The Nutrition/Neuroendocrineimmune Network

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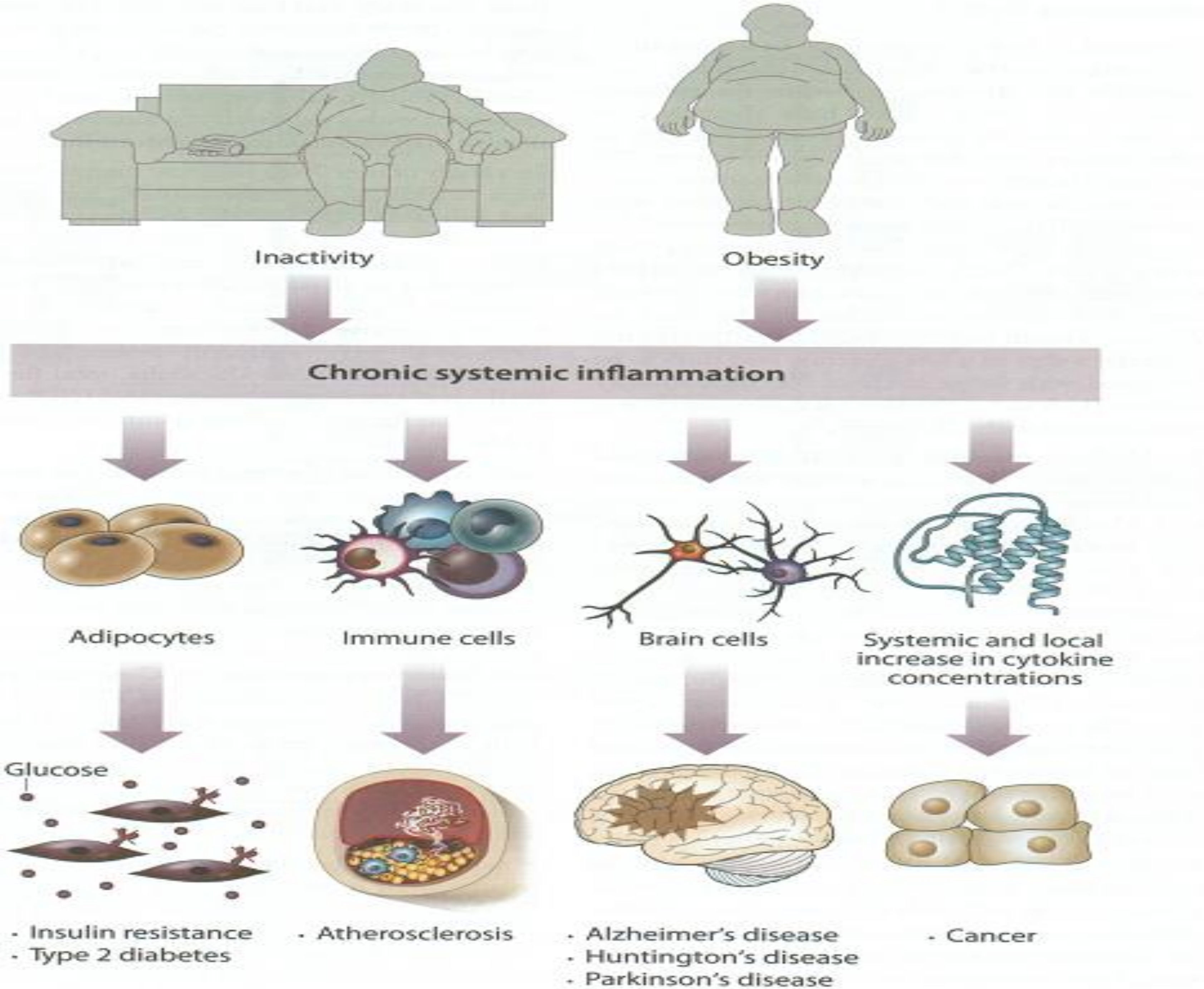
Connecting the Immune, Endocrine and Nervous Systems

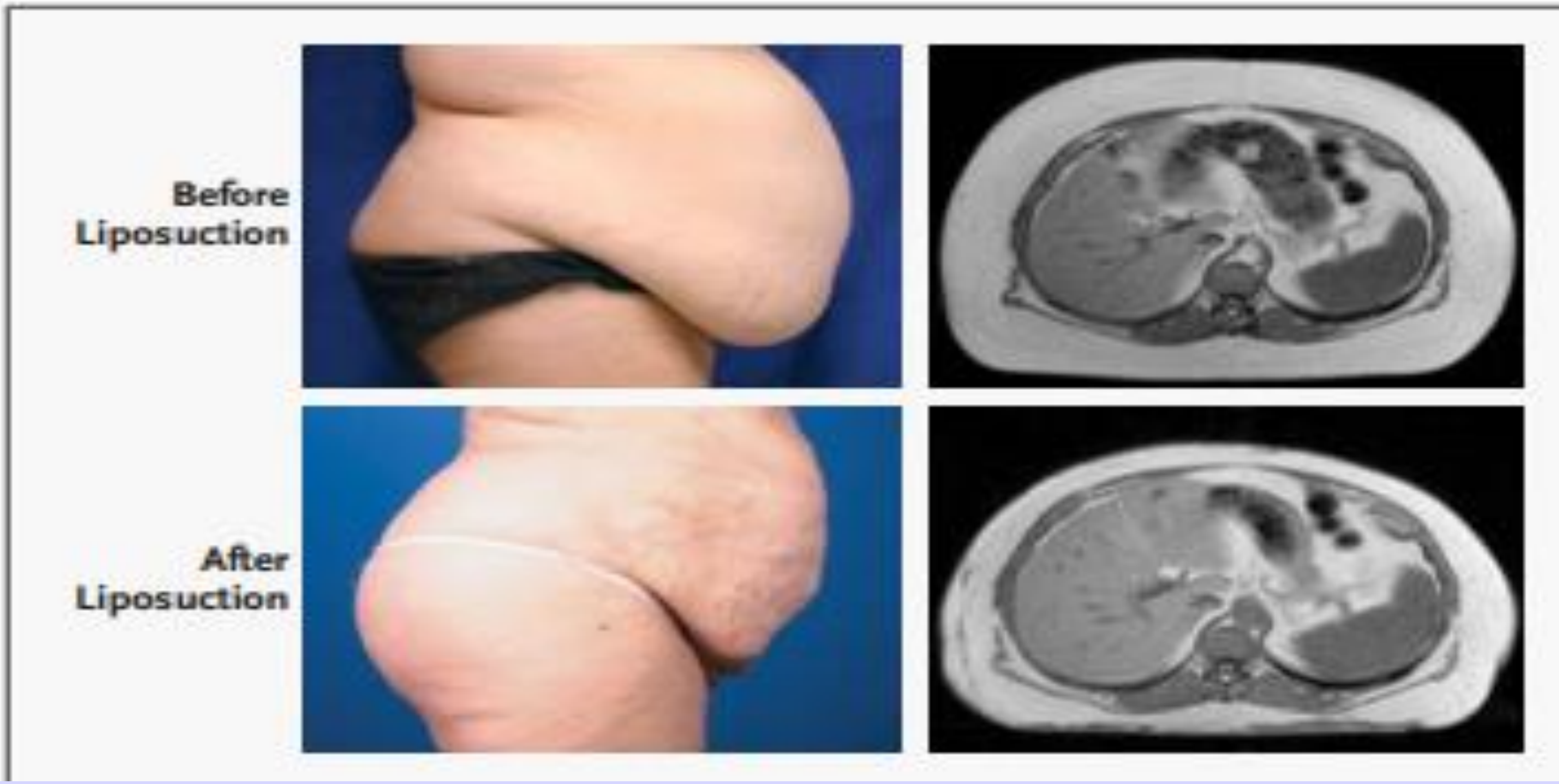
Network Biology and Functional Medicine


Inactivity
Obesity
Chronic systemic inflammation
Adipocytes
Immune cells
Brain cells
Systemic and local increase in cytokine concentrations
Glucose
· Insulin resistance
· Type 2 diabetes
· Atherosclerosis
· Alzheimer's disease
· Huntington's disease
· Parkinson's disease
· Cancer

ESTABLISHED IN 1812 JUNE 17, 2004 VOL. 350 NO. 25

Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease

Samuel Klein, M.D., Luigi Fontana, M.D., Ph.D., V. Leroy Young, M.D., Andrew R. Coggan, Ph.D., Charles Kilo, M.D., Bruce W. Patterson, Ph.D., and B. Selma Mohammed, M.D., Ph.D.



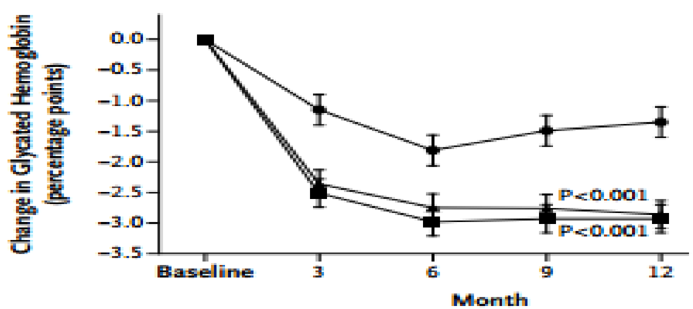
ESTABLISHED IN 1812 APRIL 26, 2012 VOL. 366 NO. 17

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.

● Intensive medical therapy ■ Roux-en-Y gastric bypass ▲ Sleeve gastrectomy

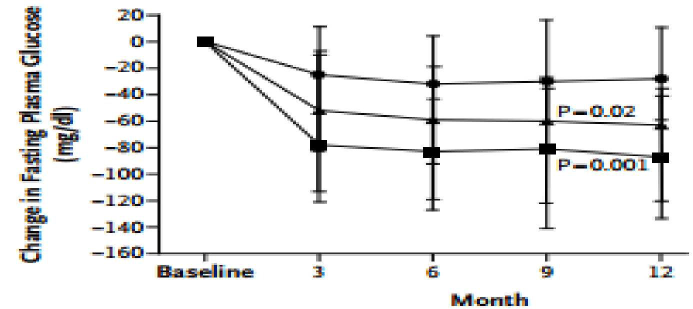
A Change in Glycated Hemoglobin



Value at Visit

	Baseline	3	6	9	12
Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6

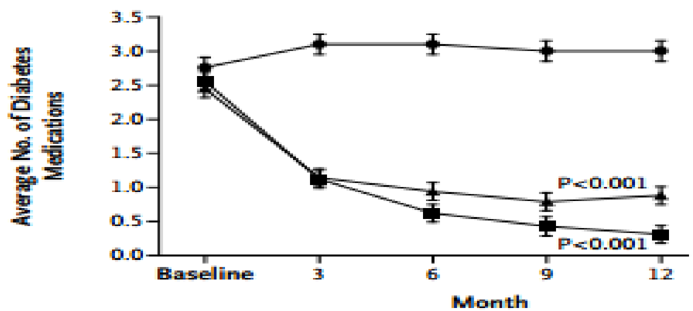
B Change in Fasting Plasma Glucose



Value at Visit

	Baseline	3	6	9	12
Intensive medical therapy	155	122	113	120	120
Roux-en-Y gastric bypass	193	109	96	96	99
Sleeve gastrectomy	164	118	104	102	97

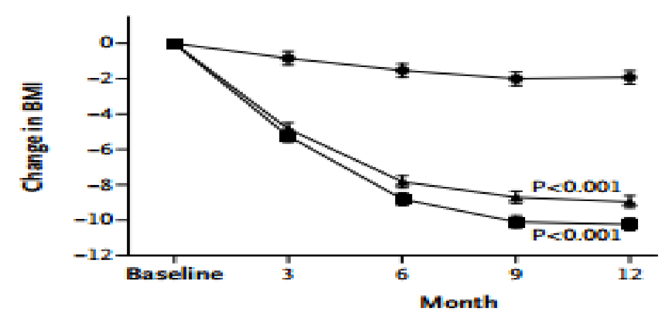
C Average No. of Diabetes Medications



Value at Visit

	Baseline	3	6	9	12
Intensive medical therapy	2.8	3.1	3.1	3.0	3.0
Roux-en-Y gastric bypass	2.6	1.1	0.6	0.4	0.3
Sleeve gastrectomy	2.4	1.1	0.9	0.8	0.9

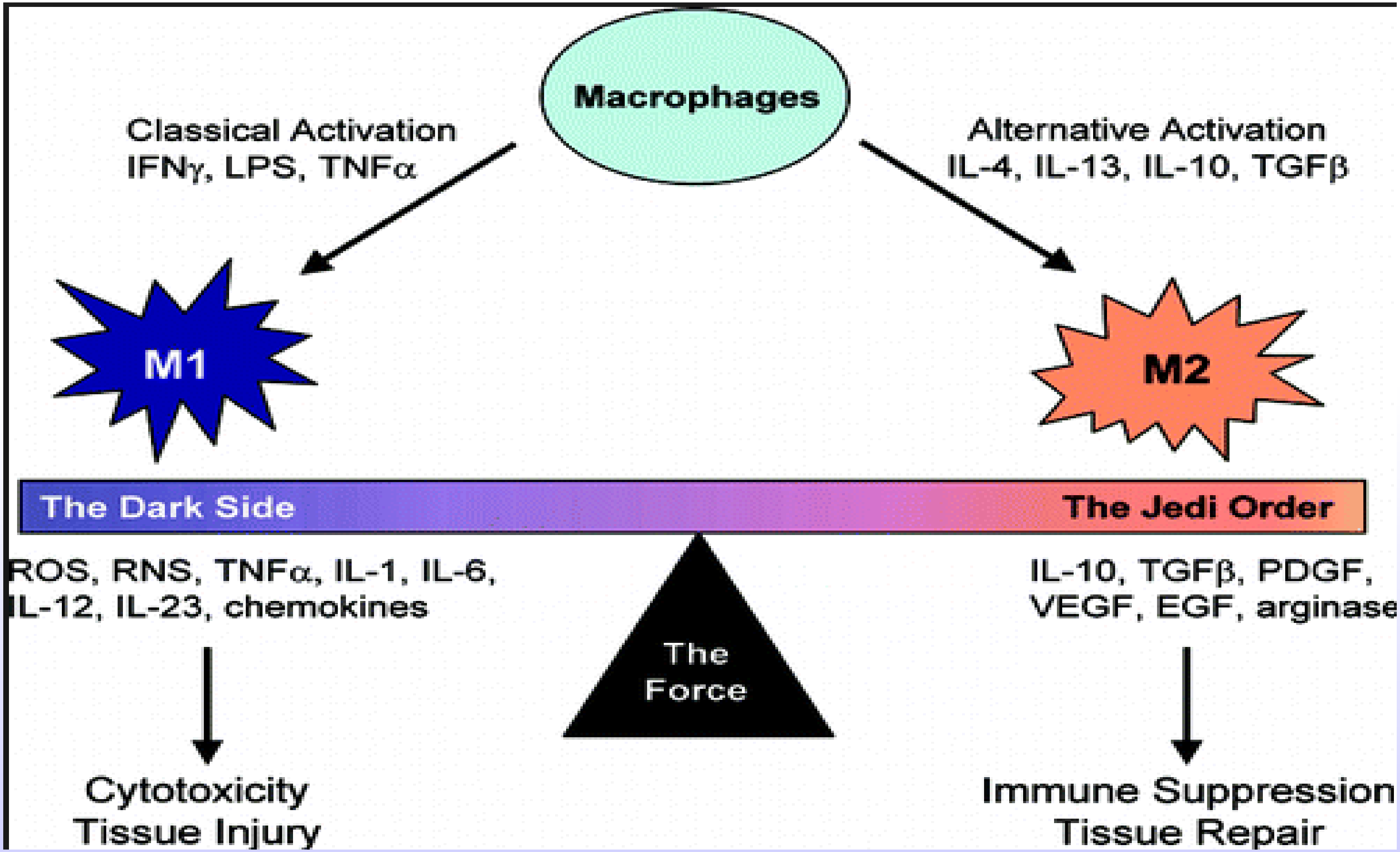
D Change in BMI



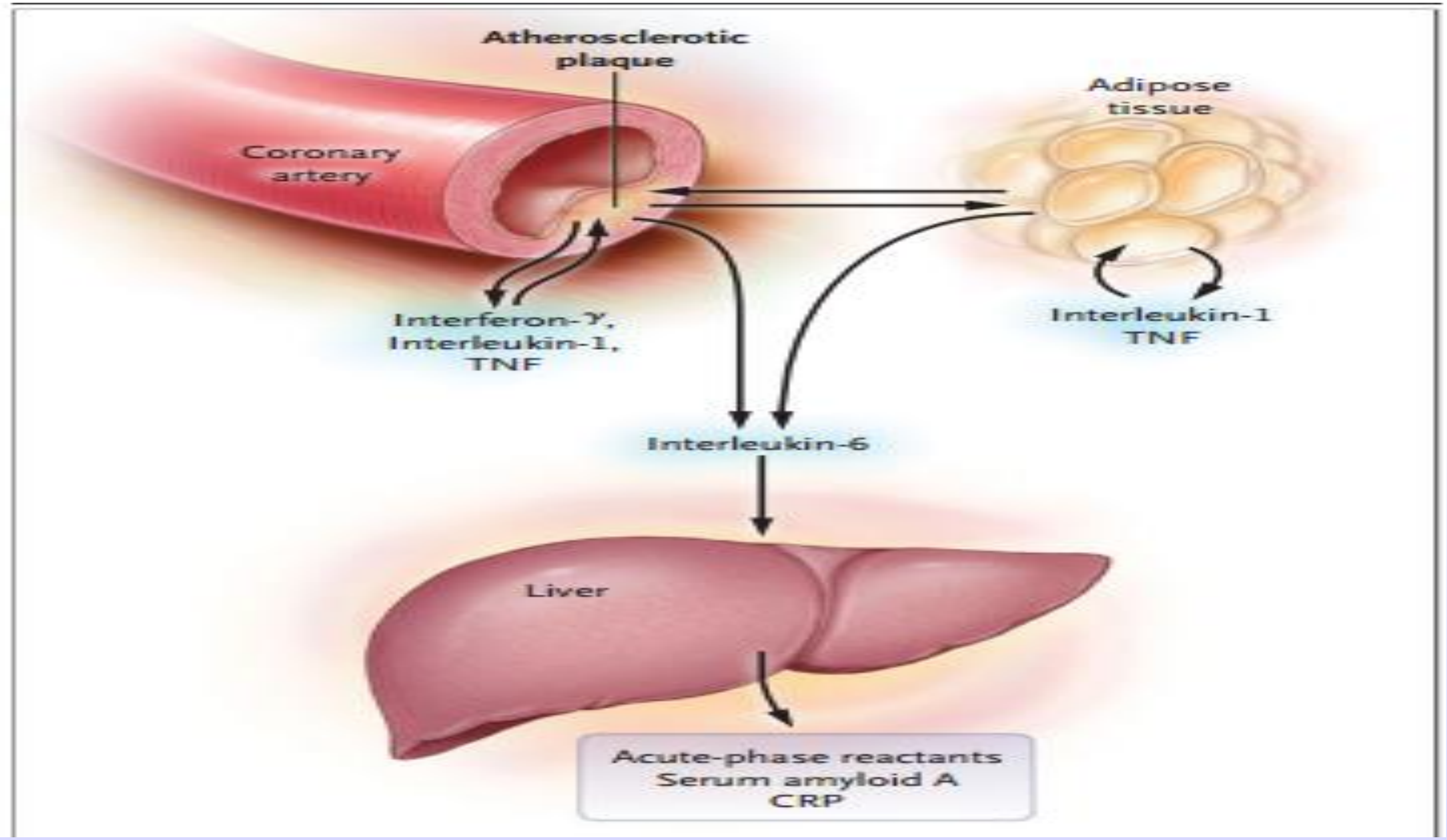
Value at Visit

	Baseline	3	6	9	12
Intensive medical therapy	36.3	35.4	34.8	34.5	34.4
Roux-en-Y gastric bypass	37.0	31.8	28.2	26.9	26.8
Sleeve gastrectomy	36.1	31.3	28.3	27.3	27.2

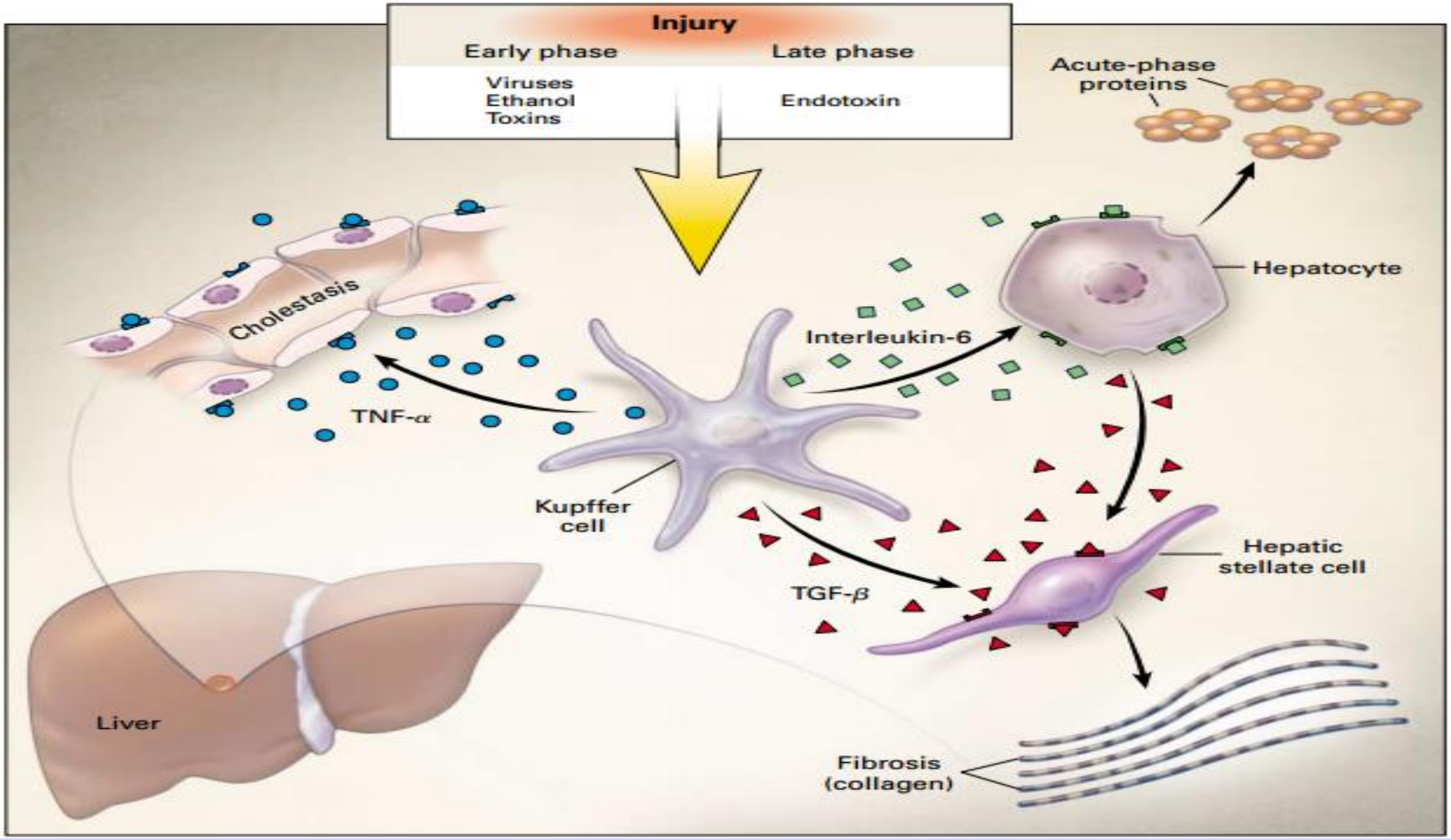
M1 and M2 Macrophages and Immune Balance



Metabolic Inflammation and the Cytokine Cascade



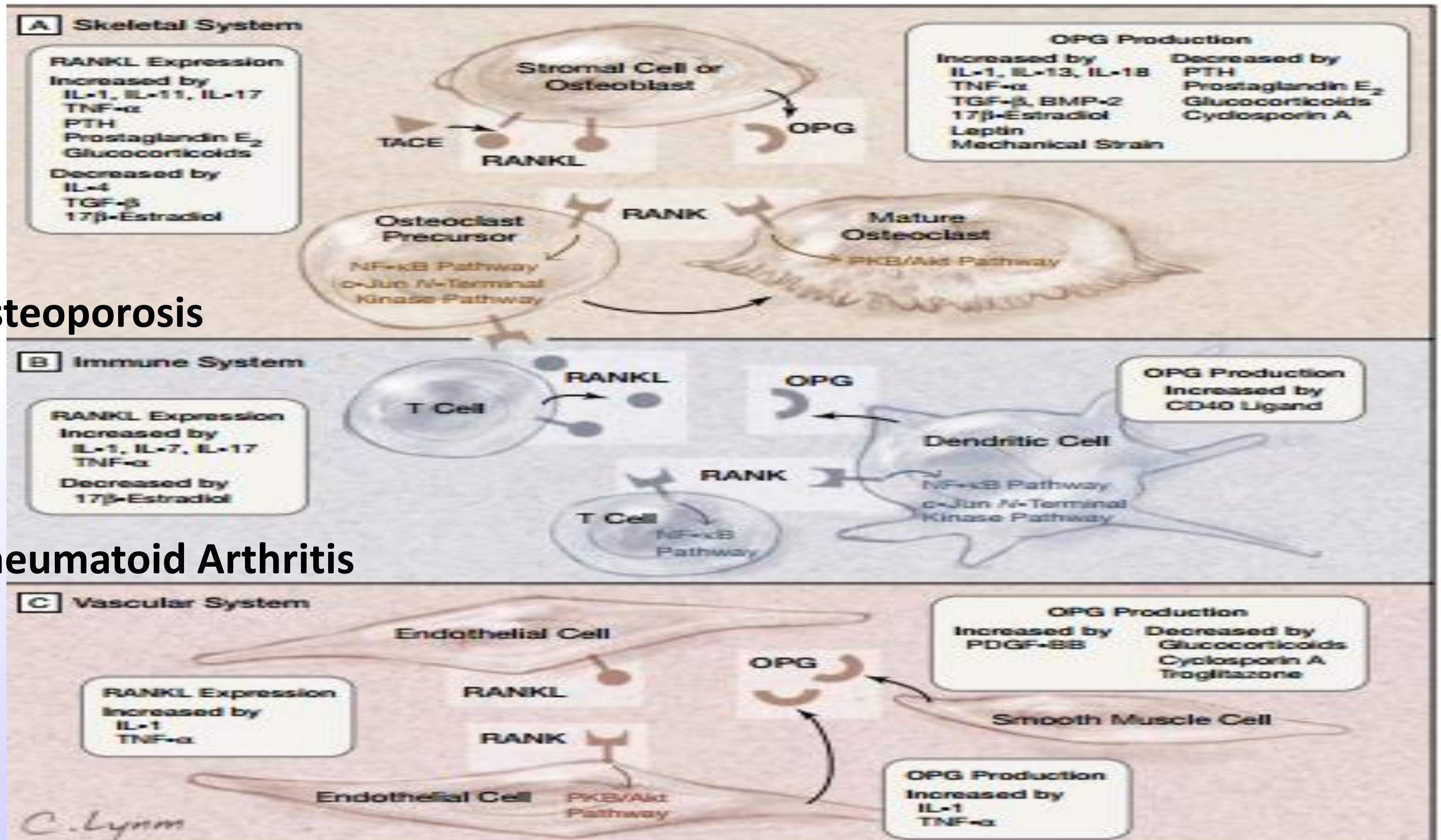
Hepatic Kupffer Cell Activation, Cytokines and Metabolic Inflammation



Clinical Implications of the Osteoprotegerin/ RANKL/RANK System for Bone and Vascular Diseases

JAMA. 2004;292:490-495

Think Shared Common Mechanism



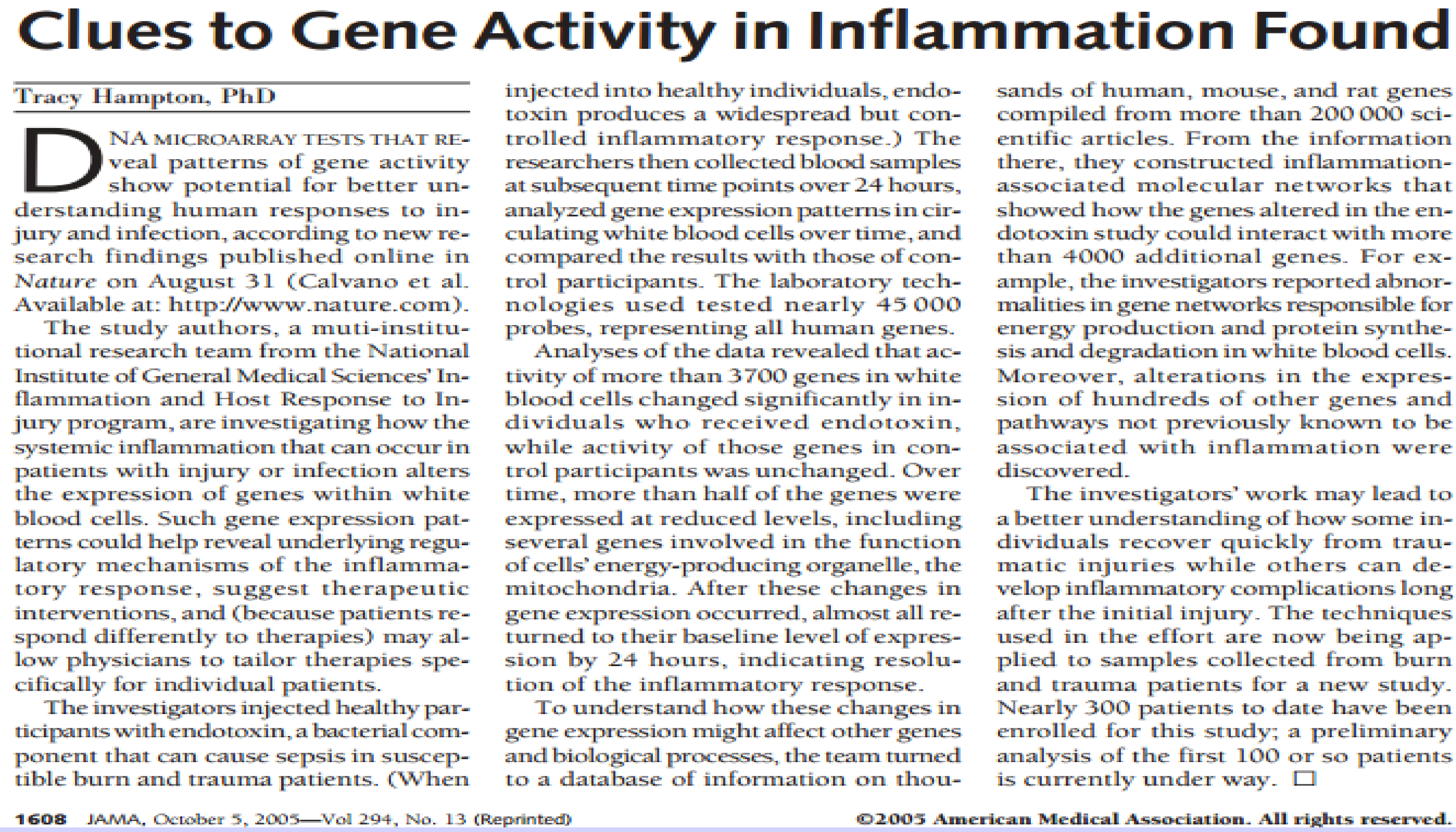
Osteoporosis

Rheumatoid Arthritis

Coronary Heart Disease

What is the Source of the Chronic Inflammation?

Endotoxin, Inflammation, and Mitochondrial Uncoupling



Clues to Gene Activity in Inflammation Found

Tracy Hampton, PhD

DNA MICROARRAY TESTS THAT REVEAL patterns of gene activity show potential for better understanding human responses to injury and infection, according to new research findings published online in *Nature* on August 31 (Calvano et al. Available at: http://www.nature.com).

The study authors, a muti-institutional research team from the National Institute of General Medical Sciences' Inflammation and Host Response to Injury program, are investigating how the systemic inflammation that can occur in patients with injury or infection alters the expression of genes within white blood cells. Such gene expression patterns could help reveal underlying regulatory mechanisms of the inflammatory response, suggest therapeutic interventions, and (because patients respond differently to therapies) may allow physicians to tailor therapies specifically for individual patients.

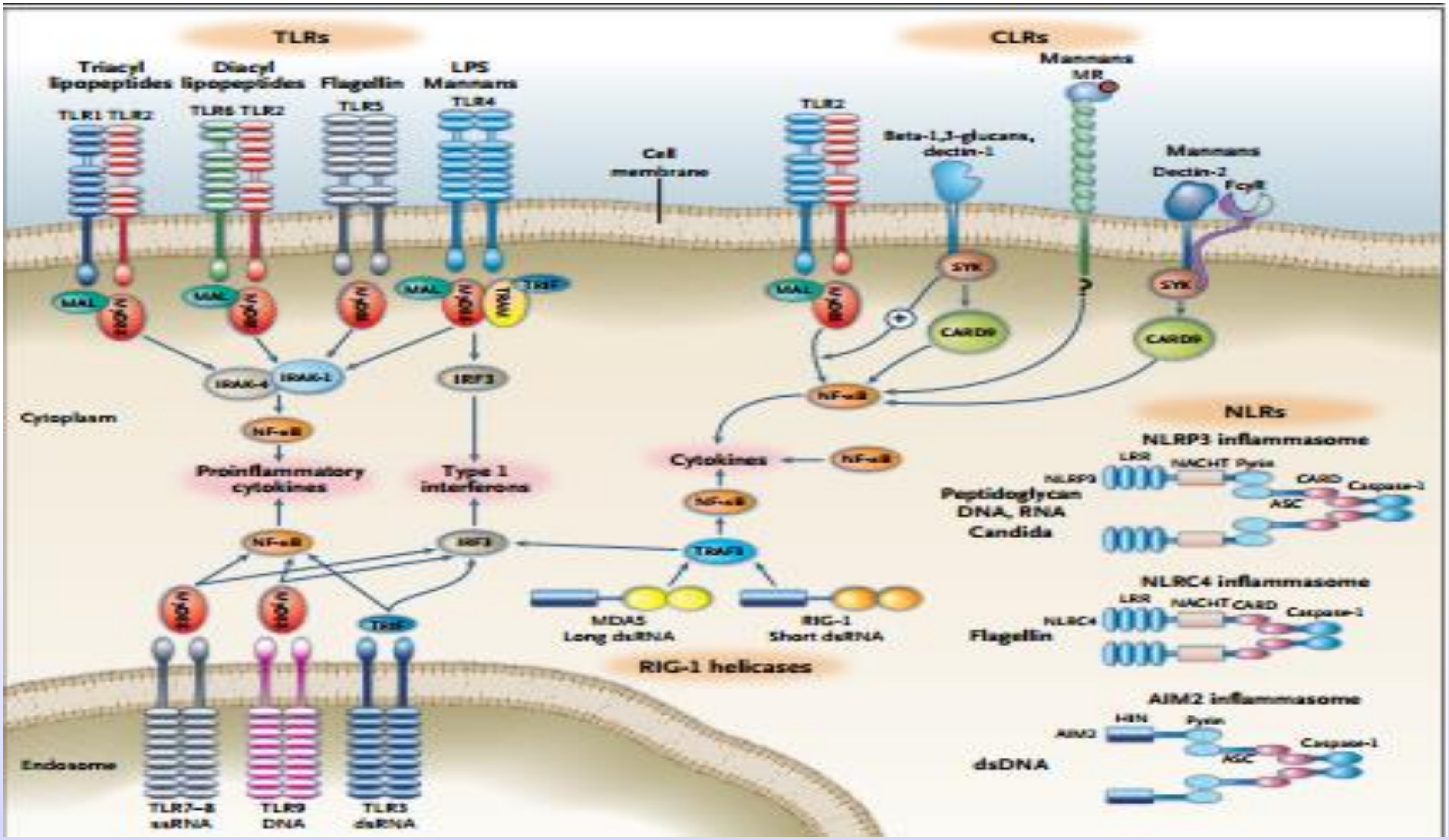
The investigators injected healthy participants with endotoxin, a bacterial component that can cause sepsis in susceptible burn and trauma patients. (When injected into healthy individuals, endotoxin produces a widespread but controlled inflammatory response.) The researchers then collected blood samples at subsequent time points over 24 hours, analyzed gene expression patterns in circulating white blood cells over time, and compared the results with those of control participants. The laboratory technologies used tested nearly 45 000 probes, representing all human genes.

Analyses of the data revealed that activity of more than 3700 genes in white blood cells changed significantly in individuals who received endotoxin, while activity of those genes in control participants was unchanged. Over time, more than half of the genes were expressed at reduced levels, including several genes involved in the function of cells' energy-producing organelle, the mitochondria. After these changes in gene expression occurred, almost all returned to their baseline level of expression by 24 hours, indicating resolution of the inflammatory response.

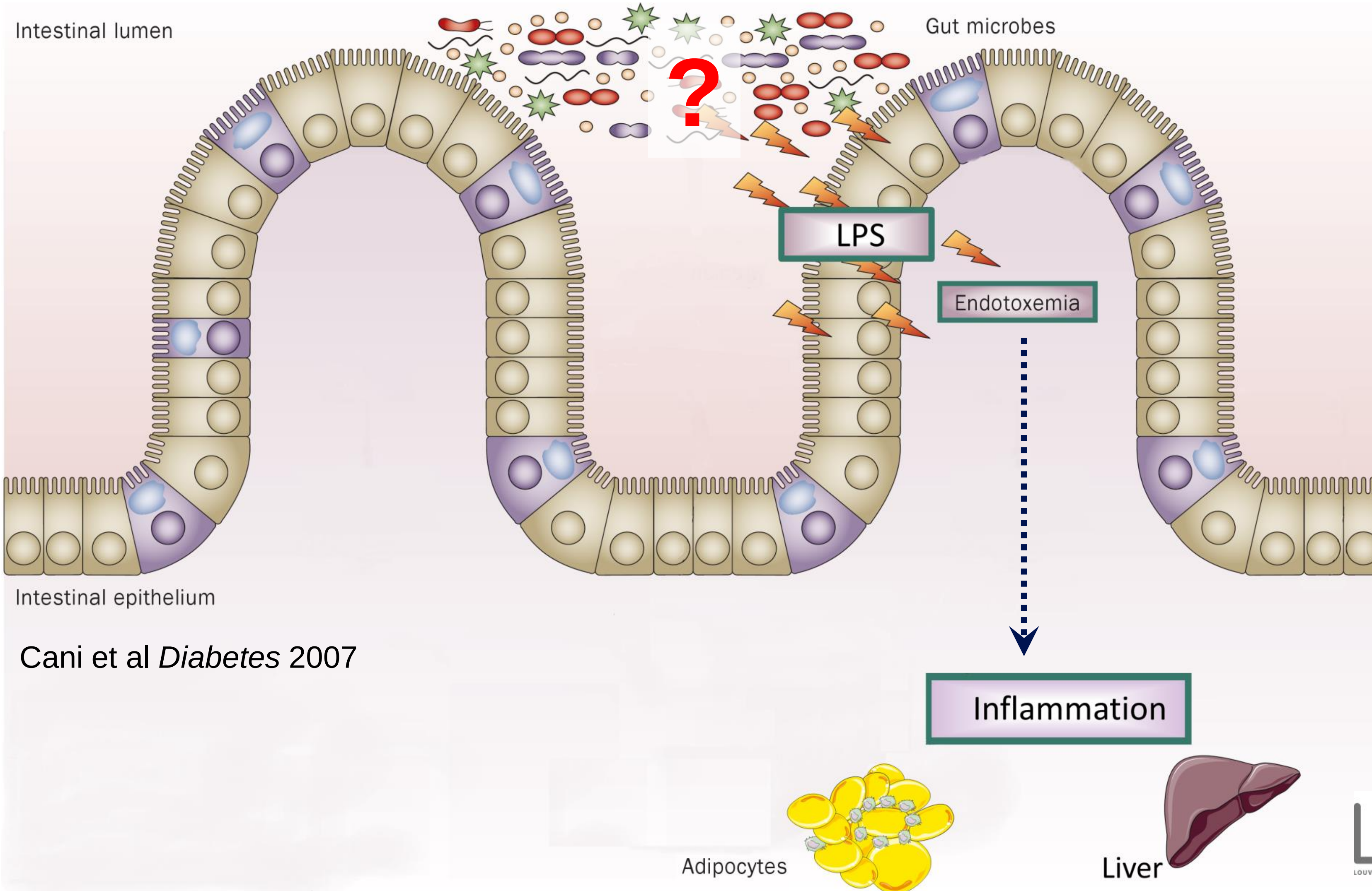
To understand how these changes in gene expression might affect other genes and biological processes, the team turned to a database of information on thousands of human, mouse, and rat genes compiled from more than 200 000 scientific articles. From the information there, they constructed inflammation-associated molecular networks that showed how the genes altered in the endotoxin study could interact with more than 4000 additional genes. For example, the investigators reported abnormalities in gene networks responsible for energy production and protein synthesis and degradation in white blood cells. Moreover, alterations in the expression of hundreds of other genes and pathways not previously known to be associated with inflammation were discovered.

The investigators' work may lead to a better understanding of how some individuals recover quickly from traumatic injuries while others can develop inflammatory complications long after the initial injury. The techniques used in the effort are now being applied to samples collected from burn and trauma patients for a new study. Nearly 300 patients to date have been enrolled for this study; a preliminary analysis of the first 100 or so patients is currently under way. ☐

4 Types of Pattern Recognition Receptors



Specific gut microbiota derived compounds are able to trigger metabolic inflammation

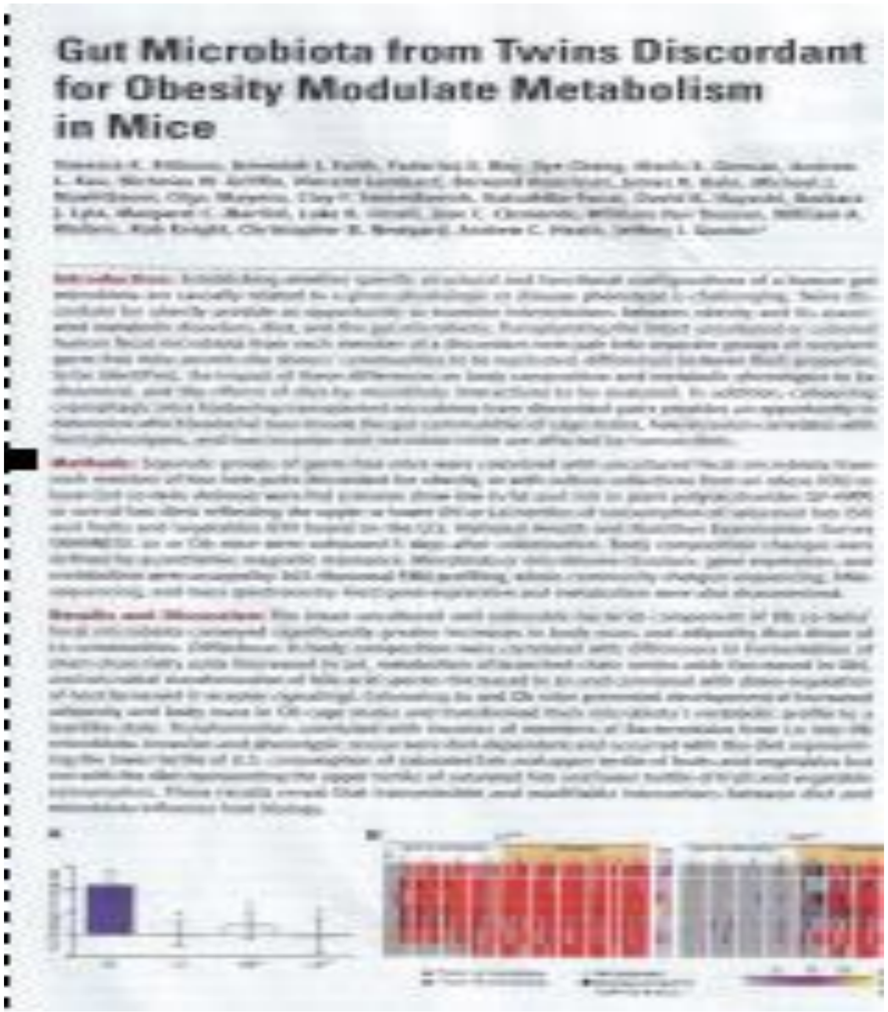


Cani et al *Diabetes* 2007

Adapted from nature REVIEWS ENDOCRINOLOGY

Nathalie M. Delzenne, Audrey M. Neyrinck, Fredrik Bäckhed and Patrice D. Cani

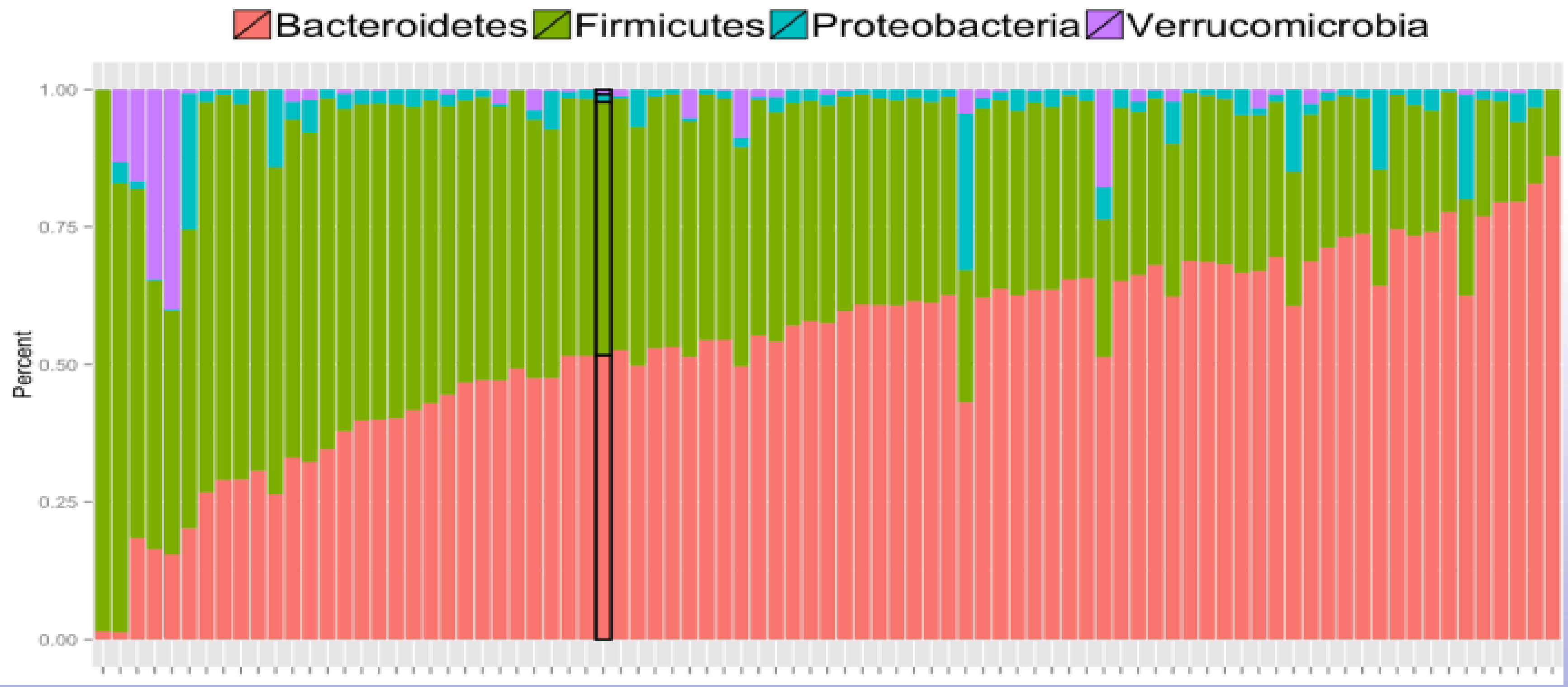
Gut Microbiota from Twins


Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

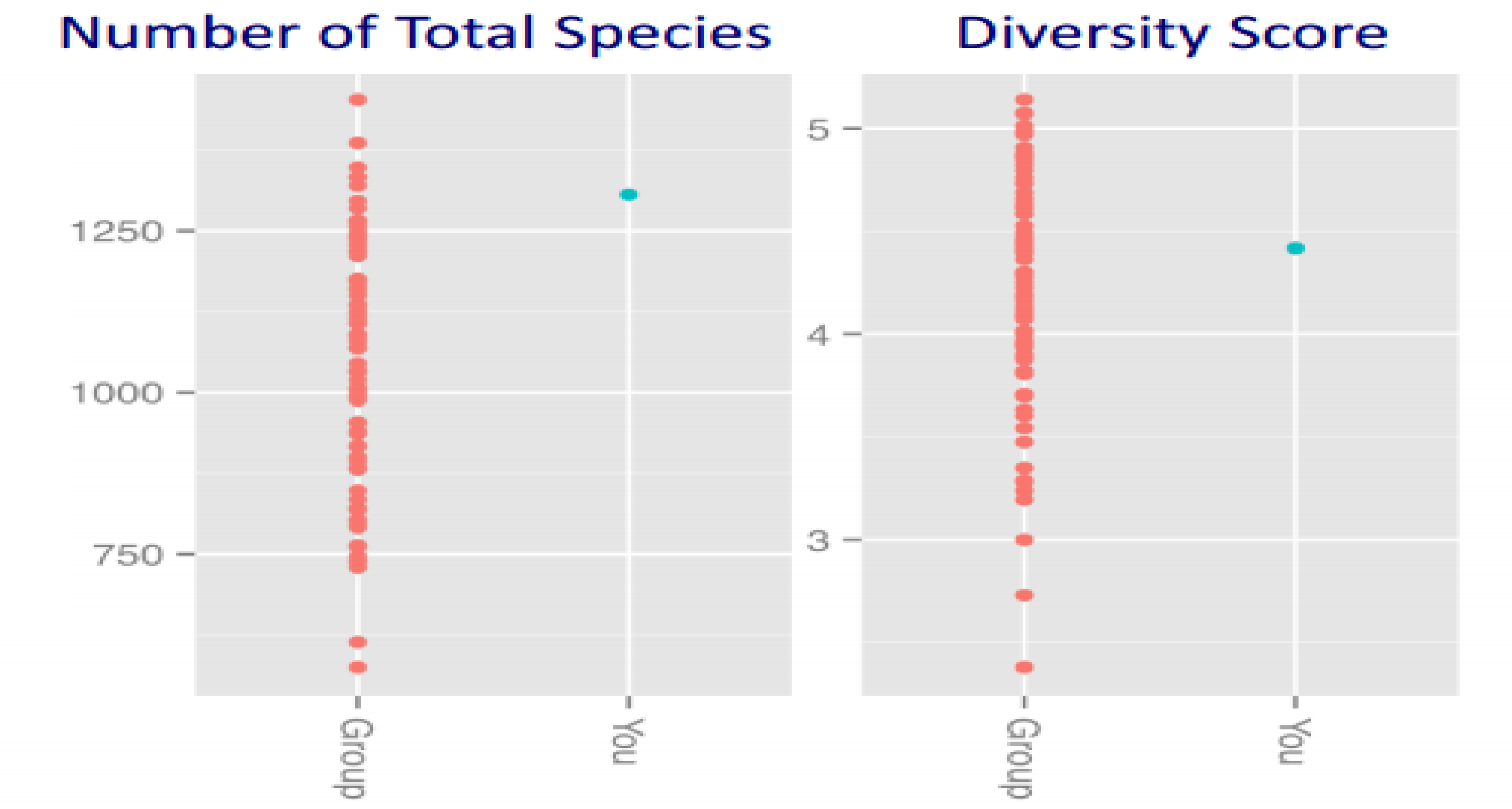
- Gut microbiota from lean animals transplanted to fat animals confer altered gene expression associated with lean phenotype of a low fat, high fiber diet
- Effect is NOT due to decreased calorie release from lean microbiota, but metabolic influence
- Science 2013; 341: 1079

Example of Species Diversity in the Gut Microbiome

We found a broad spectrum of **gut microbiome** composition among the Pioneers.



Relative Evaluation of Microbiome Species Diversity

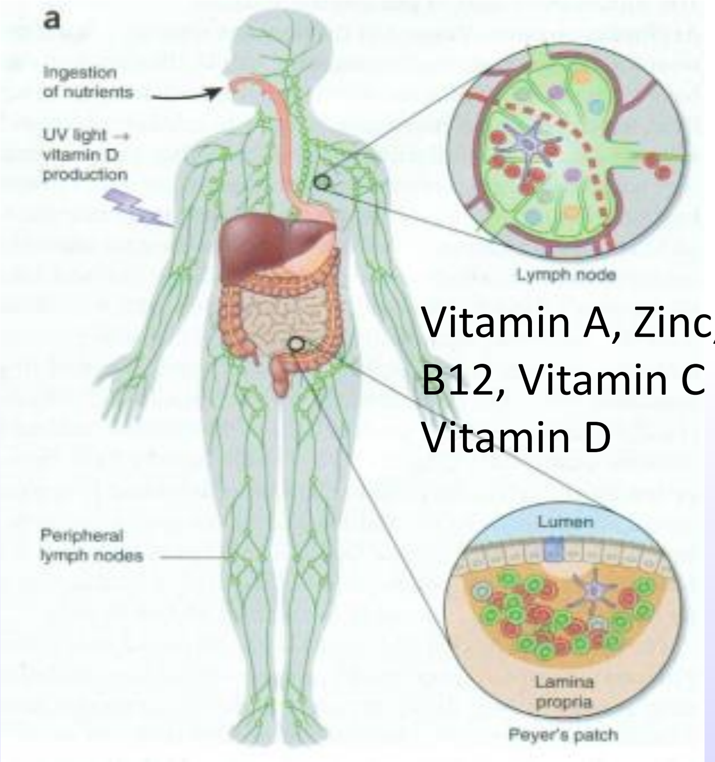


Role of Specific Nutrients on Humoral Immunity

Influence of nutrient-derived metabolites on lymphocyte immunity

Marc Veldhoen & Cristina Ferreira

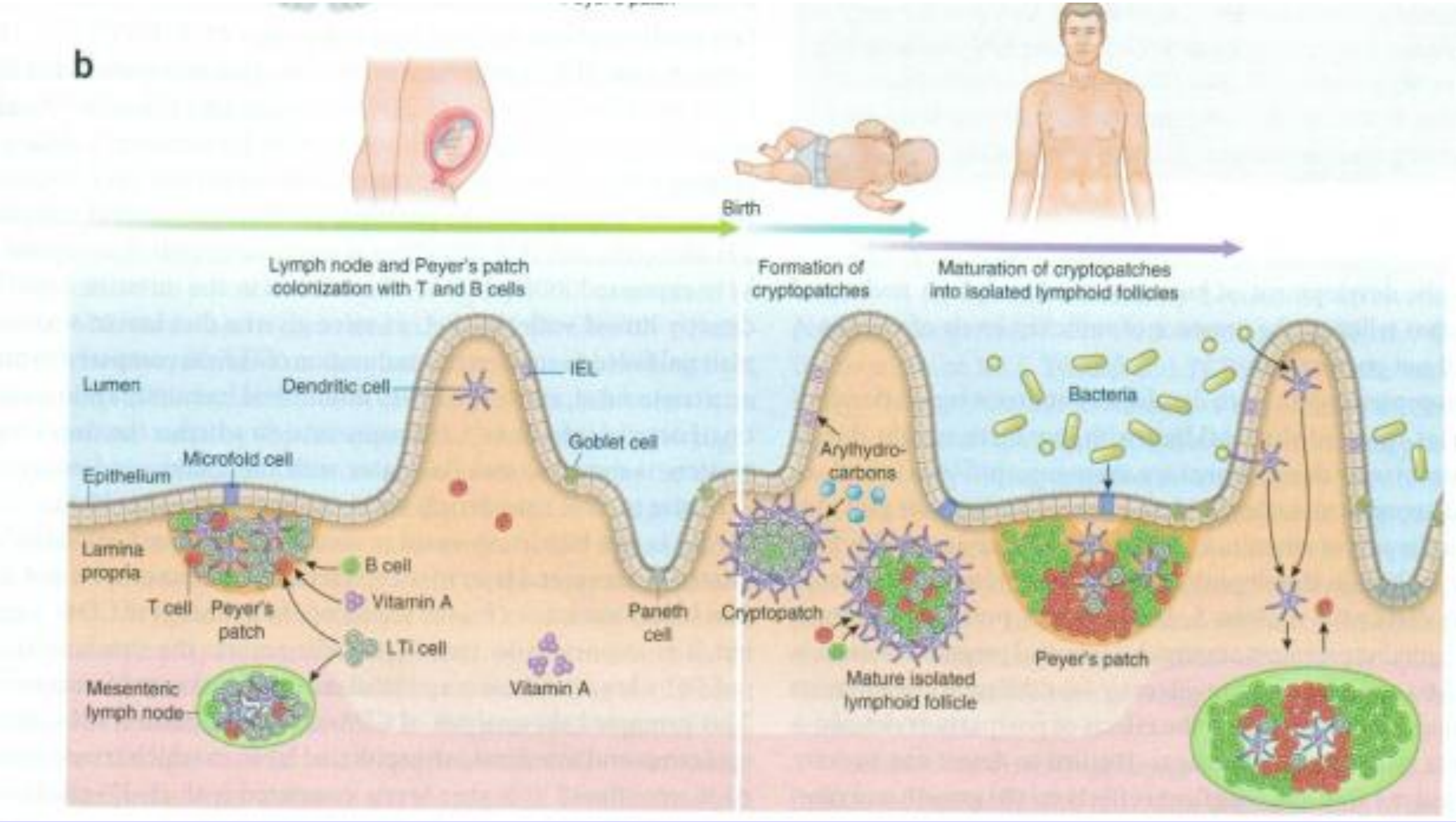
Organisms need to protect themselves against potential dangers from their surroundings, yet they require constant and intimate interactions with the same environment for their survival. The immune system is instrumental for protection against invading organisms and their toxins. The immune system consists of many cell types and is highly integrated within other tissues. Immune activity is particularly enriched at surfaces that separate the host from its environment, such as the skin and the gastrointestinal tract. This enables protection at sites directly at risk but also enables environmental factors to influence the maturation and function of immune structures and cells. Recent work has indicated that the diet in particular is able to influence the immune system and thus affect the development of inflammatory disease. This review aims to highlight recent work on how external factors, with a focus on those derived from the diet such as vitamin A, can have a direct or indirect deterministic influence on the activity and function of immunity.



Vitamin A, Zinc, Folate, B12, Vitamin C , Vitamin D

Nature Medicine 2015; 21: 709-717

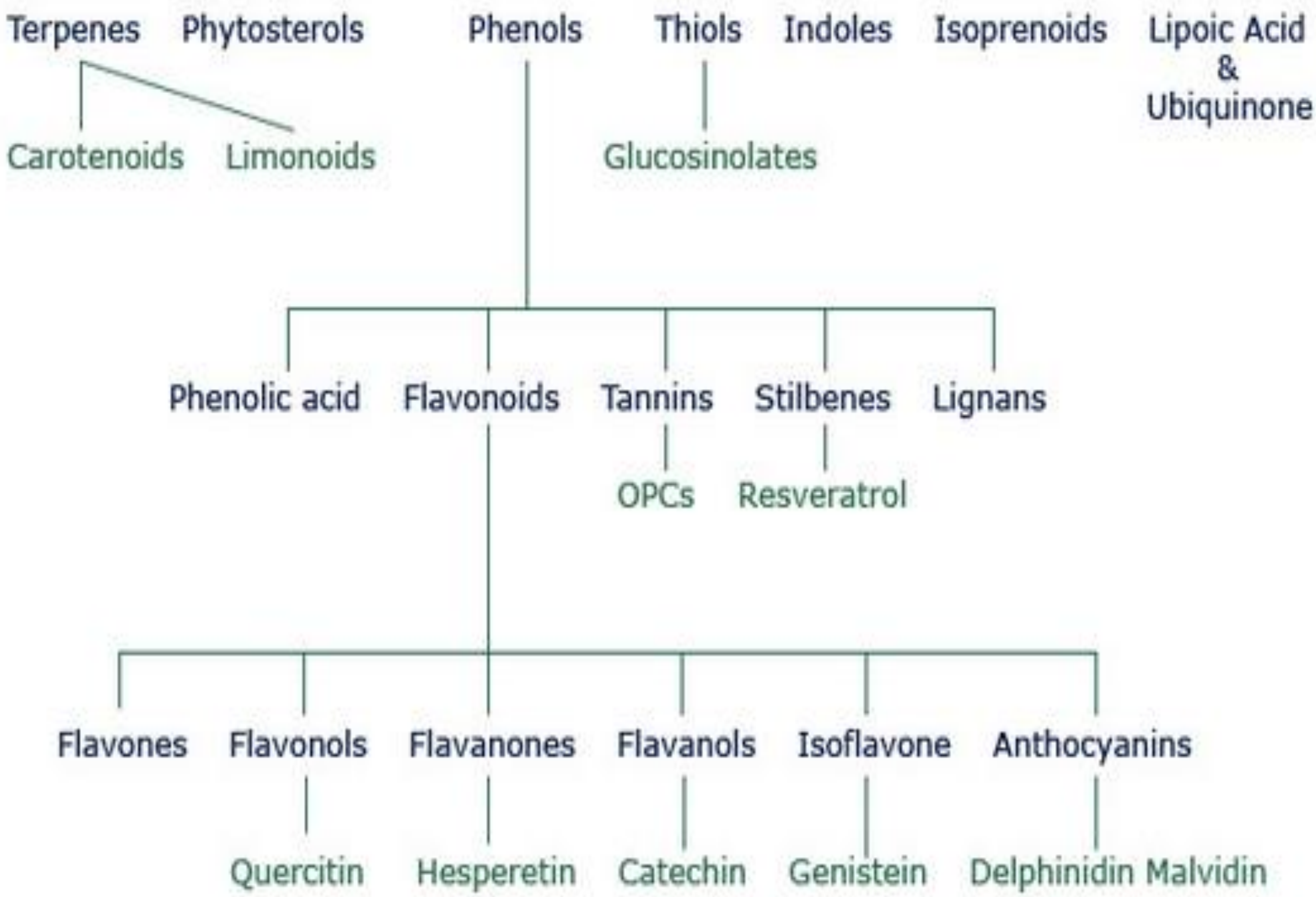
Development of GALT immune Function



Phytochemical Regulation of Neuroendocrineimmune Networks

Food is Much More than We Thought for the Previous 100 years in the Western World

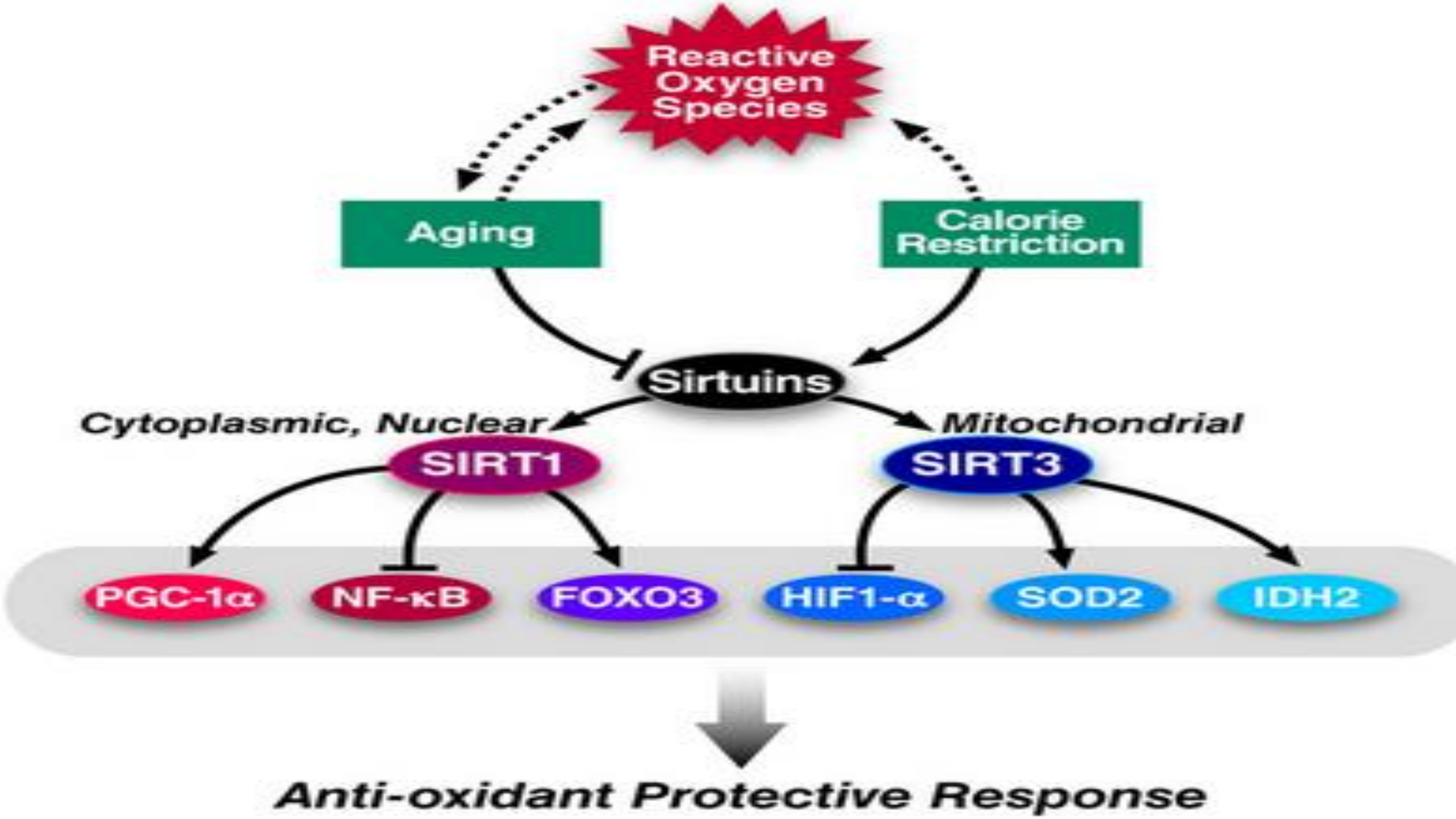
Phytochemicals



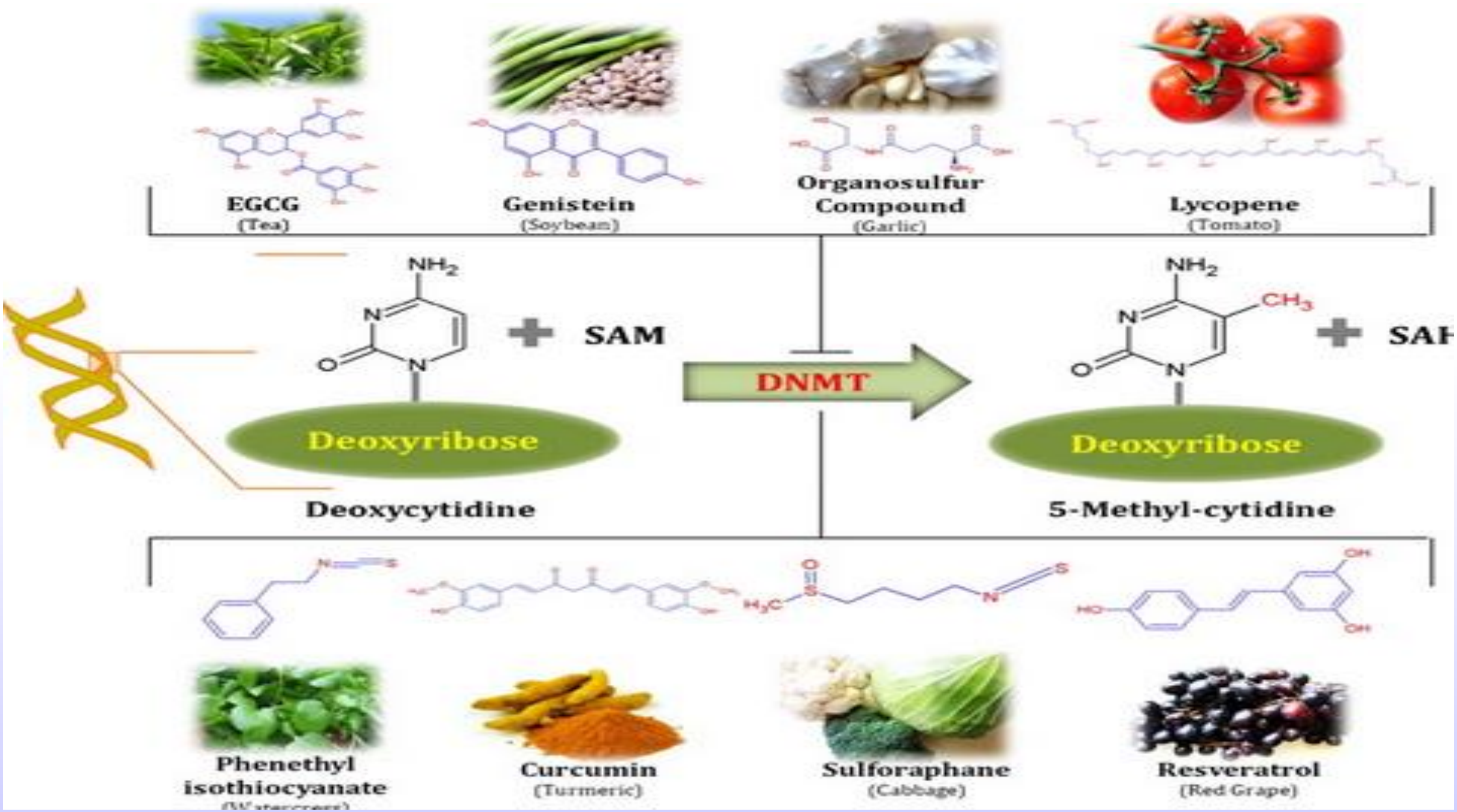
The Sirtuin-Histone Deacetylase Story

Upregulation of Sirtuin Activity by Specific Phytochemicals

Sirtuins as Regulators of Gene Expression



Foods and Phytochemicals that Influence Genome Methylation and Sirutins

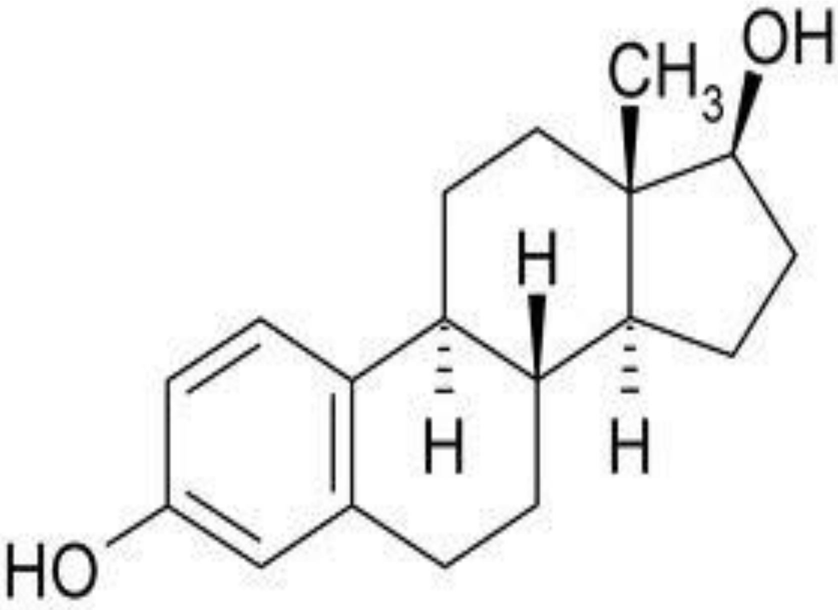


Example of How Phytochemicals Influence the Endocrine System

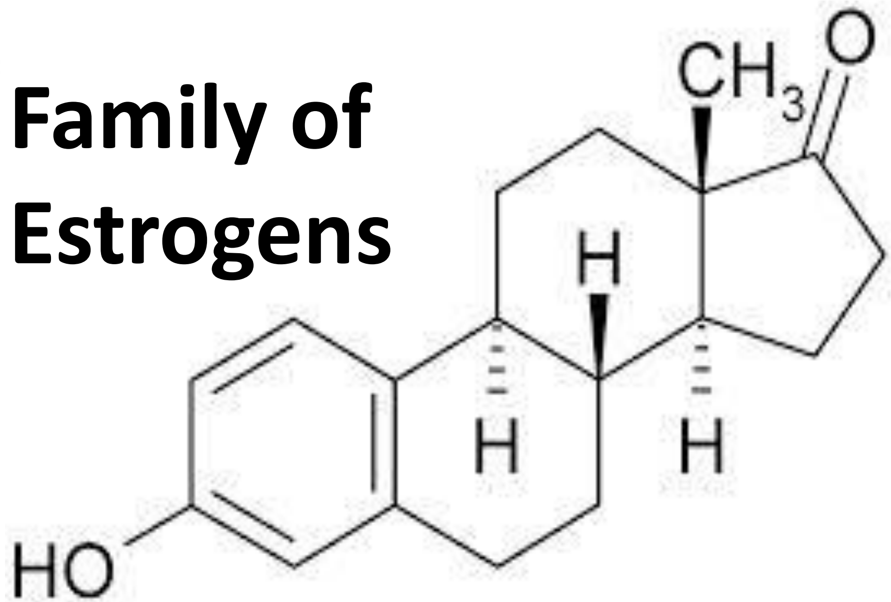
Elizabeth Rogan, Ph.D.
Phytochemicals and Estrogen Metabolism

- PROFESSOR AND CHAIR
- Department of Environmental, Agricultural & Occupational Health
- College of Public Health
- Professor
- Eppley Institute for Research in Cancer and Allied Diseases
- University of Nebraska Medical Center

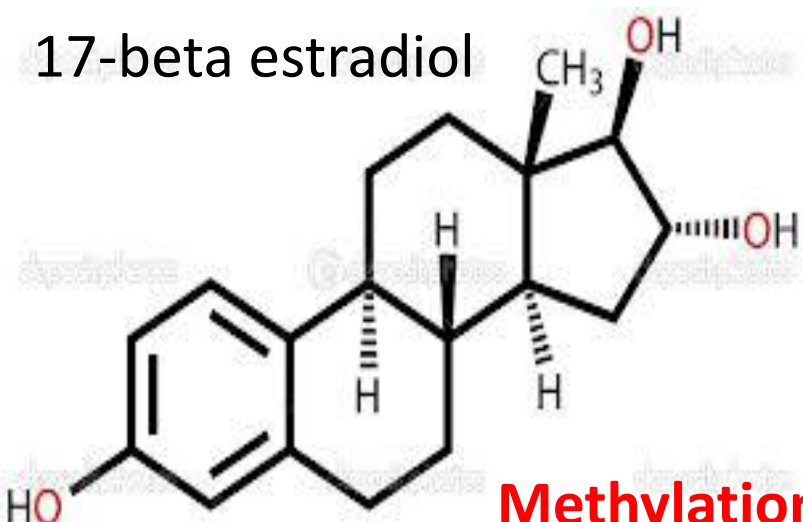
Family of Estrogens



17-beta estradiol

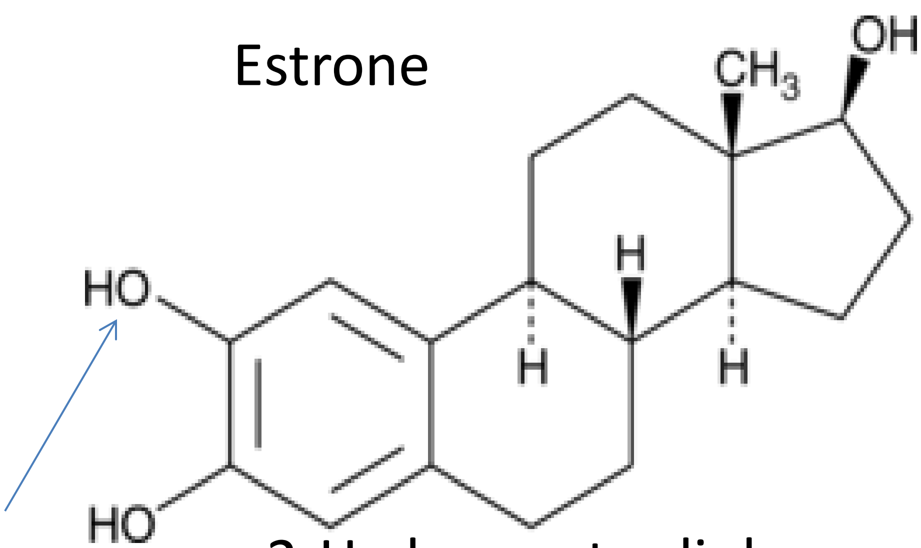


Estrone



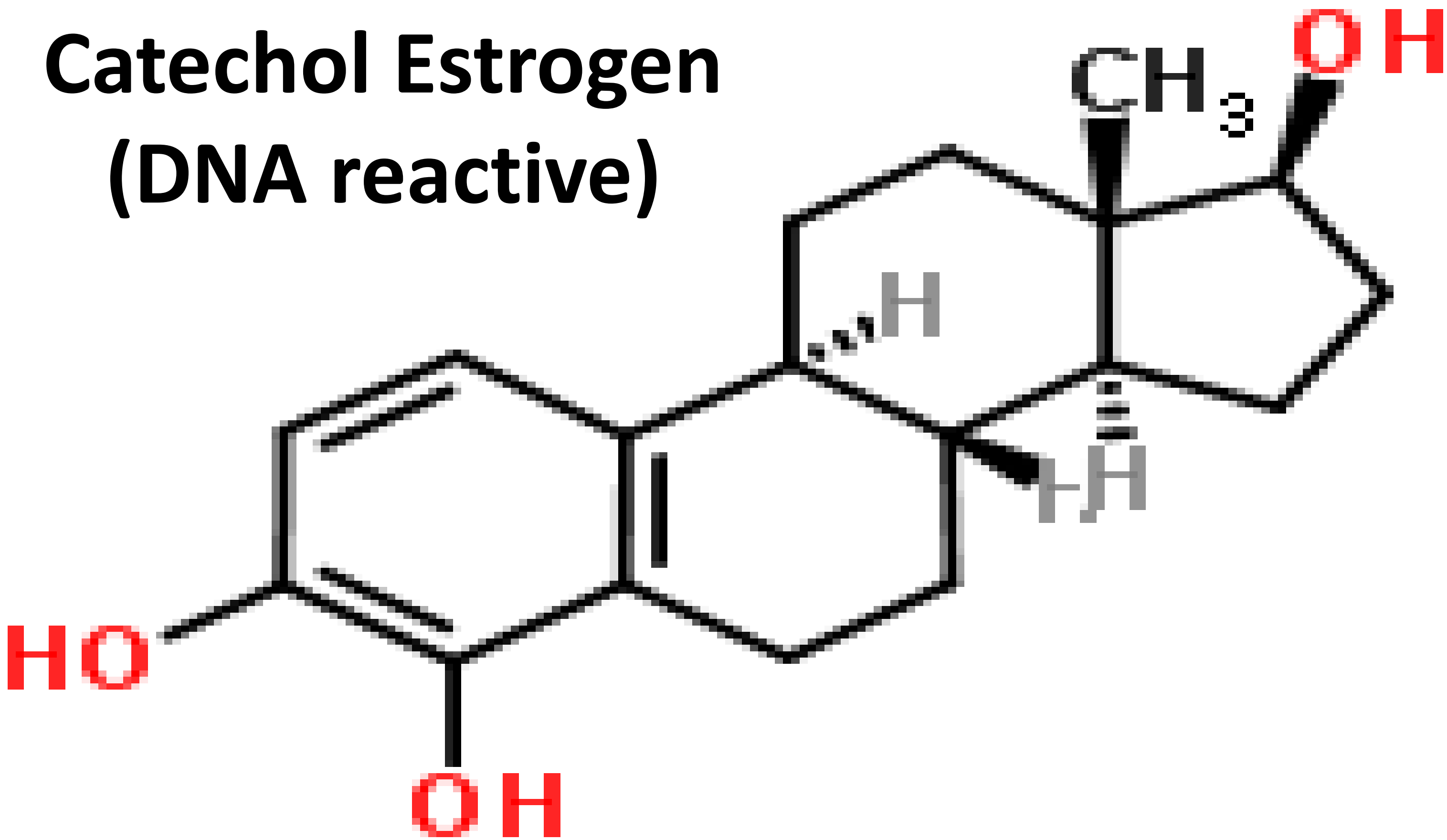
Estriol

Methylation Site



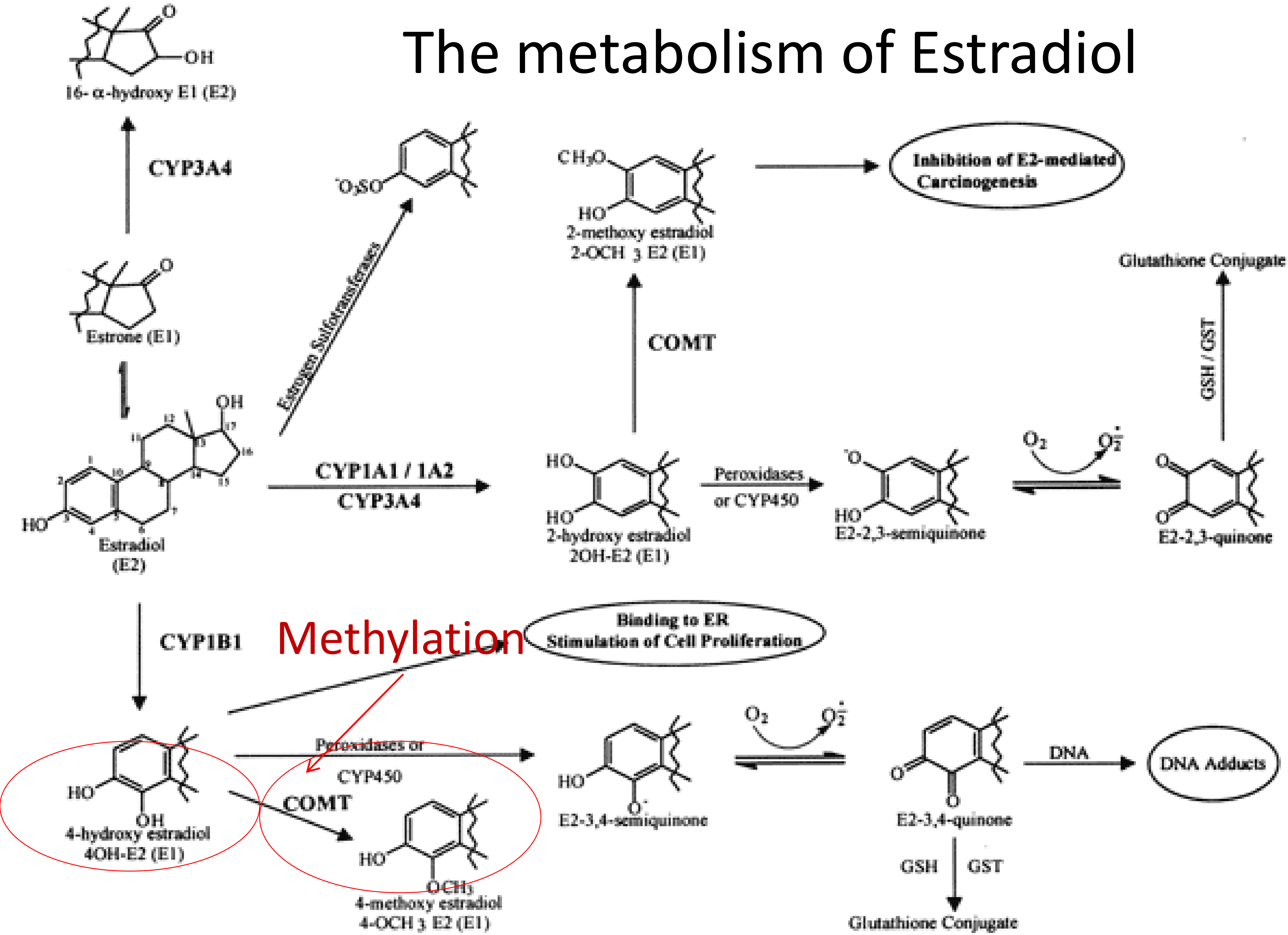
2-Hydroxyestradiol

Catechol Estrogen (DNA reactive)

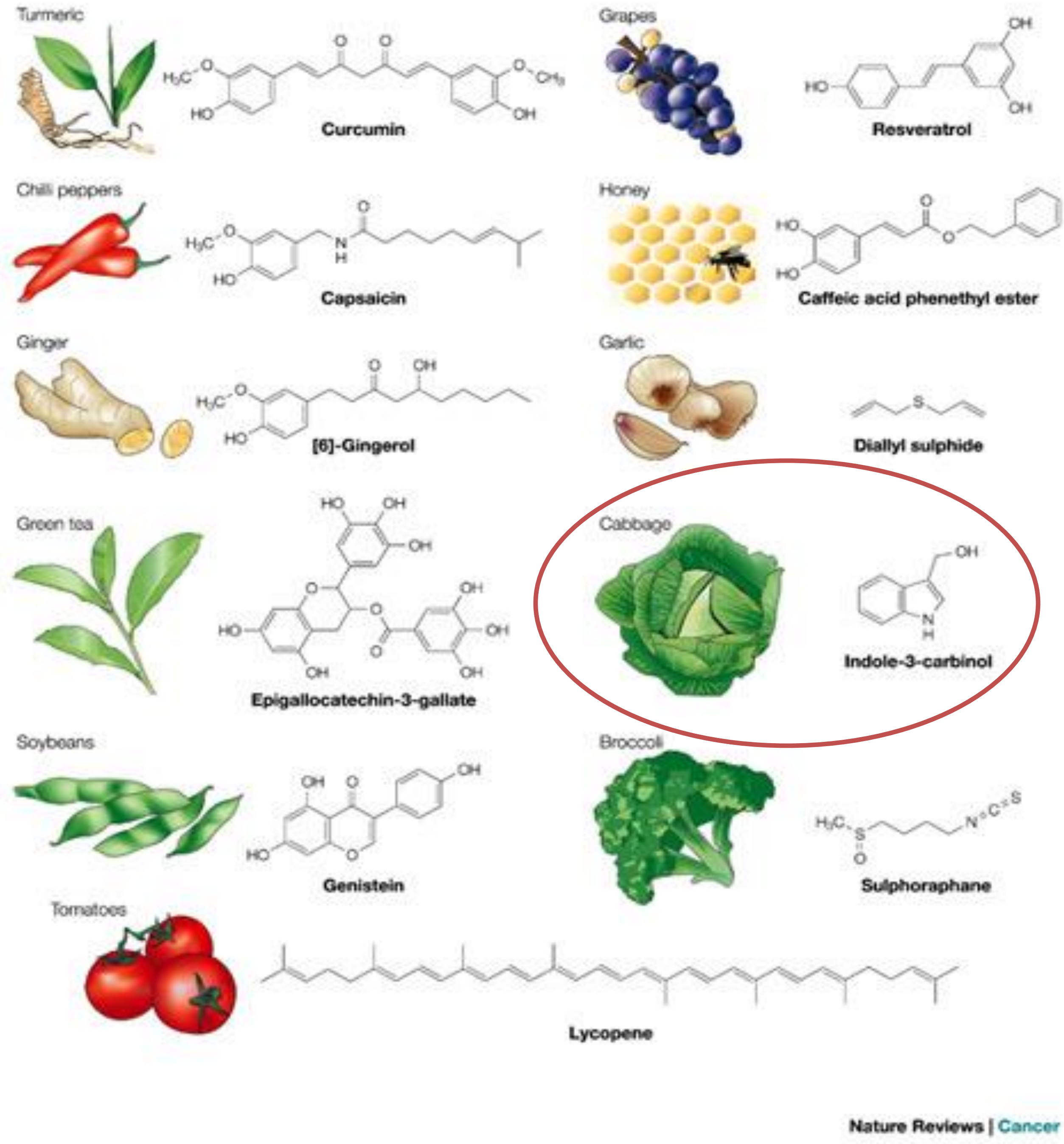


4-Hydroxyestradiol

The metabolism of Estradiol



Bioactive Phytochemical Components Modulating Estrogen



Surh Y-J, (2003) Nature Reviews Cancer. 2003;3:768-780.

Indole-3 Carbinol Intervention and the Risk to Cervical Cancer

- Gynecol Oncol. 2000 Aug;78(2):123-9.
  - **Placebo-controlled trial of indole-3-carbinol in the treatment of CIN**
  - "Thirty patients with biopsy proven CIN II-III were randomized to receive placebo or 200, or 400 mg/day I-3-C administered orally for 12 weeks".
  - "None (0 of 10) of the patients in the placebo group had complete regression of CIN. In contrast 4 of 8 patients in the 200 mg/day arm and 4 of 9 patients in the 400 mg/day arm had complete regression based on their 12-week biopsy".

Nutrition and Phytochemicals for Dementia Neuroendocrineimmune Treatment

www.impactaging.com AGING, September 2014, Vol 6 N 9

Review

Reversal of cognitive decline: A novel therapeutic program

Dale E. Bredesen[1,2]

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Key words: *Alzheimer's, dementia, mild cognitive impairment, neurobehavioral disorders, neuroinflammation, neurodegeneration, systems biology*
Received: *9/15/14;* **Accepted:** *9/26/14;* **Published:** *9/27/14*
Correspondence to: *Dale E. Bredesen, MD;* **E-mail:** dbredesen@mednet.ucla.edu; dbredesen@buckinstitute.org

Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer's disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time the longest patient follow-up is two and one-half years from initial treatment, with sustained and marked improvement. These results suggest that a larger, more extensive trial of this therapeutic program is warranted. The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system.

ELSEVIER Alzheimer's & Dementia ■ (2015) 1-8 Alzheimer's & Dementia

MIND diet associated with reduced incidence of Alzheimer's disease

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[b] *Department of Clinical Nutrition and the Rush Alzheimer's Disease Center at Rush University Medical Center*
[c] *Department of Nutrition, Harvard School of Public Health*
[d] *Department of Behavioral Sciences and the Rush Alzheimer's Disease Center at Rush University Medical Center*
[e] *Department of Neurology and the Rush Alzheimer's Disease Center at Rush University Medical Center*

Abstract

Background: In a previous study, higher concordance to the MIND diet, a hybrid Mediterranean-Dietary Approaches to Stop Hypertension diet, was associated with slower cognitive decline. In this study we related these three dietary patterns to incident Alzheimer's disease (AD).
Methods: We investigated the diet-AD relations in a prospective study of 923 participants, ages 58 to 98 years, followed on average 4.5 years. Diet was assessed by a semiquantitative food frequency questionnaire.
Results: In adjusted proportional hazards models, the second (hazards ratio or HR = 0.65, 95% confidence interval or CI 0.44, 0.98) and highest tertiles (HR = 0.47, 95% CI 0.26, 0.76) of MIND diet scores had lower rates of AD versus tertile 1, whereas only the third tertiles of the DASH (HR = 0.61, 95% CI 0.38, 0.97) and Mediterranean (HR = 0.46, 95% CI 0.26, 0.79) diets were associated with lower AD rates.
Conclusion: High adherence to all three diets may reduce AD risk. Moderate adherence to the MIND diet may also decrease AD risk.

Keywords: Cognition; Alzheimer disease; Nutrition; diet; Epidemiological study; Aging

The Nutrition Connection to the Neuroendocrineimmune Network