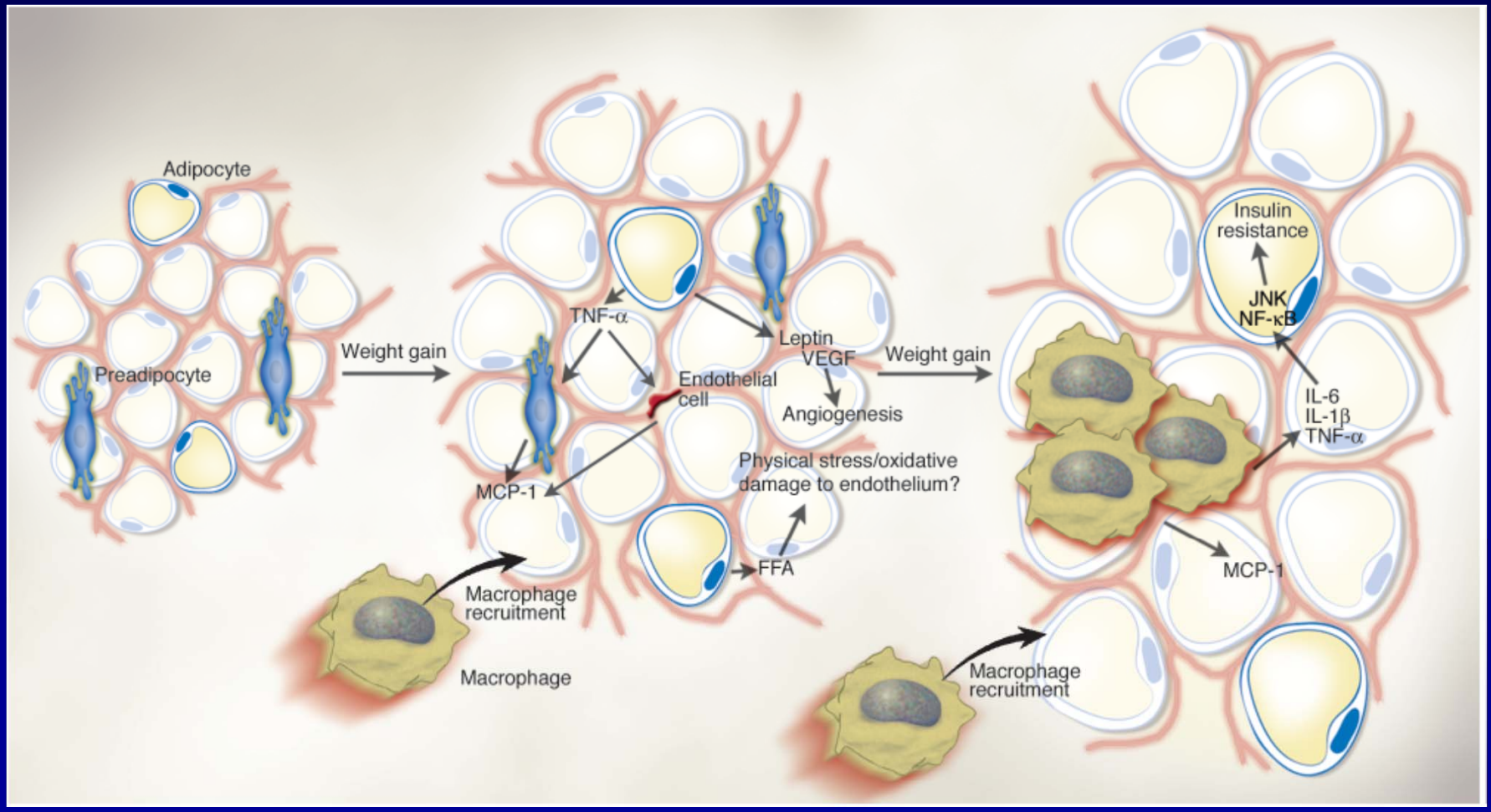
Inflammatory products
CVD
Alzeheimer's disease
Osteoprosis
Type II Diabetes
Cancer
Inflammatory products
Type II Diabetes

Aging, Insulin Resistance, T2D incidence

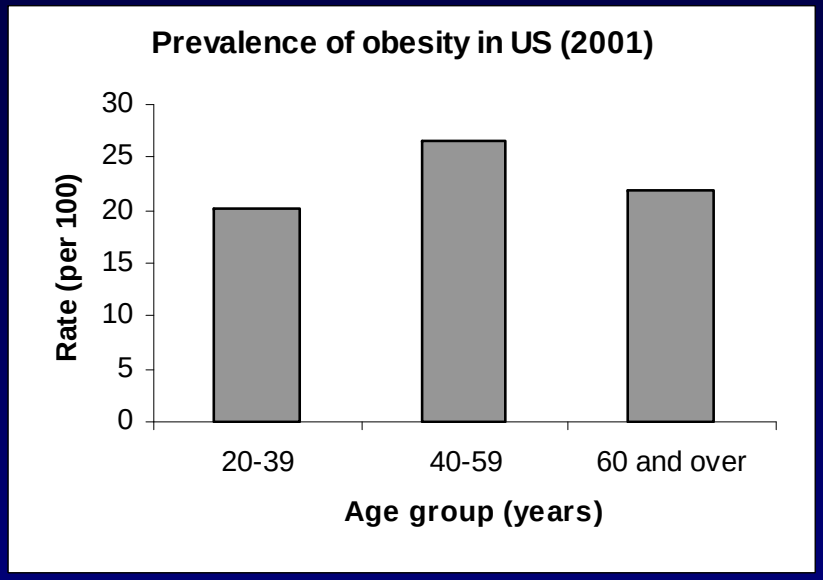
- It has been known for a long time that glucose intolerance, insulin resistance, and T2D incidence are increased with advancing age.

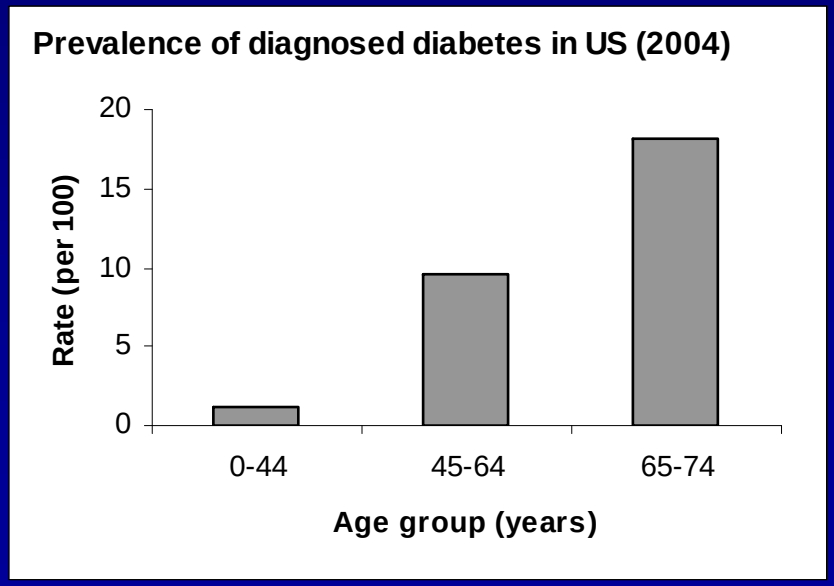
Obesity Results in Insulin Resistance Through Inducing Macrophage Infiltration and Their Production of Inflammatory Cytokines

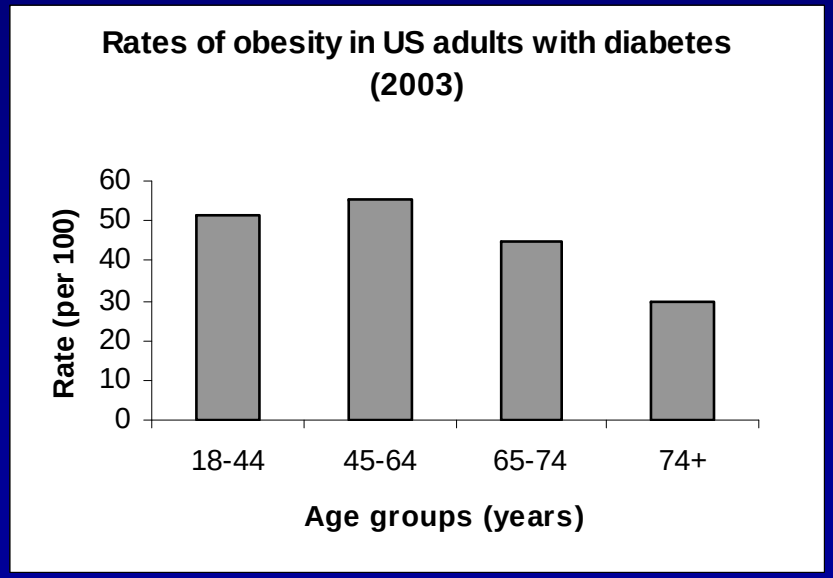


Wellen and Hotamisligil, JCI, 112:1785, 2003

Sharp increase with age in diabetes incidence can't be entirely explained by the change in body weight and body composition

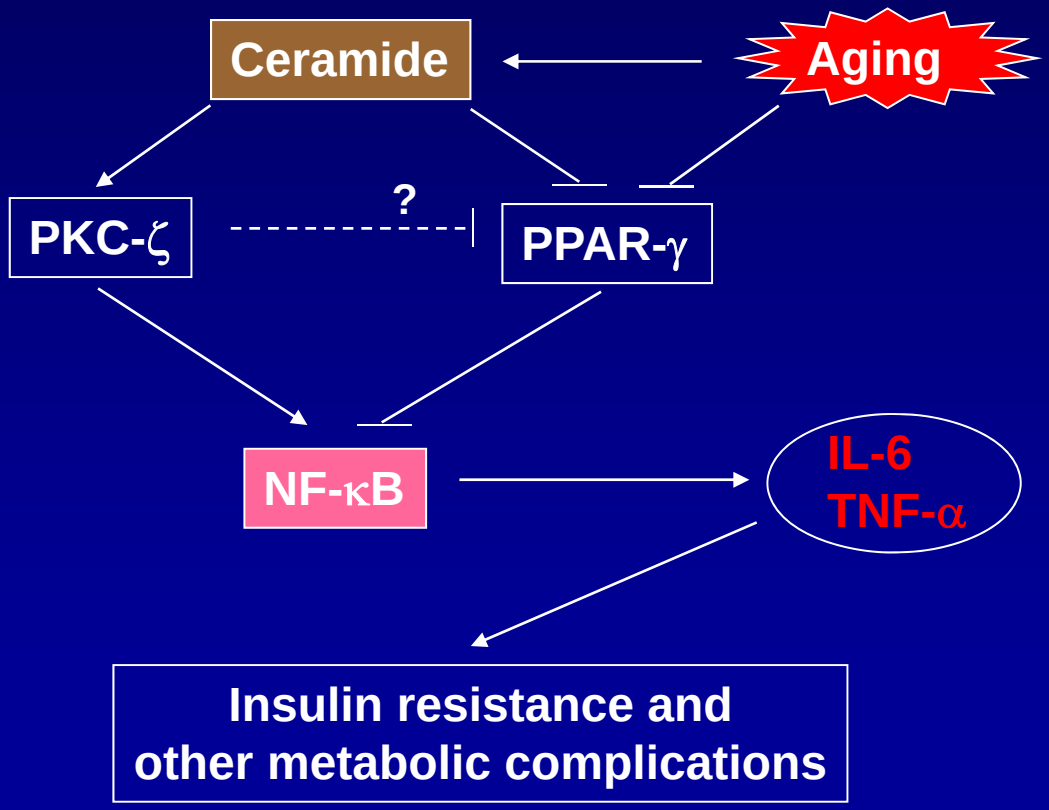


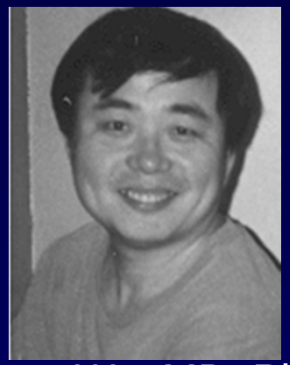




CDC data (http://www.cdc.gov)

Age-related Increase in Adipose Tissue Inflammation and its Underlying Mechanisms



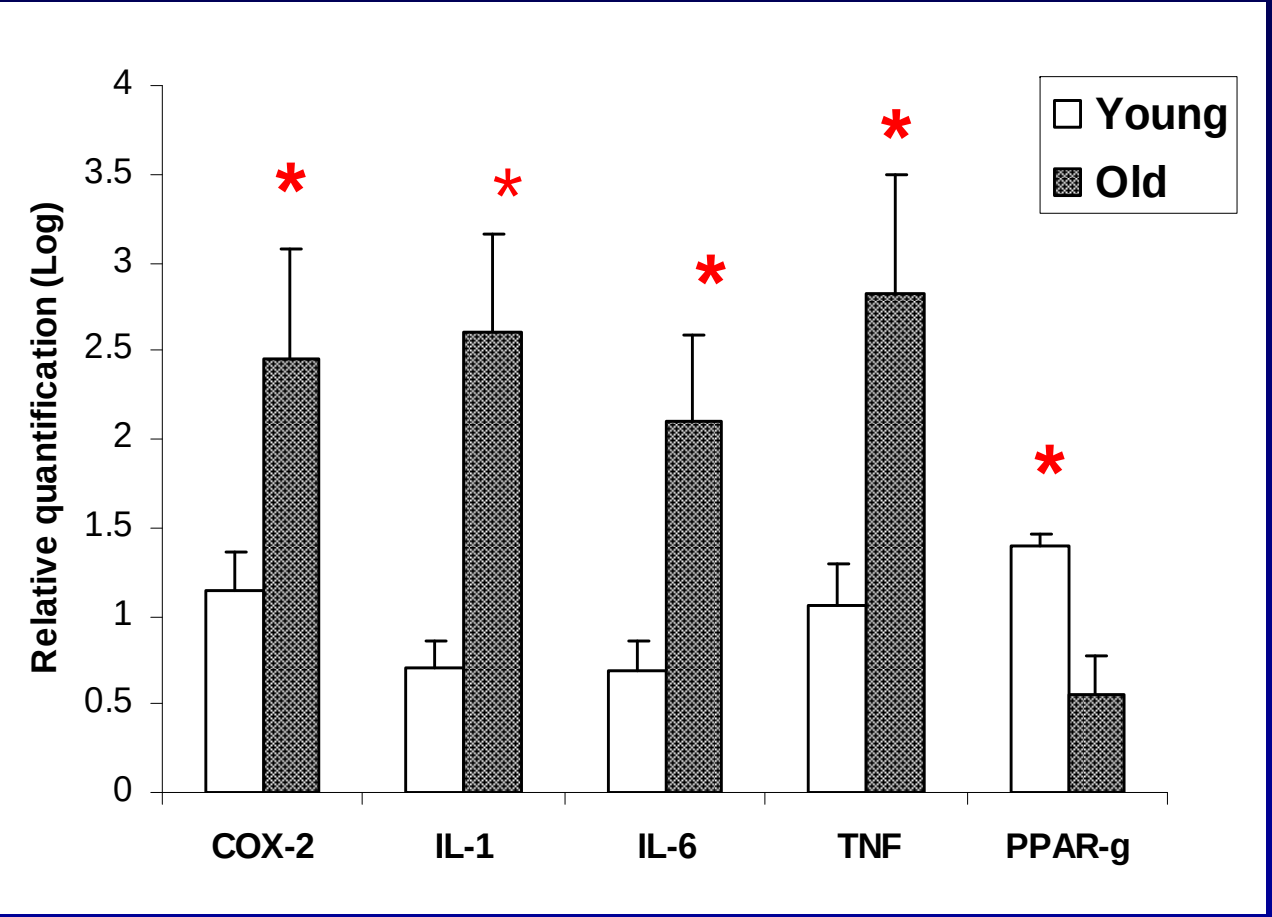


Dayong Wu, MD, PhD

Methods

- **Animals:** C57BL mice Young (5-6 mo)
  Old (23-24 mo)
- **Adipocyte and SVC isolation:** collagenase digestion
- **mRNA analysis:** Real time RT-PCR
- **Mϕ in AT:** FACS and immunohistochemistry
- **IL-6 and TNF-α assay:** ELISA
- **PGE_2 assay:** RIA
- **Cell viability:** MTS and LDH assays

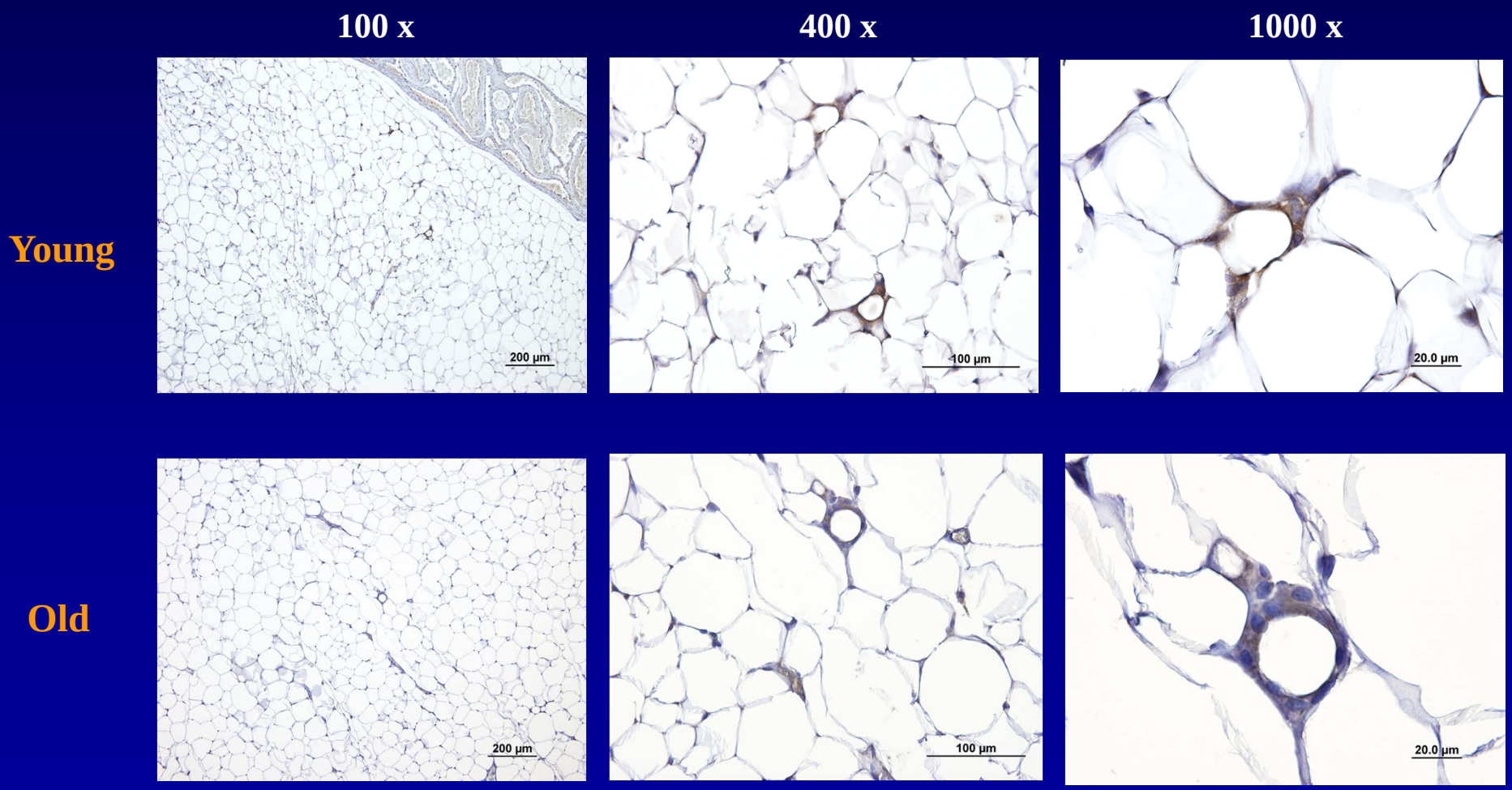
Epididymal Adipose Tissue From Old Mice Have Higher Expression of Inflammatory Genes



*Significantly different from Young mice

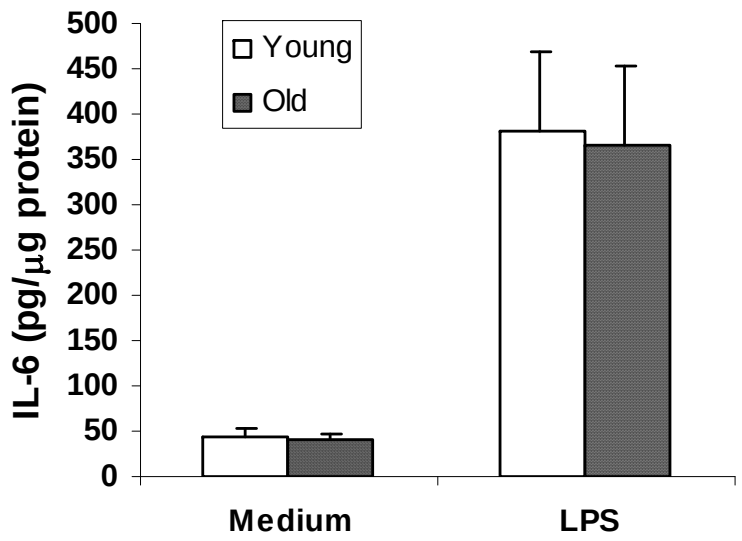
Wu et al., JI, 179:4829, 2007

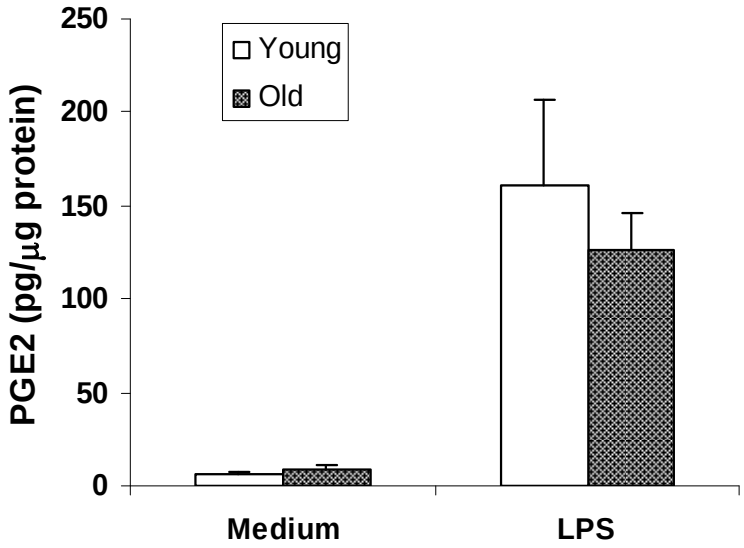
Mϕ (F4/80+ cells) in epididymal adipose tissues of young and old mice



Wu et al., JI, 179:4829, 2007

IL-6 and PGE_2 Production Is Not Significantly Different Between Stromal Vascular Cells of Young and Old Mice

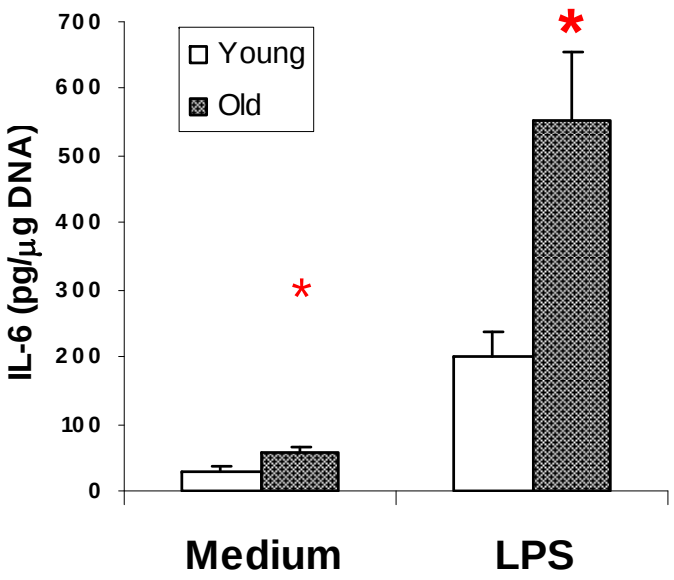


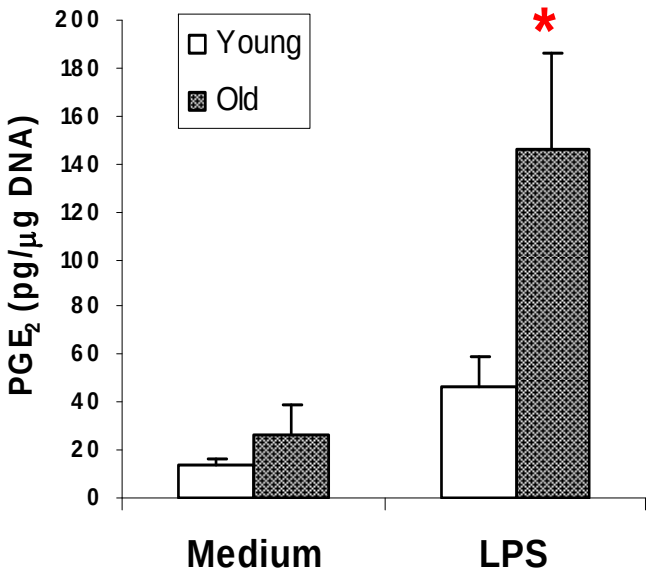


Mean± SE, n=6

Wu et al., JI, 179:4829, 2007

Adipocytes From Old Mice Have Higher IL-6 and PGE_2 Production Than Those of Young Mice

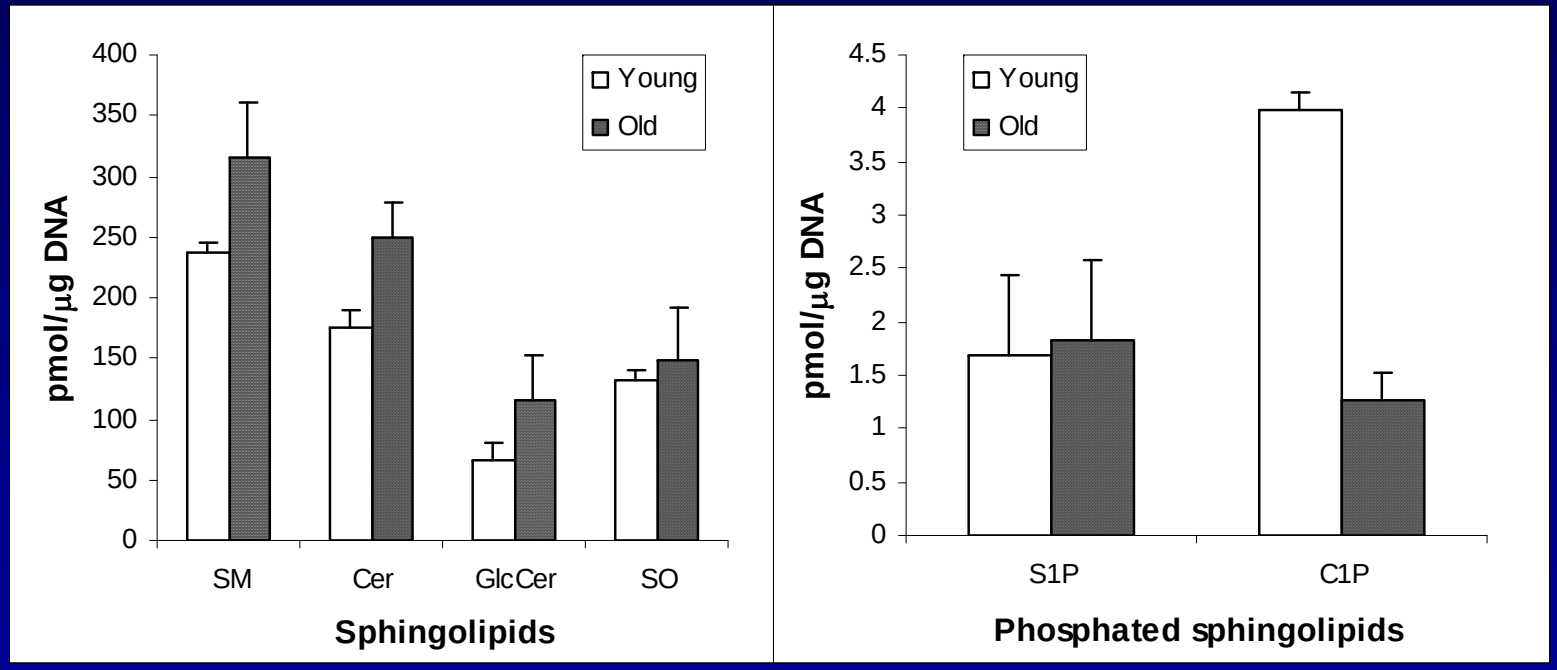




*Significantly different from young mice. Mean±SE, n=7-10

Wu et al., JI, 179:4829, 2007

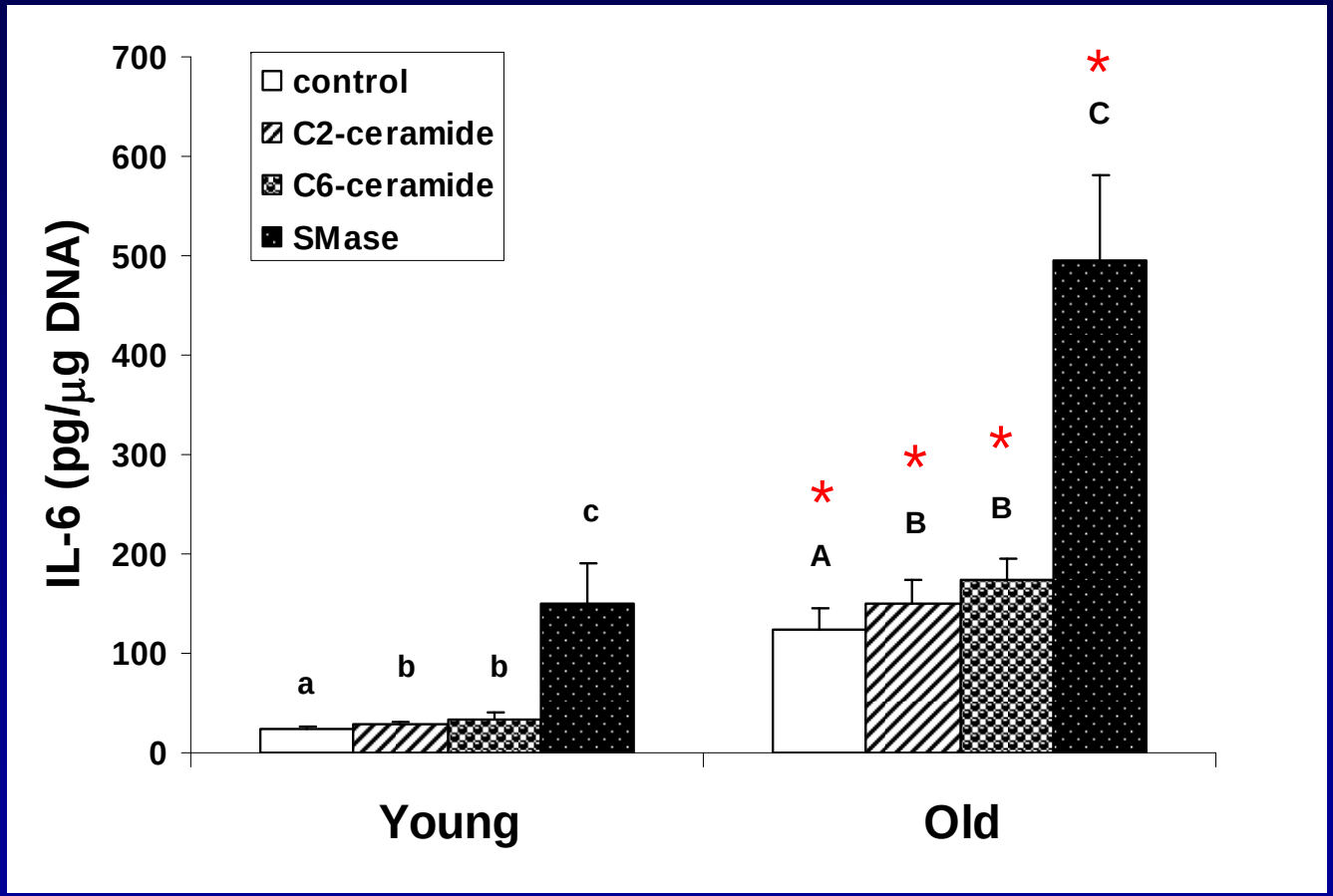
Old Adipocytes Have Higher Levels of Ceramide and Sphingomyelin Compared to Those From Young



SM: sphingomyelin; Cer: ceramide; ClcCer: glucosylated ceramide; SO: sphingosine;
S1P: **sphingosin-1-phosphate; C1P: ceramide-1-phosphate.**

Wu et al., JI, 179:4829, 2007

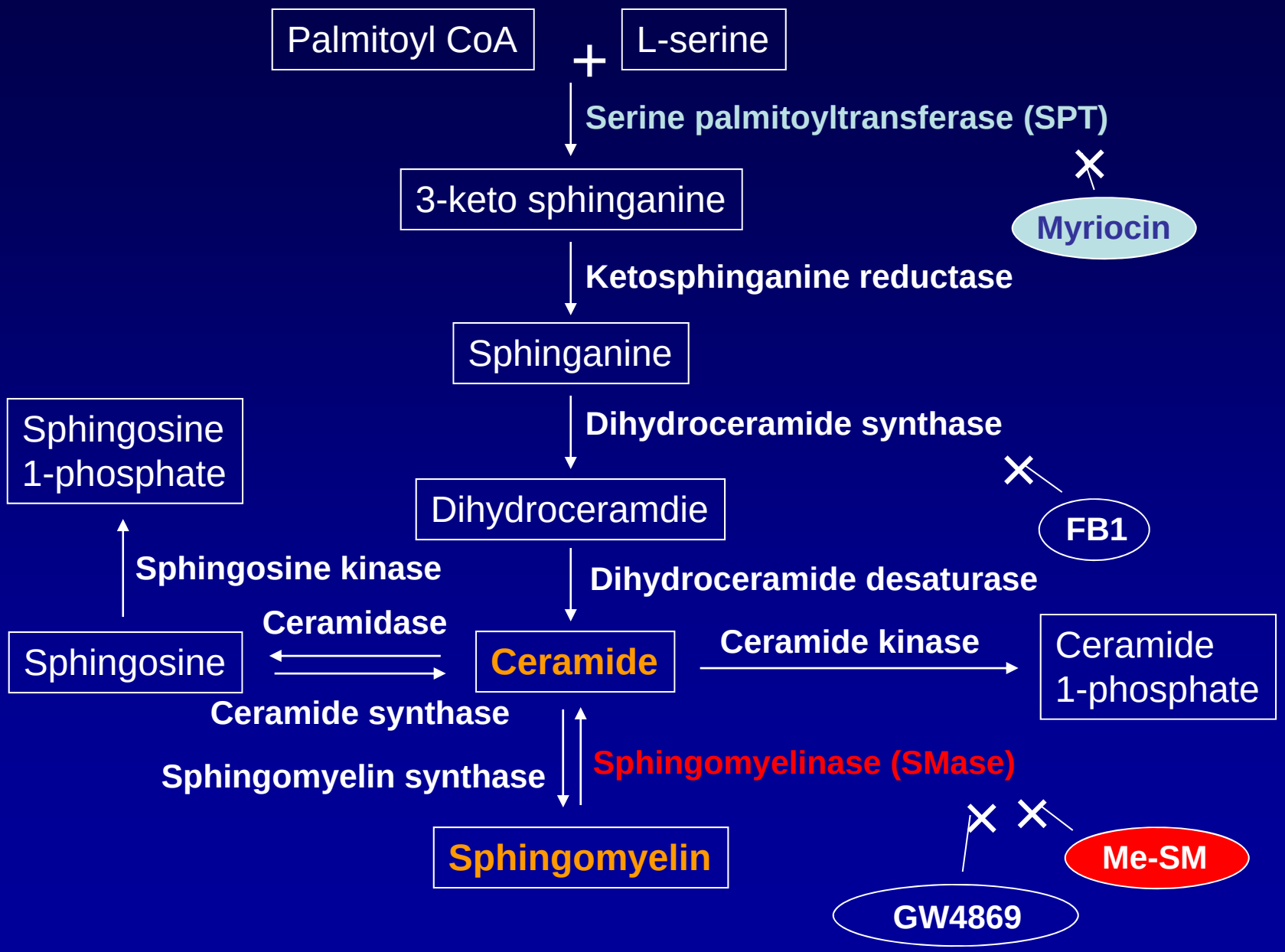
Ceramide Increases IL-6 Production by Adipocytes of Young and Old Mice



***Significan age difference within each treatment.**
Mean±SE, n=6

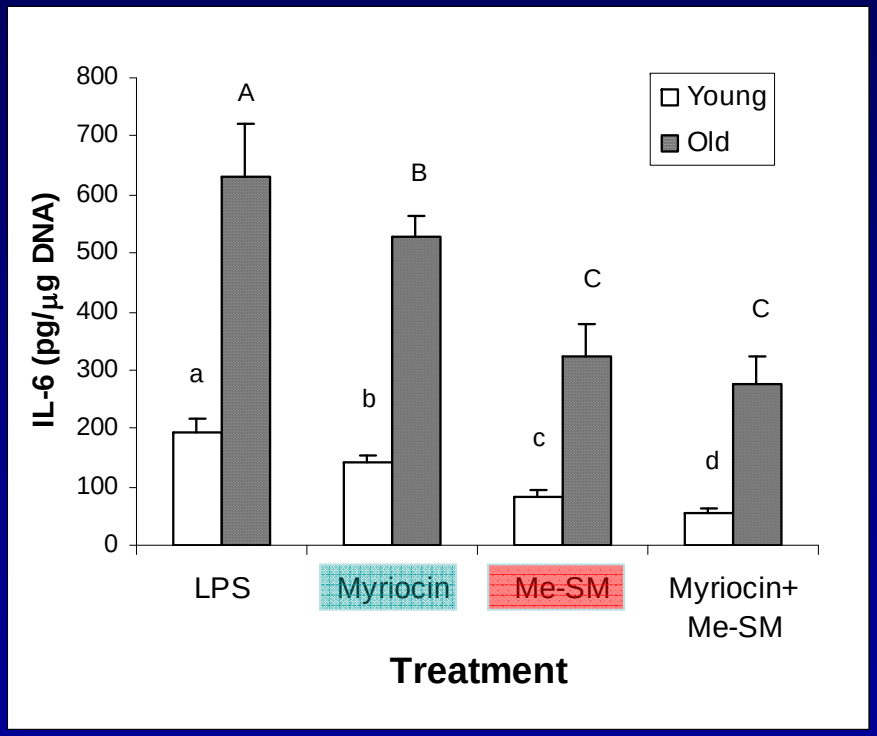
Wu et al., JI, 179:4829, 2007

Ceramide Synthesis, Related Enzymes and Enzyme Inhibitors

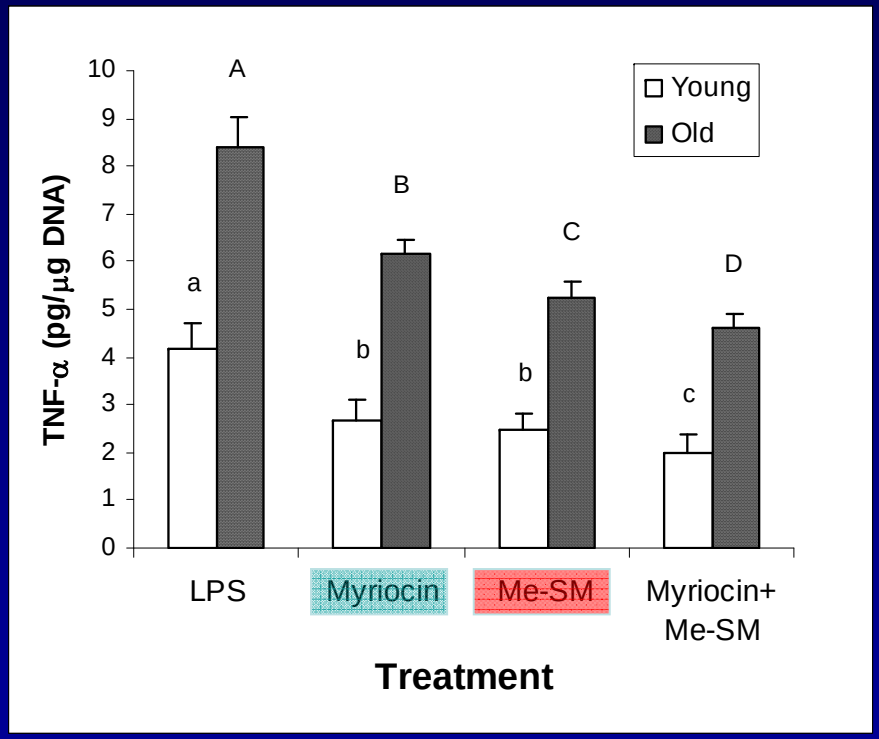


Effect of inhibiting de novo ceramide synthesis and nSMase on LPS-stimulated IL-6 and TNF-α production by adipocytes

IL-6

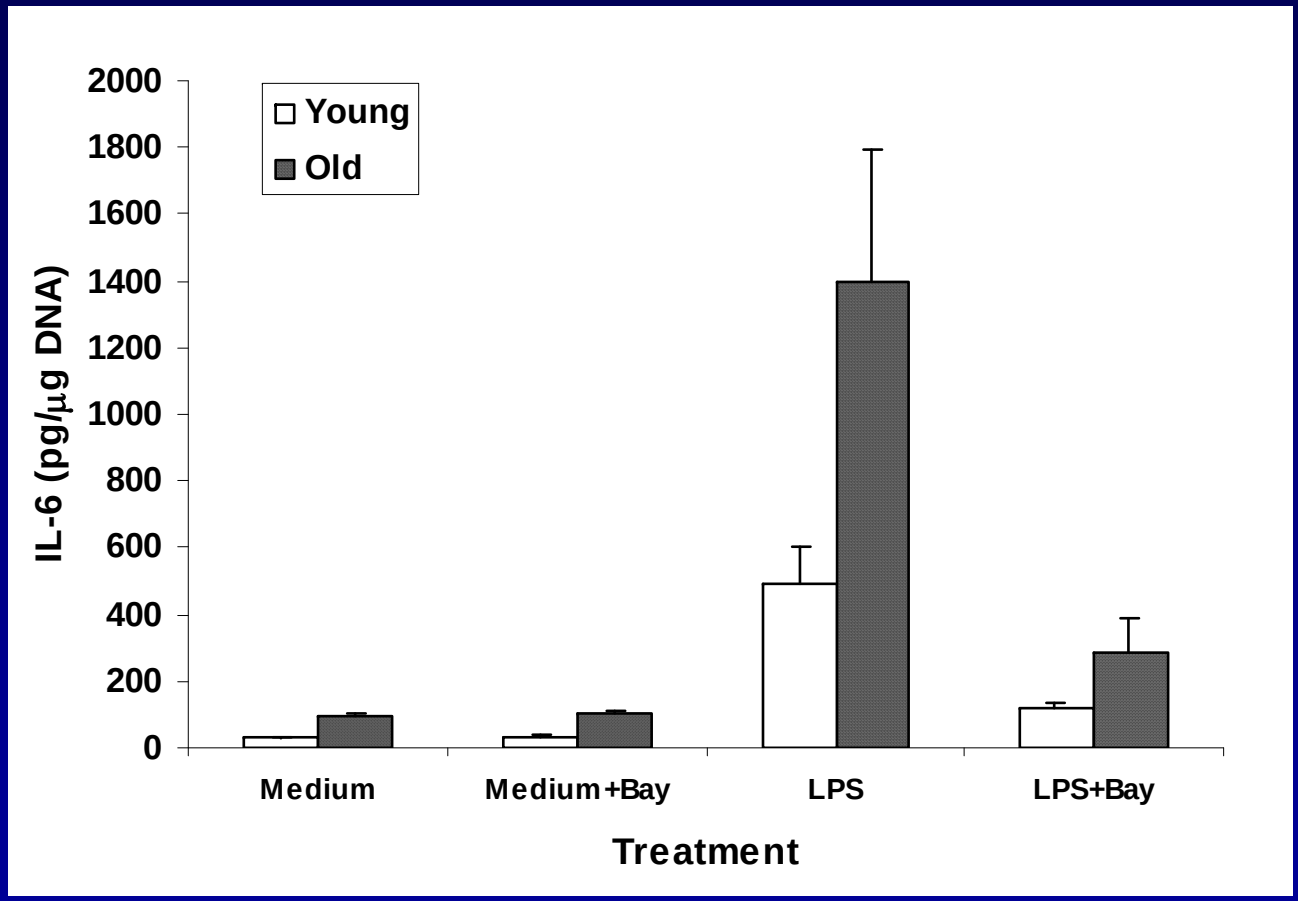


TNF-α



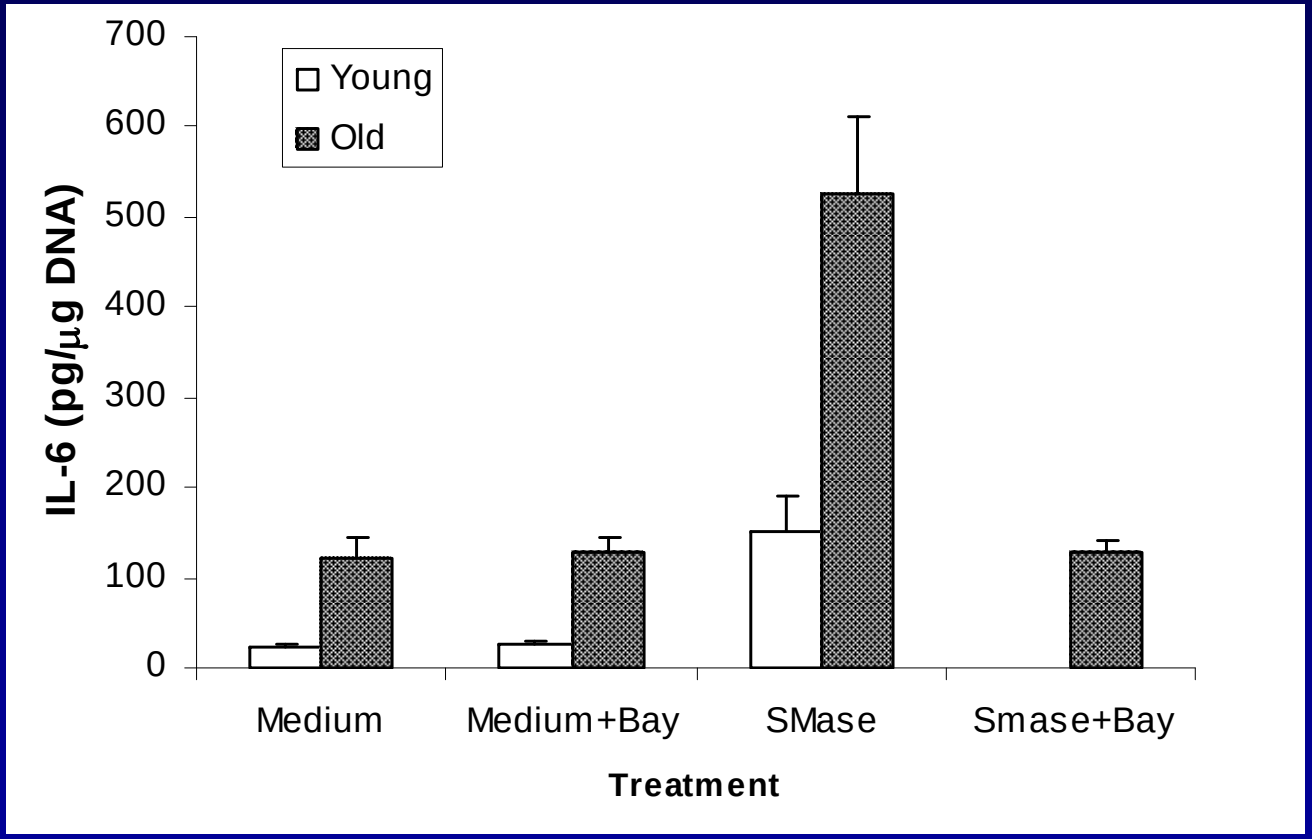
Mean ± SE, n=10
Different letters within each age denote significant difference at p<0.05.
There is a significant difference between age group in every treatment.

Inhibiting NF-κB Activation Reduces IL-6 Production by Adipocytes of Young and Old Mice



Wu et al., JI, 179:4829, 2007

Inhibiting NF-κB Activation Reduces Sphingomyelinase-induced IL-6 Production by Mouse Adipocytes



Wu et al., JI, 179:4829, 2007

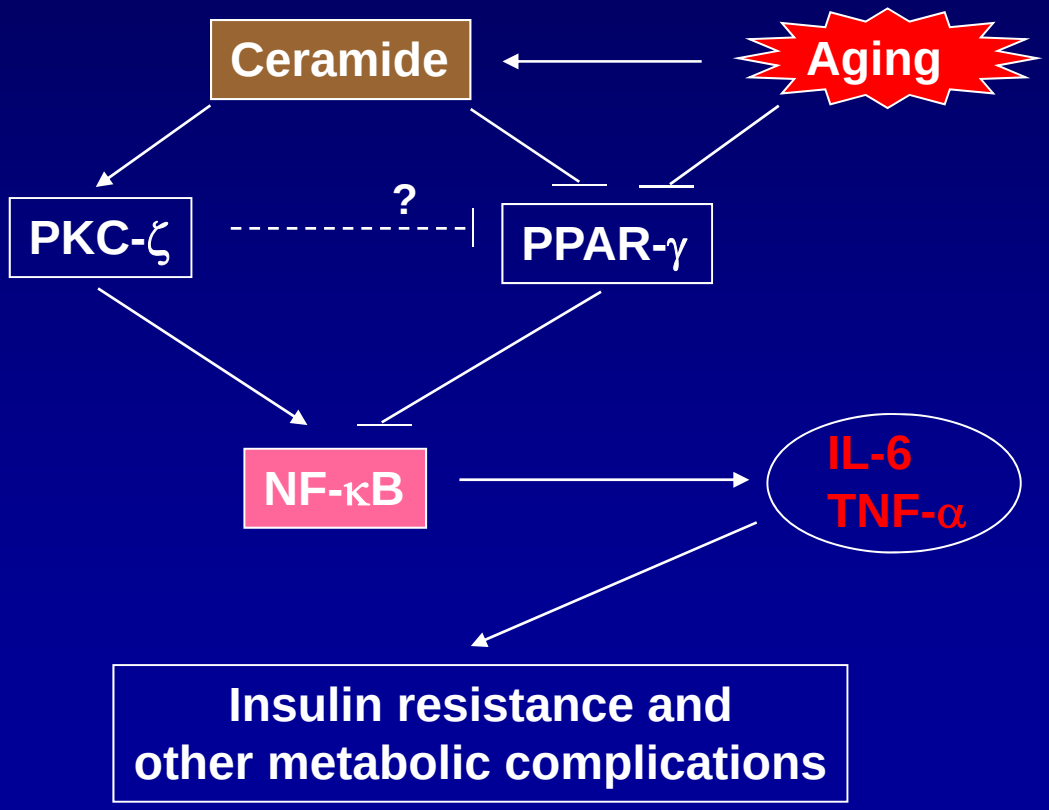
Summary

1. **Adipose tissue expression of pro-inflammatory mediators is upregulated while anti-inflammatory and insulin-sensitizing factor PPAR-γ is downregulated with aging.**

2. **Unlike the changes observed in obesity, there is no apparent age-related difference in either Mϕ infiltration into adipose tissue or MCP-1 production by adipocytes.**

3. **Adipocytes and not non-adipocytes (stromal vascular cells) in adipose tissue may be the major player responsible for age-related upregulation of inflammatory products, suggesting a different mechanism from that in obesity.**

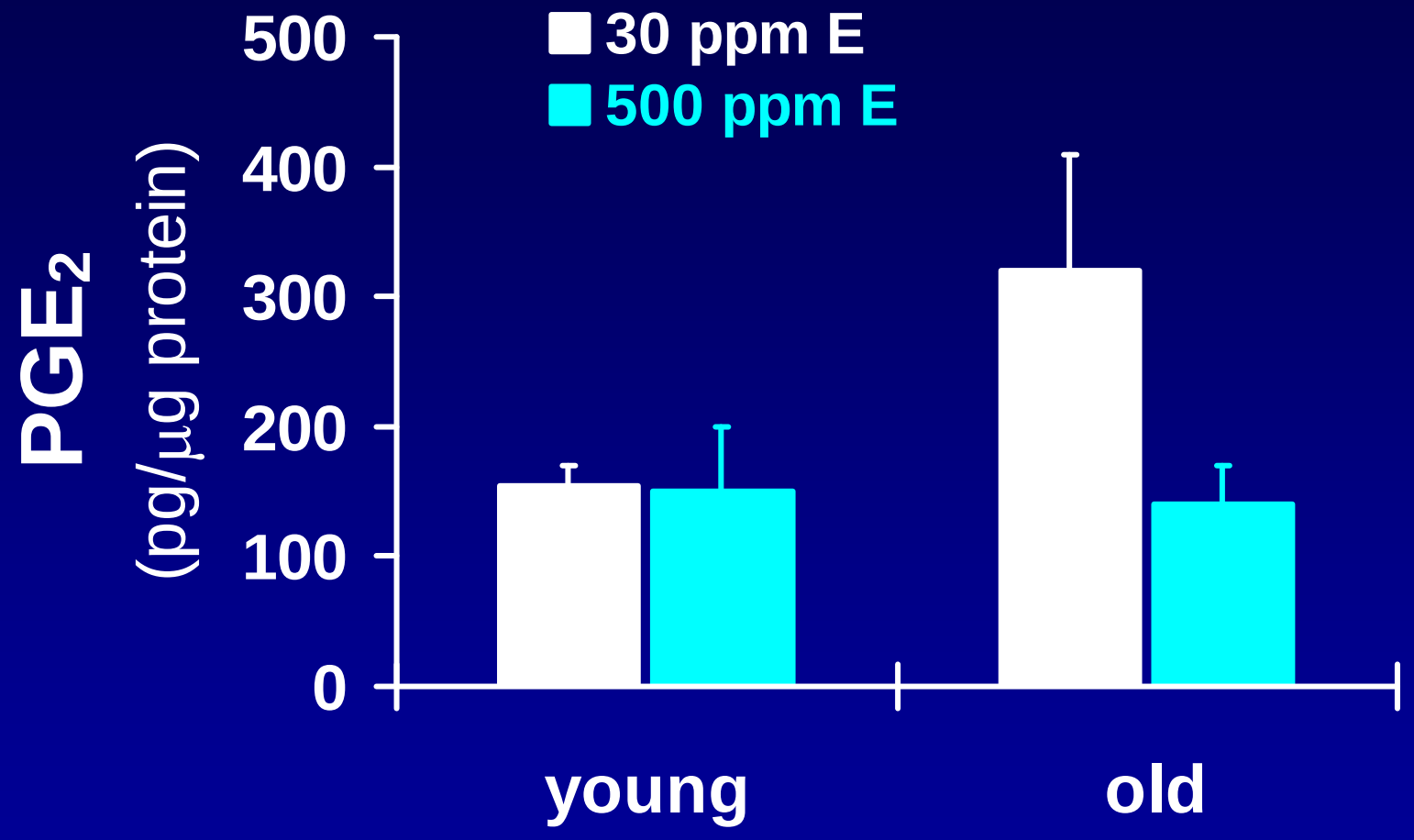
Age-related Increase in Adipose Tissue Inflammation and its Underlying Mechanisms



Nutritional Intervention and Age- associated Inflammation

- Vitamin E
- n-3 PUFA
- Calorie restriction

Vitamin E and PGE_2 Production



Wu, et al., AJP 1998;275:C661

Vitamin E and Immune Response in the Older Adults

Vitamin E supplementation of healthy elderly significantly improves in vivo and in vitro indices of T cell-mediated function.

Meydani et al. AJCN 1990; 52:557-563

Meydani et al. JAMA 1997; 277:1380-1386.

Pallast et al. AJCN 69: 1273-1281,1999.

Effect of Vitamin E Supplementation on Respiratory Infections

	Placebo	Vitamin E	OR (CI)
All respiratory Infections	74%	65%	0.65* (0.43-0.97)
Upper respiratory infections	62%	50%	0.62* (0.43-0.91)
Lower respiratory infections	32%	33%	1.03 (0.69-1.53)

*Significantly difeent from Placebo at $p<0.05$

Meydani et al. JAMA, 292:828-836, 2004.

- Vitamin E treatment did not have an overall effect on TNFα production

Genetics influence cytokine production

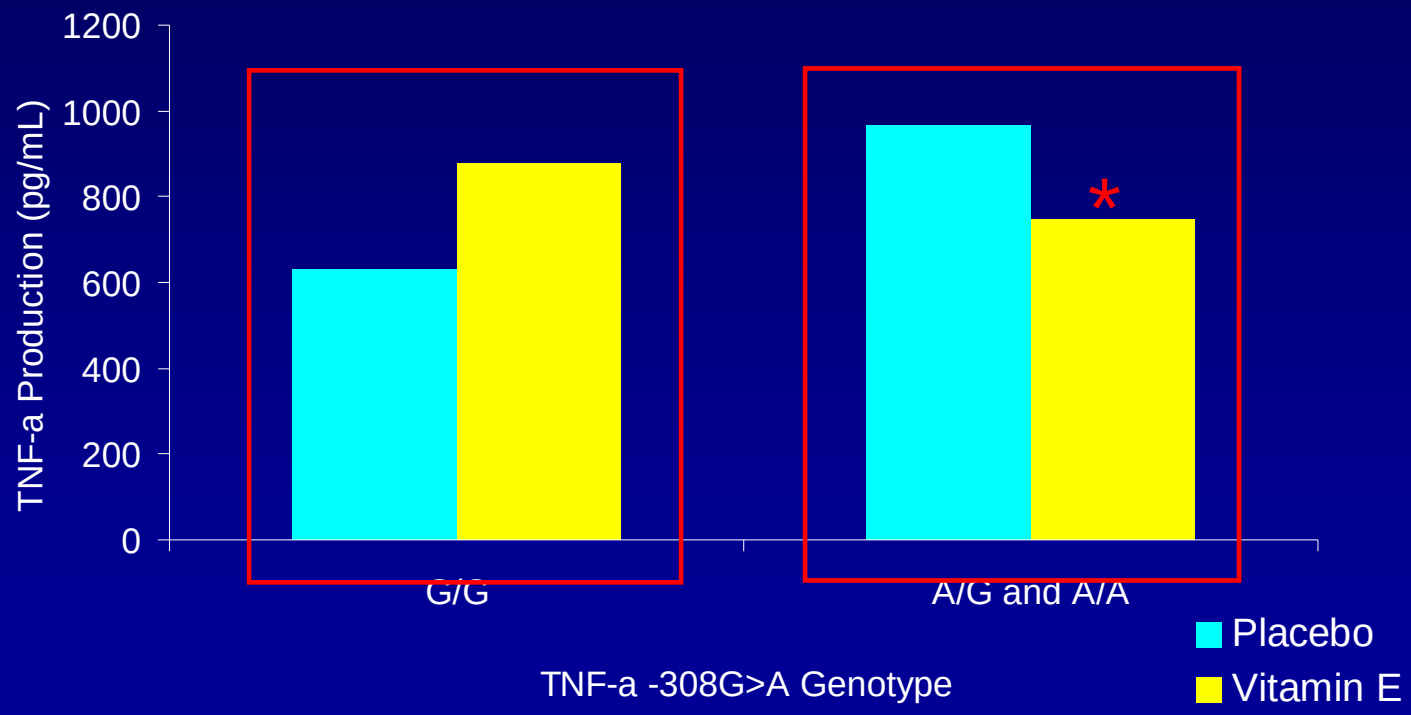
- **There is a high degree of variability in cytokine production between healthy individuals**
  - **Genetic factors** may explain variability in cytokine production

- **SNPs may account for individual variability**
  - Single nucleotide polymorphisms (SNPs) are single base pair changes in the DNA.
  - Identified at genes that encode cytokine proteins.

SNP→ influence cytokine response→ impact infection

The Effect E on TNF-α Production Depends on TNF-α -308G>A

- Interaction: vitamin E and TNF-a -308G>A p=0.039*



*Adjusted for baseline TNF-α production

Placebo n=56 (G/G =46; A/G and A/A =10); Vitamin E group n=39 (G/G=22; A/G and A/A =17)

Belisle et al., JN, 2009

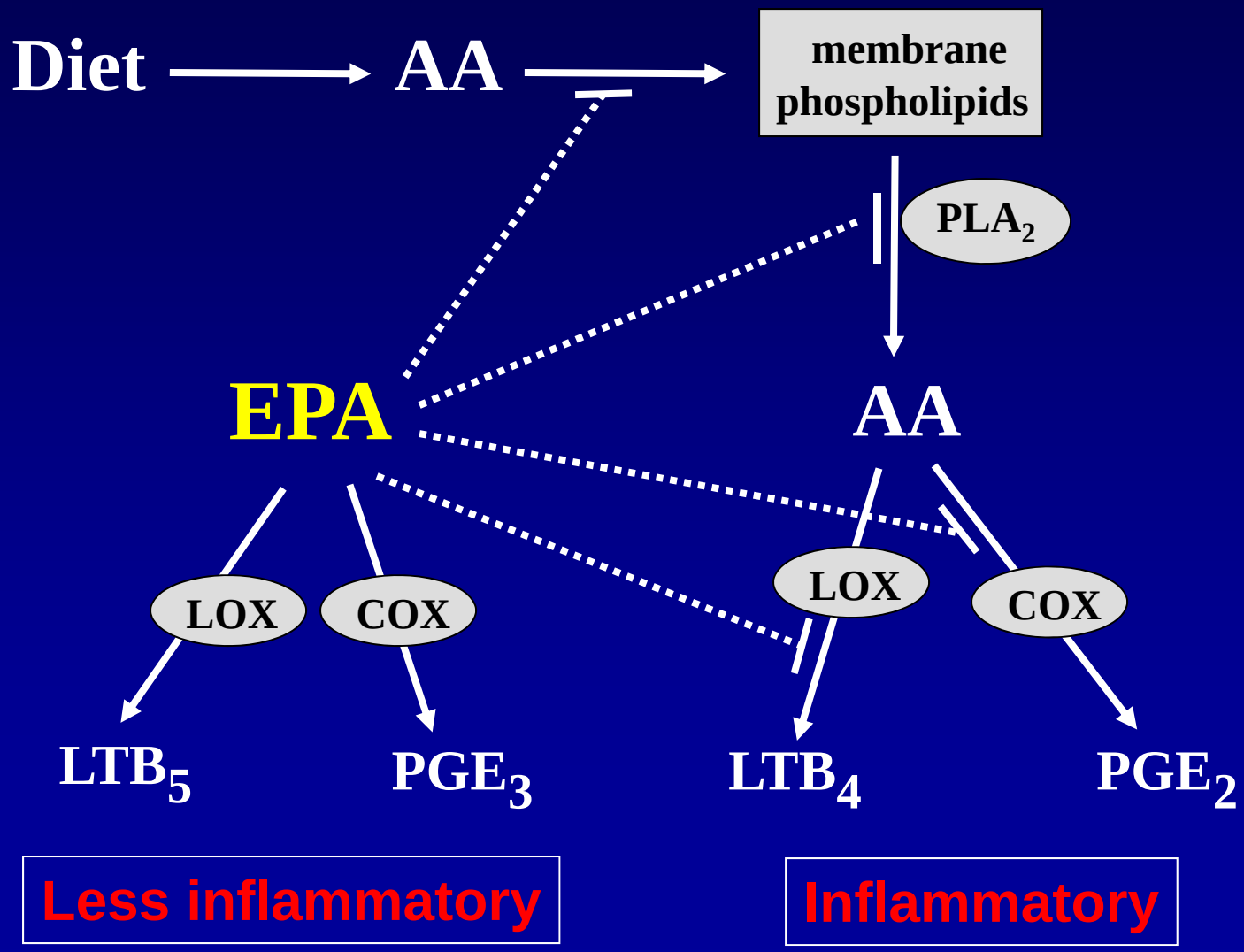
Concolusions

- These observations suggest that individual immune responses to vitamin E supplementation are in part mediated by genetic factors.
- Because A allele at TNFα is associated with higher TNFα levels, our observation suggest that the antiinflammatory effect of vitamin E is specific to those genetically predispose to higher inflammation.

Fish Oil Was Shown to Improve Clinical Symptoms In:

- Cardiovascular diseases
- Rheumatoid arthritis
- Psoriasis
- Multiple sclerosis
- Systemic lupus erythematosus
- Atopic dermatitis
- Ulcerative colitis

Modulatory Effect of EPA on Eicosanoid Synthesis



Effect of Low-fat Diets High and Low in Fish on Ex-vivo Cytokine and PGE_2 Production

	Low fat, high fish	low fat, low fish
	% change #	
IL-1β	-40*	62*
TNF	-35*	17
IL-6	-34*	0
PGE2	-63*	30

Compared to their own baseline

Meydani et al., JCI; 92:105-1, 1993

Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

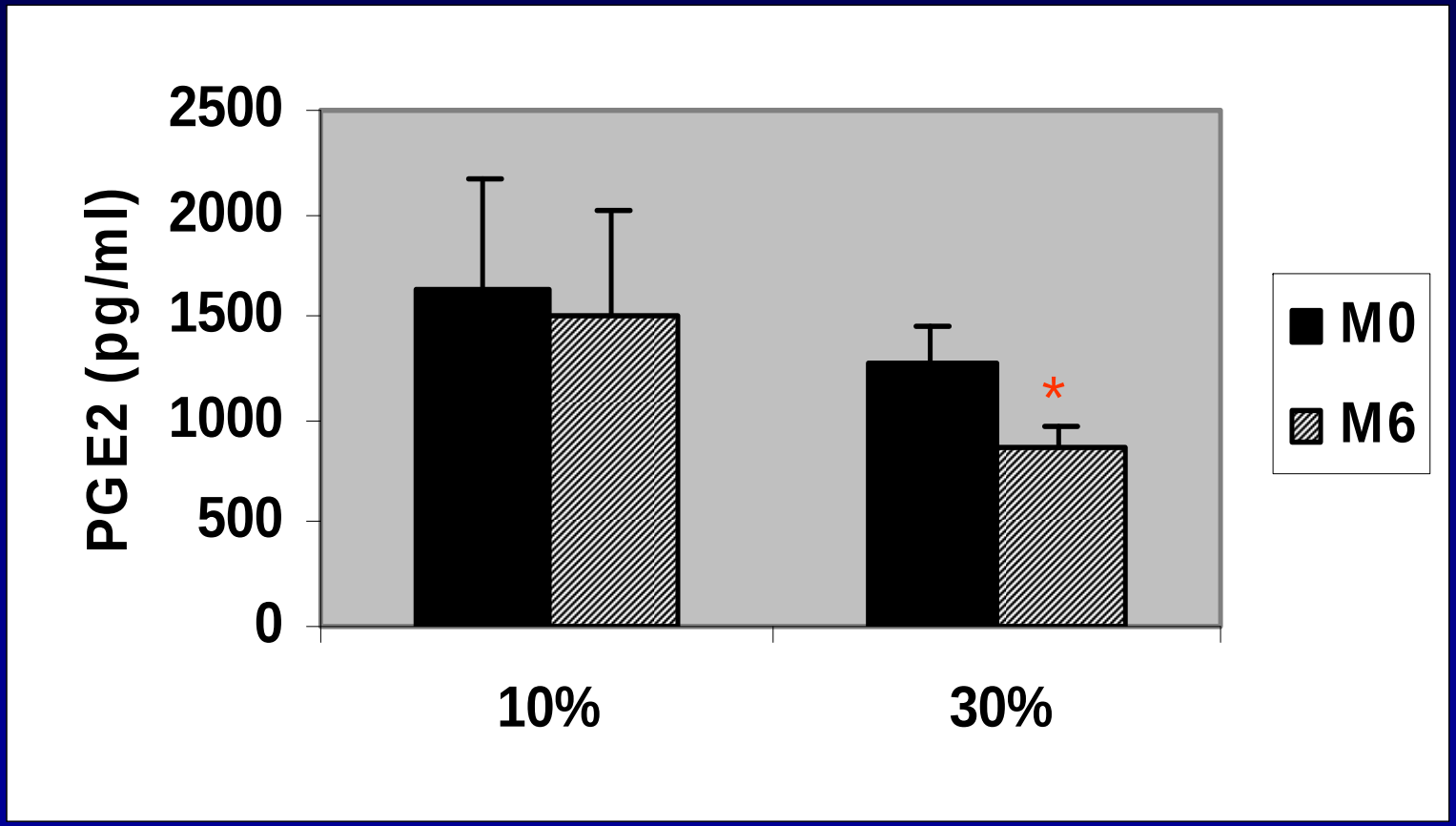
CALERIE

Jean Mayer USDA HNRCA
at TUFTS UNIVERSITY
BOSTON, MA

Experimental Design

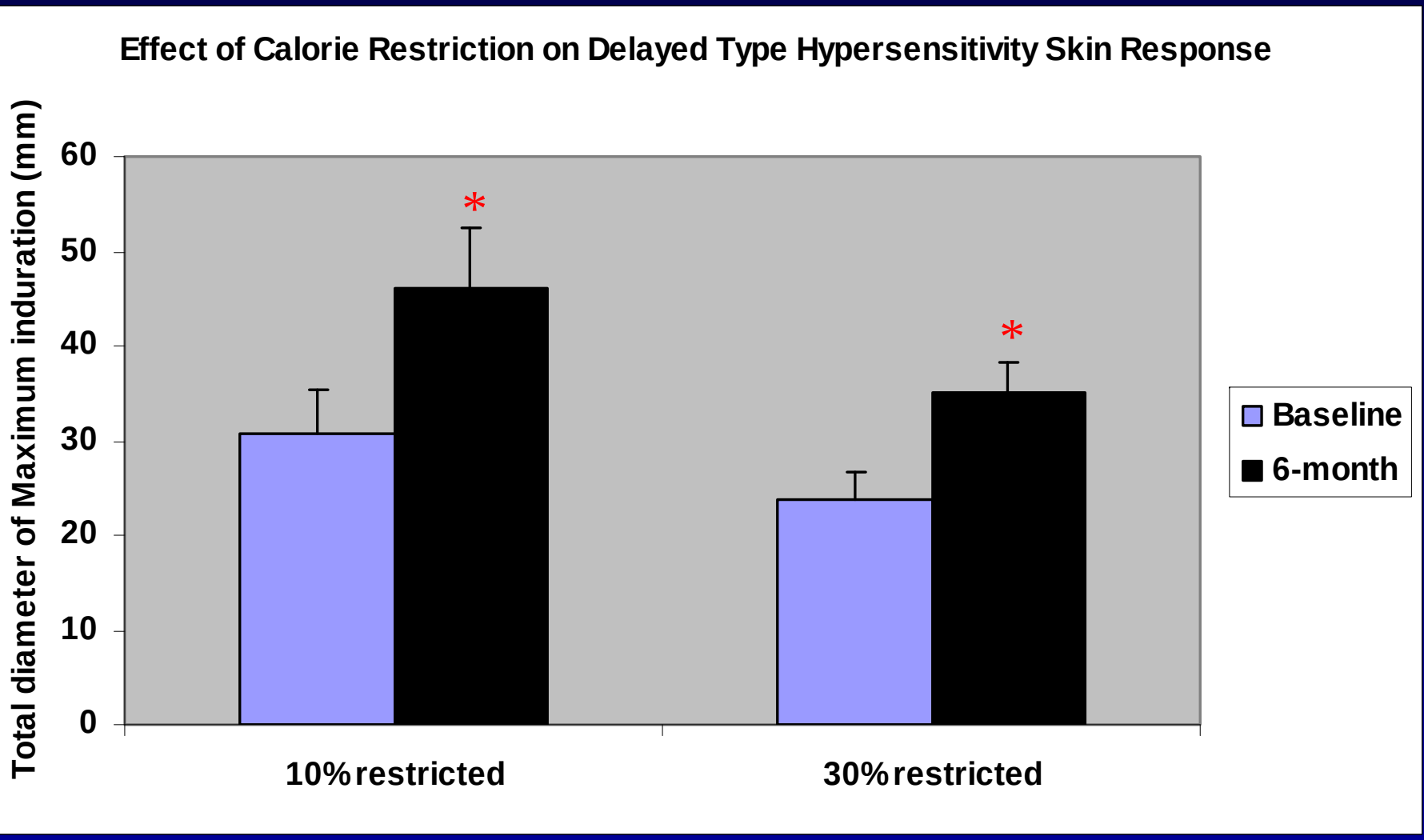
- **Design:** **Randomized, controlled , single-blind**
- **Subjects:** **Men and women, 25-45 years old, with BMI of 25-29 Kg/m^2**
- **Intervention:** **10 or 30% calorie restriction.**
- **DTH:** **Baseline and after 6 mo.**
- **In vitro immune measures:** **Baseline and after 6 mo.**

Effect of Calorie Restriction on LPS-Stimulated PGE_2 Production



* Significantly different from baseline

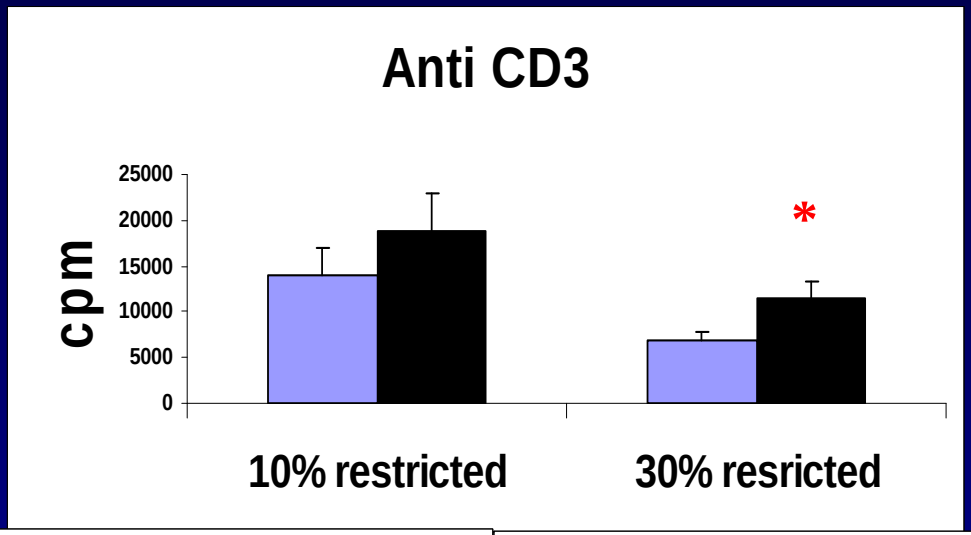
Ahmed et al. J. Gerontology, 2009



* Significantly different from baseline

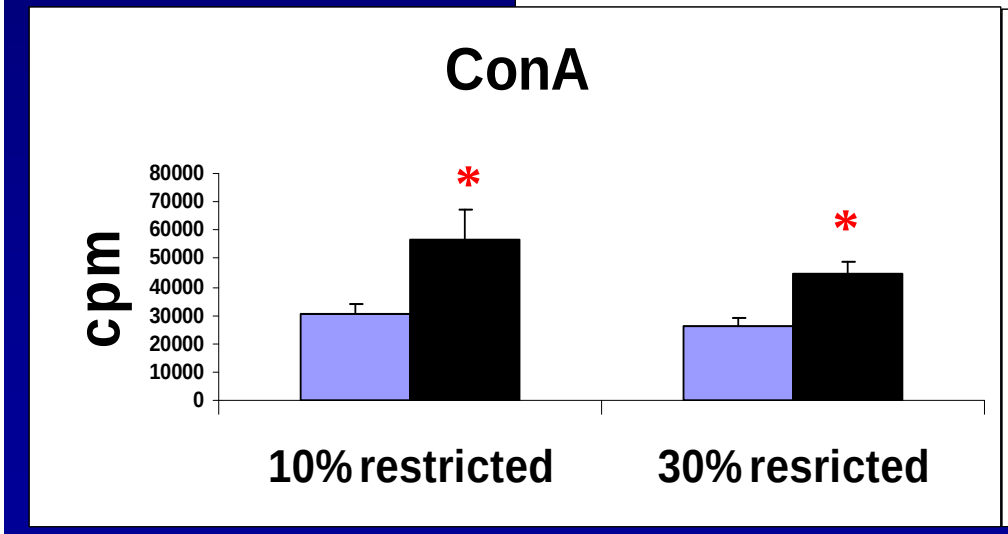
Ahmed et al. J. Gerontology, 2009

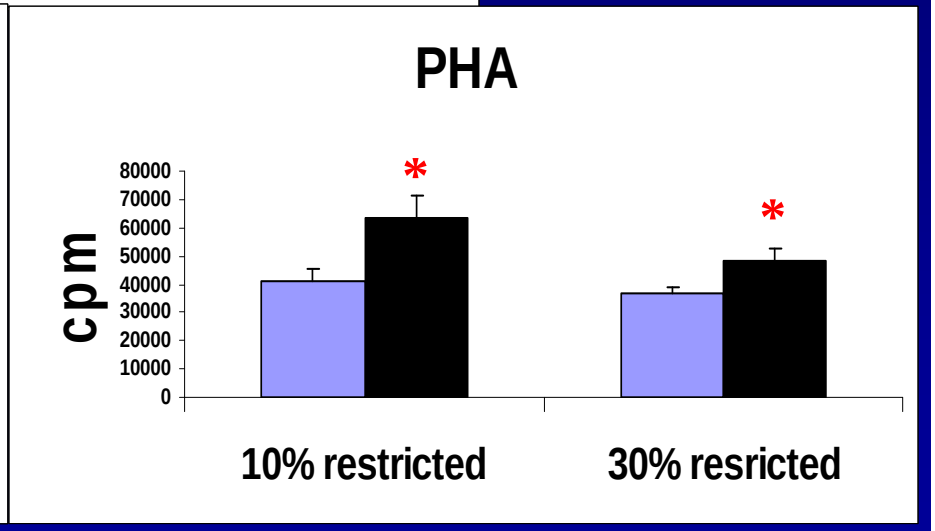
Effects of Calorie Restriction on Lymphocyte Proliferation



Baseline

6-month





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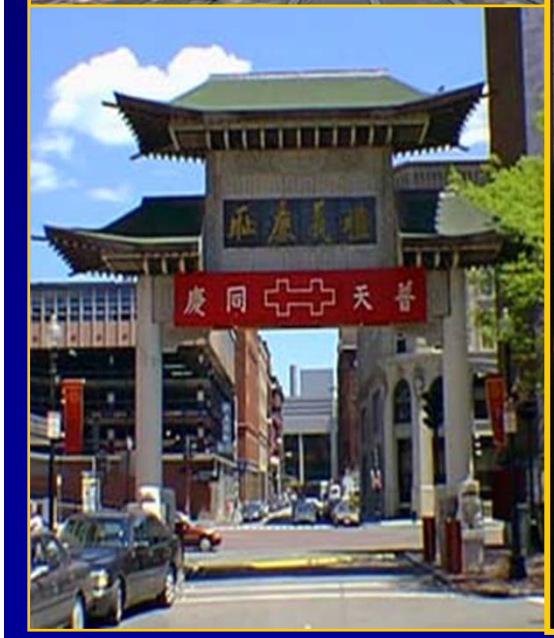
Ahmed et al. J. Gerontology, 2009



Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Advancing Healthy Aging Through Nutrition Research