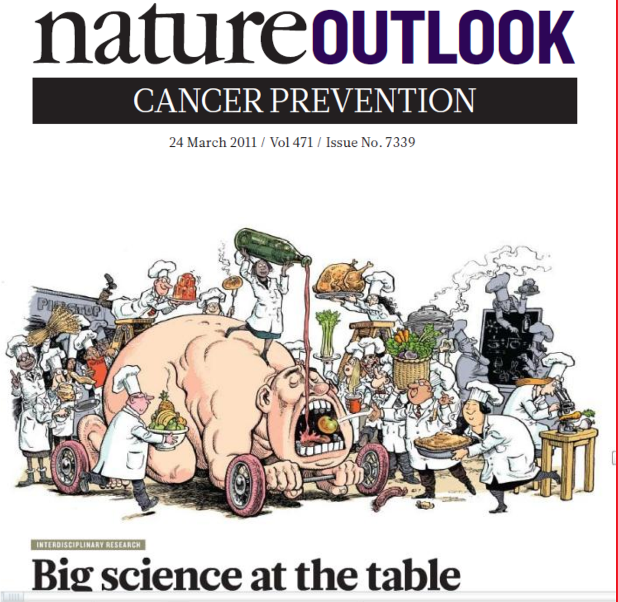


Phytochemicals and diet in health & disease: epigenetic friends or foe?

Sitges 2011

Wim Vanden Berghe

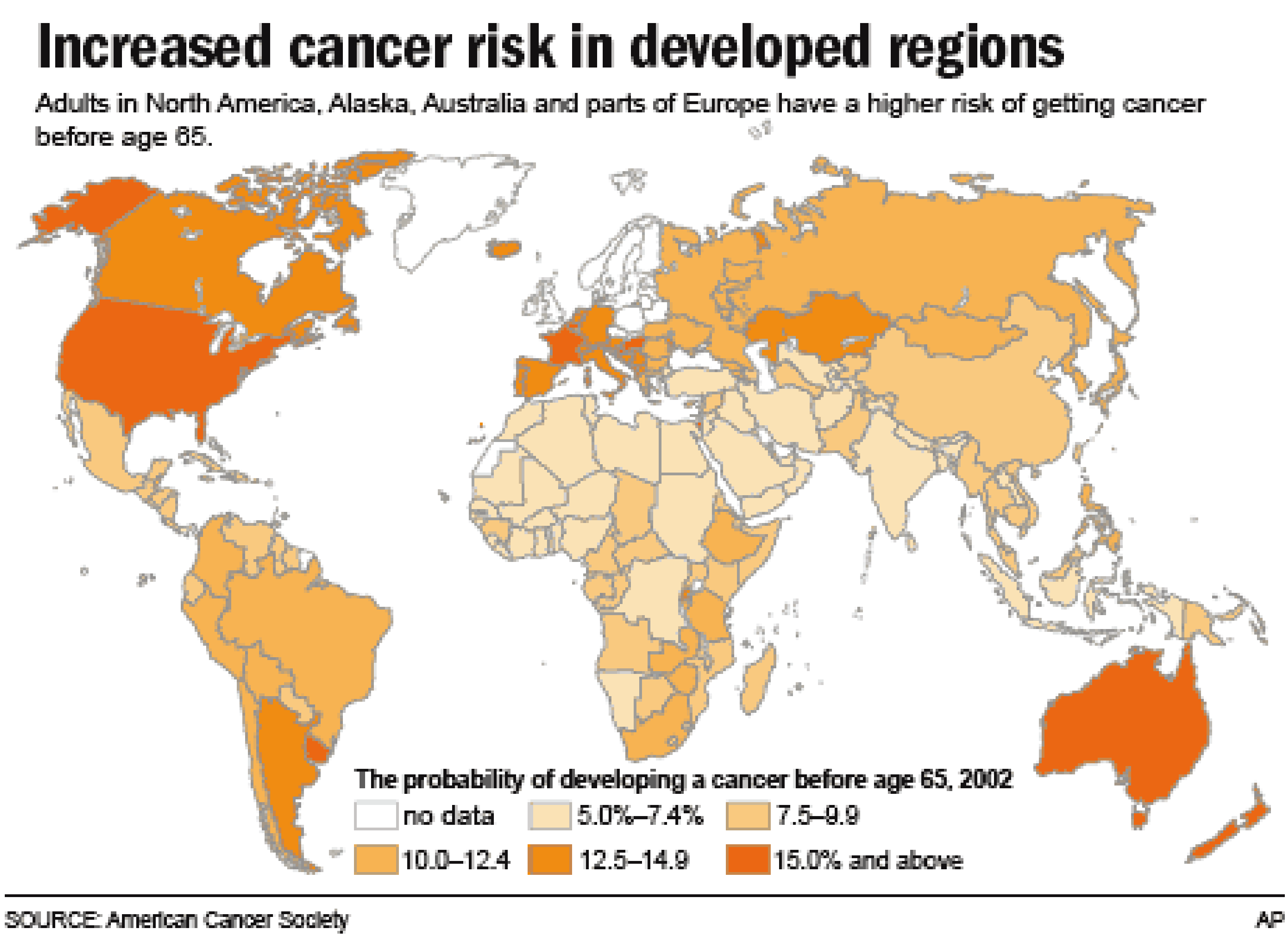
Universiteit Antwerpen

UNIVERSITEIT GENT

Outline

1. Nutrition & cancer-inflammation: the good and the bad
2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects?
3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects

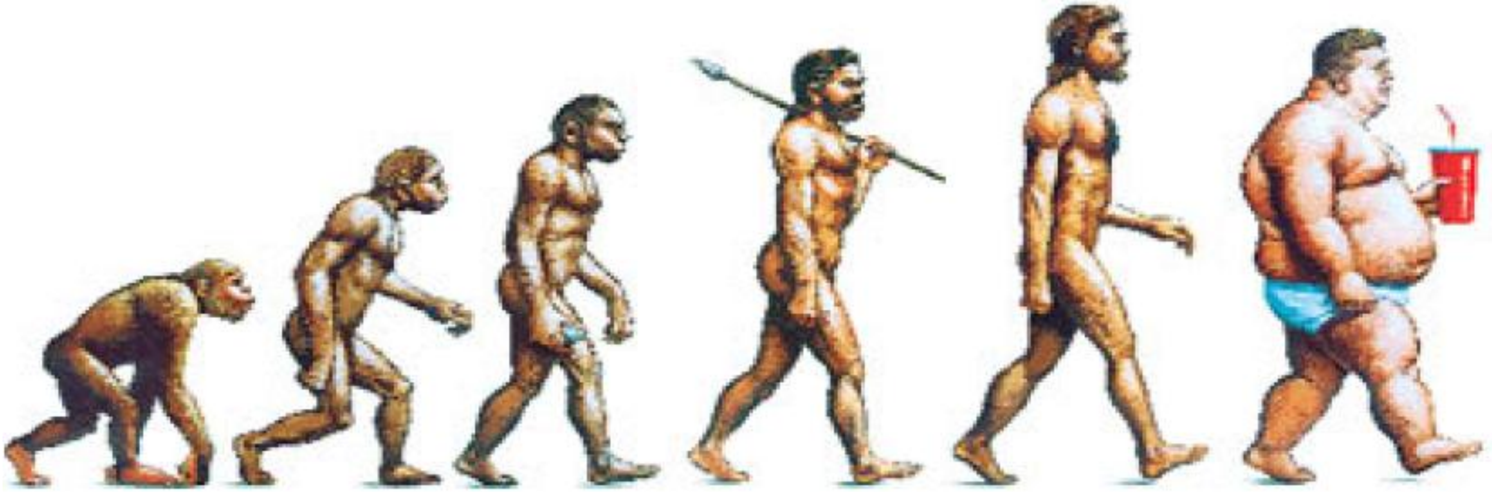
1. Nutrition & cancer-inflammation: the bad news

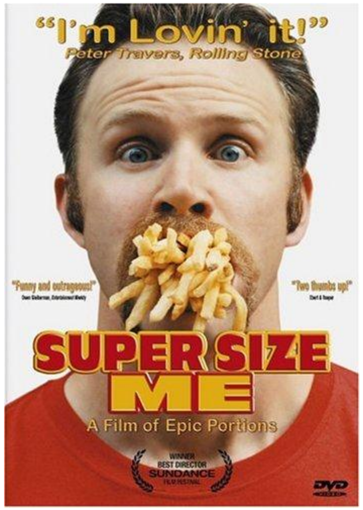


1. Nutrition & cancer-inflammation: the bad news

Disease / condition	Influence of diet, %
Cardiovascular	> 30
Cancers	> 35
Constipation	> 70
Obesity	> 50
Diabetes type 2	> 25
Dental caries	> 30

Table 1. Estimated influence of diet on specific diseases





1. Nutrition & cancer: the good news?

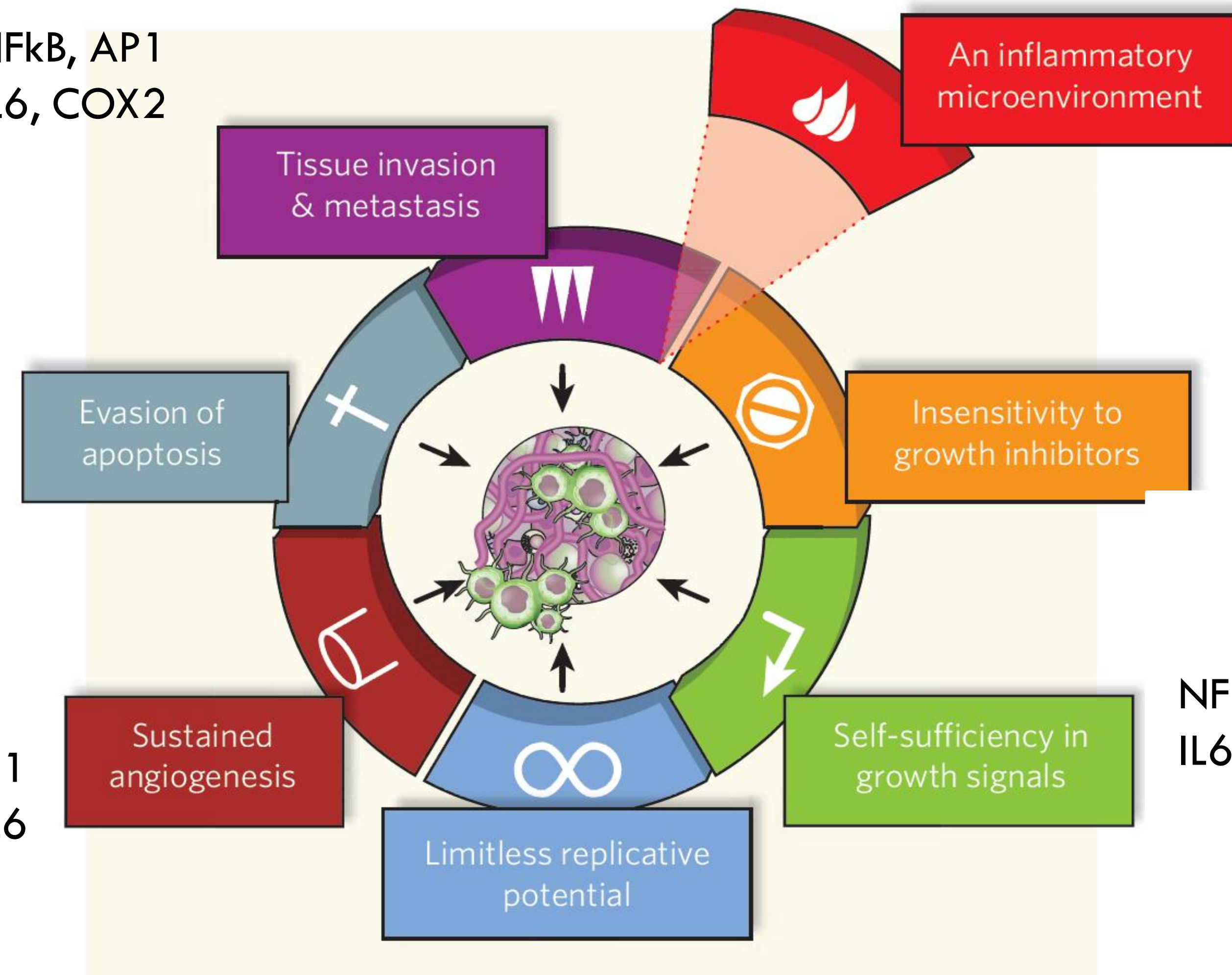
Differences in cancer incidence related to diet preference?

Cancer	USA Cases	USA Deaths	India Cases	India Deaths	Japan Cases	Japan Deaths
Oral cavity	50	11	102	60	29	12
Nasopharynx	4	2	4	3	3	2
Other Pharynx	19	9	57	42	10	7
Oesophagus	31	31	63	59	58	43
Stomach	56	34	43	39	489	225
Colon/Rectum	356	139	40	26	342	143
Liver	30	31	17	16	186	146
Pancreas	72	68	11	11	76	71
Larynx	33	11	35	22	17	5
Lung	463	402	55	51	262	214
Melanoma of skin	113	21	3	1	3	2
Breast	914	212	191	99	314	77
Cervix uteri	78	33	307	174	111	30
Corpus uteri	155	20	17	5	45	13
Ovary etc.	106	62	49	29	66	37
Prostate	1043	179	46	28	111	55
Testis	40	2	6	3	13	2
Bladder	144	28	20	16	56	17
Kidney etc.	86	31	8	6	42	19
Brain, nervous system	54	37	21	16	24	9
Thyroid	46	3	14	4	31	5
Non-Hodgkin lymphoma	135	59	24	19	58	30
Hodgkin's disease	22	4	8	4	3	1
Multiple myeloma	35	26	8	6	16	12
Leukemia	80	54	26	20	48	34
All sites but skin	3223	1391	1017	688	2230	1213

Showing cases were after standardized with world standard population, called World Standardized incidence or mortality rate. It is also expressed per million. J. Ferlay, etal.GLOBOCAN 2000.URL: http://www-dep.iarc.fr/globocan/globocan.htm

2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects

NFkB promotes 7 cancer hallmarks and its activity is increased in most tumors



NFkB, AP1
MMP, IL6, COX2

NFkB, Stat3
IL6,IL8
MCP1
COX2

NFkB
A1/Bfl
A20
cIAP
Mdr/Pgp
BclXl

NFkB, p53
p21

NFkB, AP1
IL6

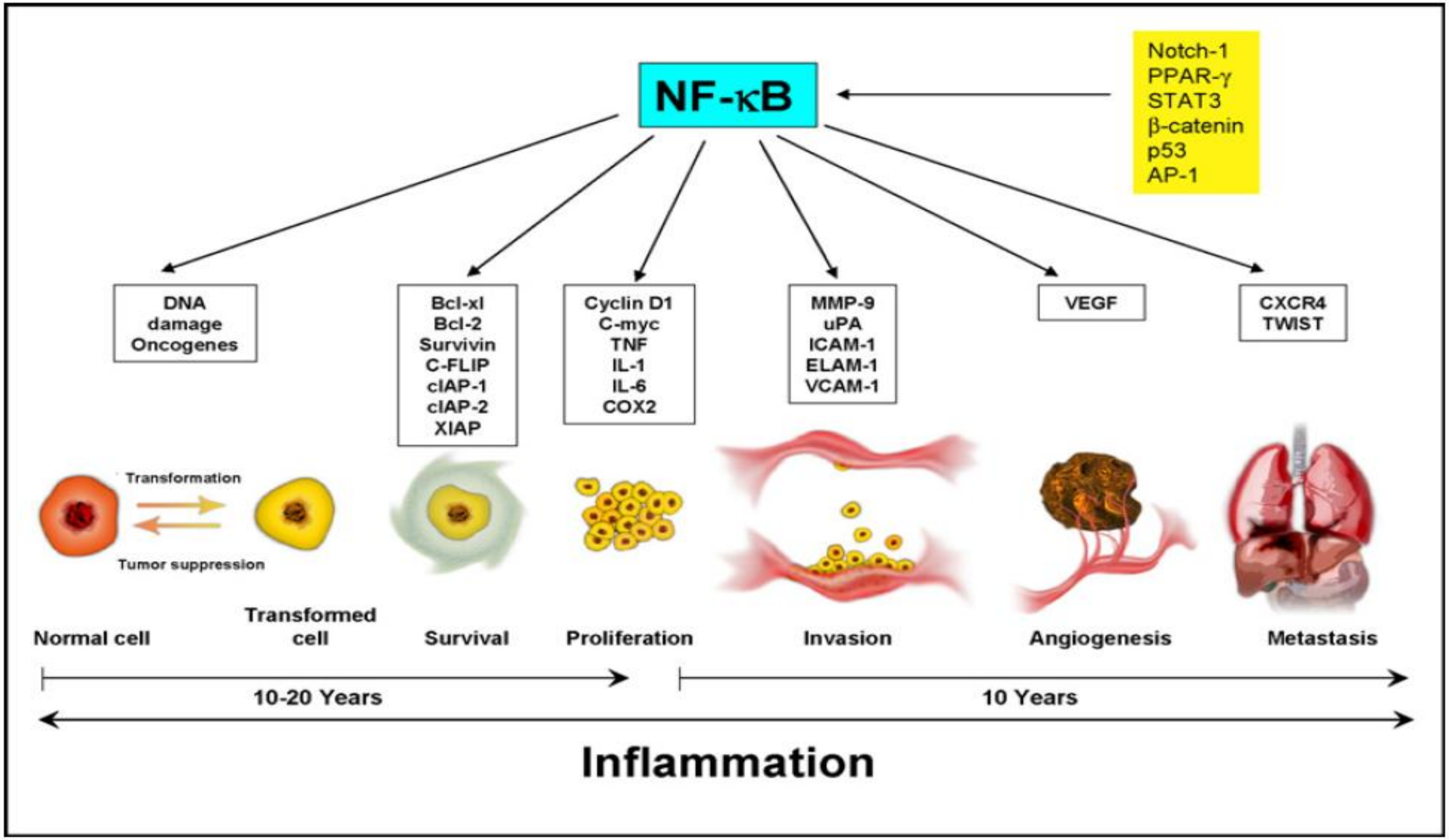
NFkB, AP1
VEGF, IL6

NFkB, AP1 Cyclin D, c-myc, telomerase

NATURE|Vol 457|1 January 2009

2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects

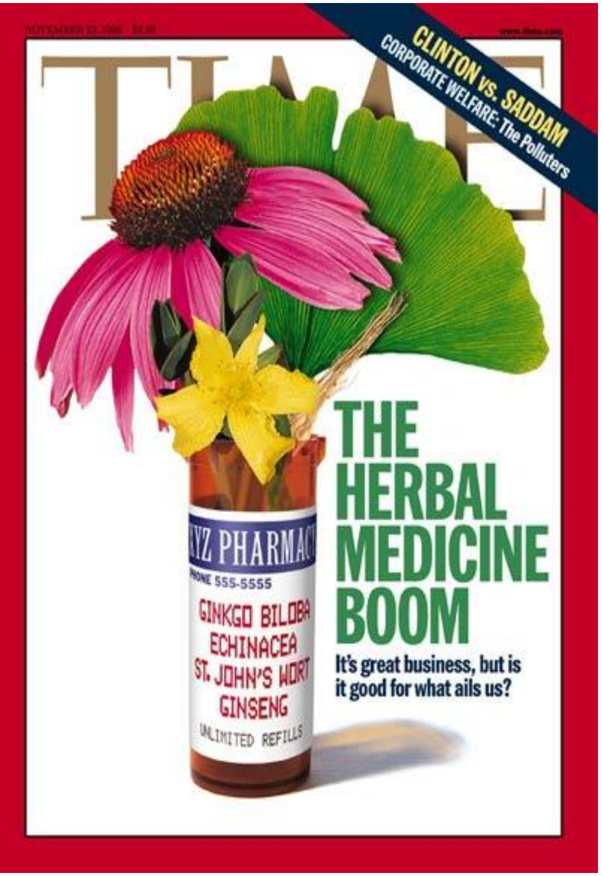
Chronic inflammation promotes tumorinitiation-progression, angiogenesis and metastasis

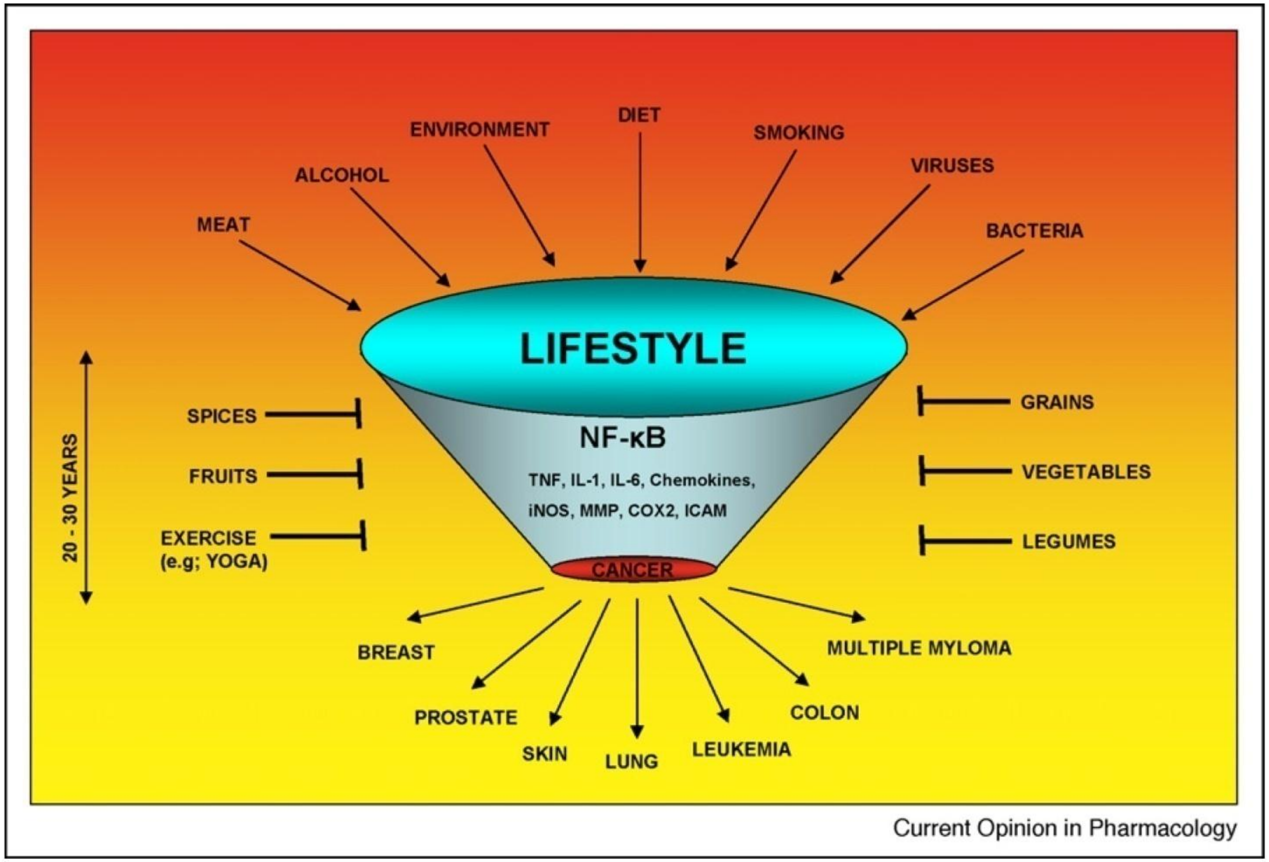


Aggarwal, Curr Opin Pharmacol. 2009 Aug;9(4):347-50

2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects

Curr Opin Pharmacol. 2009 Aug;9(4):347-50

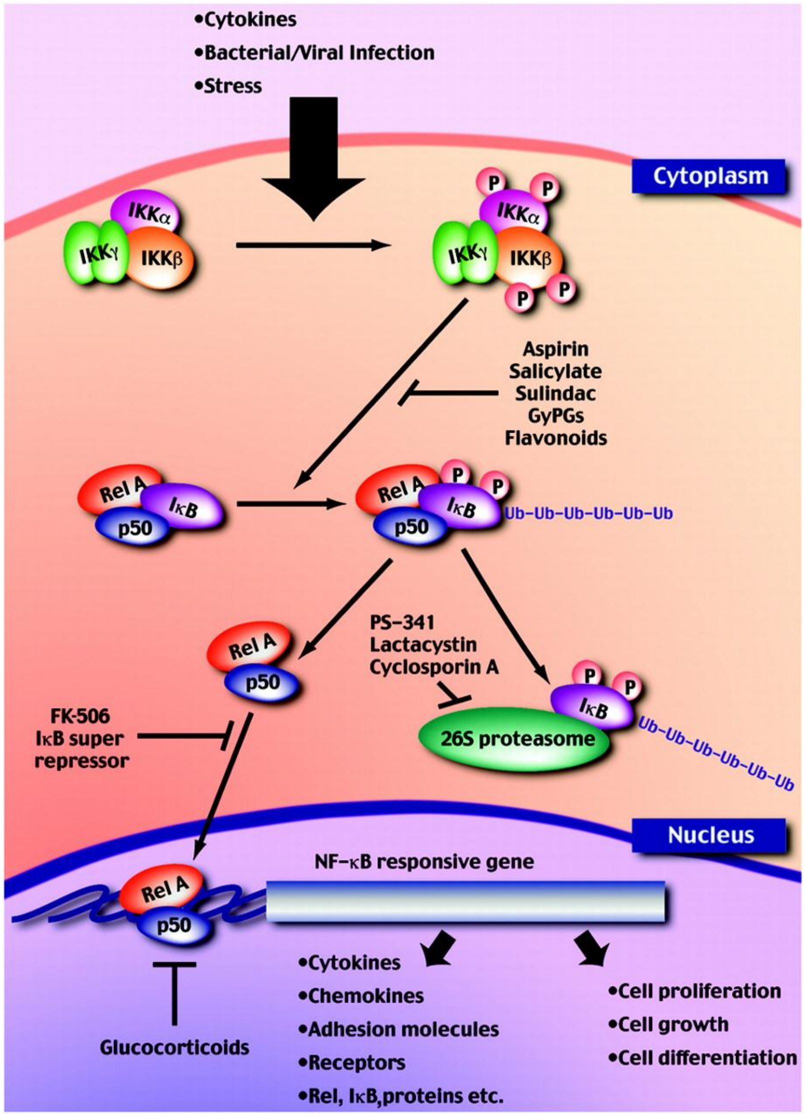




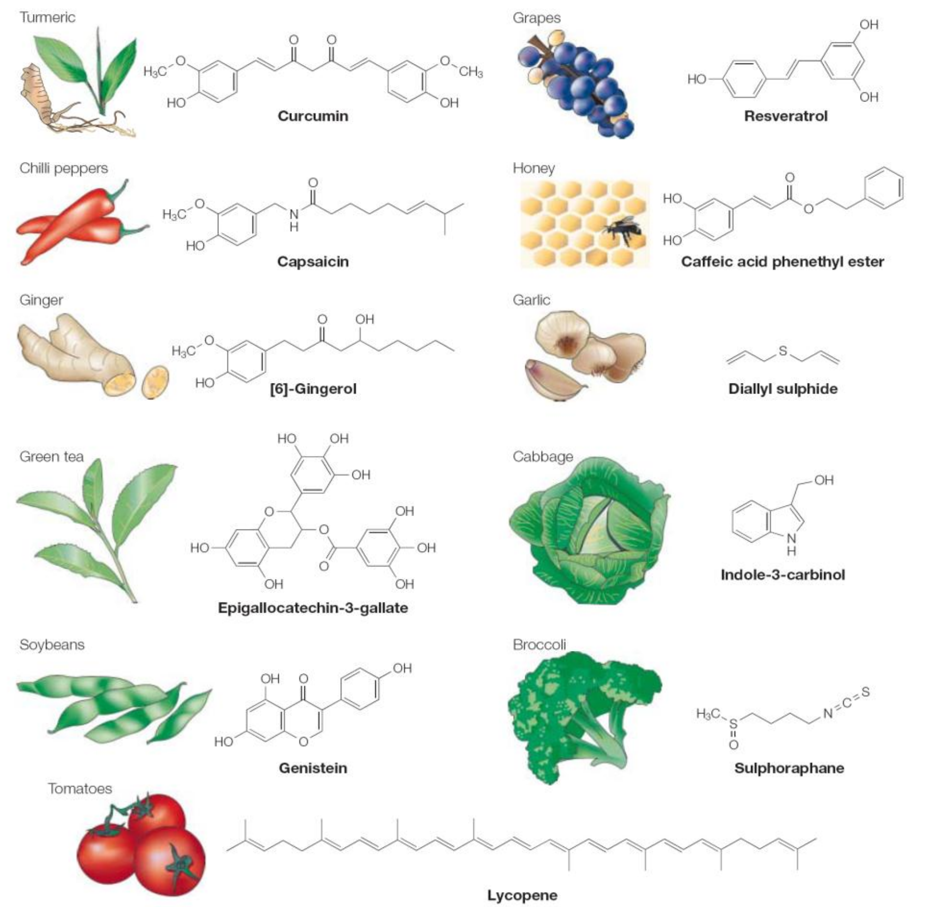
Hypothesis: Various dietary phytochemicals lower basal inflammatory state

2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects

Plant derived NFkB inhibitors attenuate cancer hallmarks in vitro in concentration range >10µM ….



Natural products can inhibit NFkB activity at various levels:



Outline

1. Nutrition & cancer: the good and the bad
2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects?

   Problem: various anti-inflammatory mechanisms are demonstrated at supraphysiological concentrations >10μM

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects
4. Conclusions

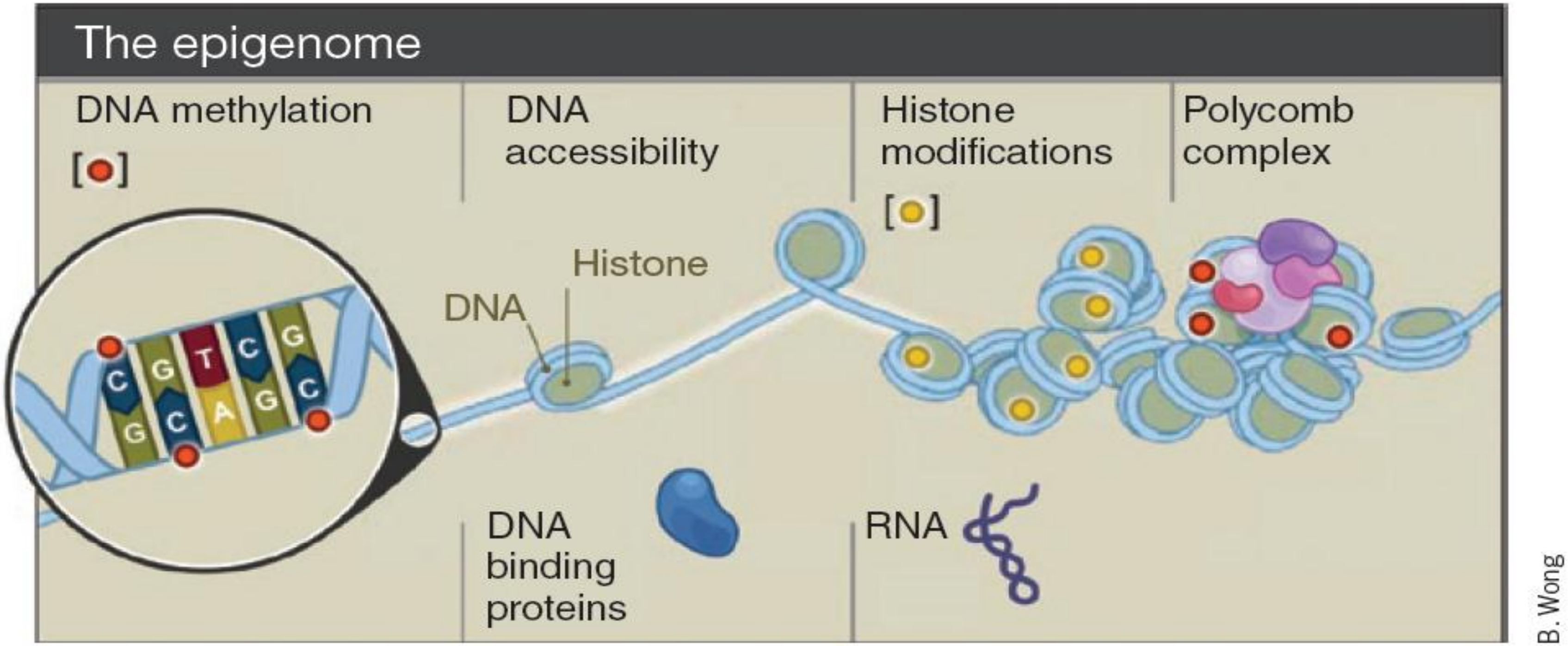
Outline

1. Nutrition & cancer: the good and the bad
2. Can anti-inflammatory effects of phytochemicals explain their potential anti-cancer effects?
3. Can **epigenetic effects** of phytochemicals explain their potential anti-cancer effects?

Epigenetics definition: **Heritable** changes in phenotype and/or gene expression that occur without a change in DNA sequence

Heritable: transgenerational, mitotic stable,
perpetuation of gene activity in absence of the original signal

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects



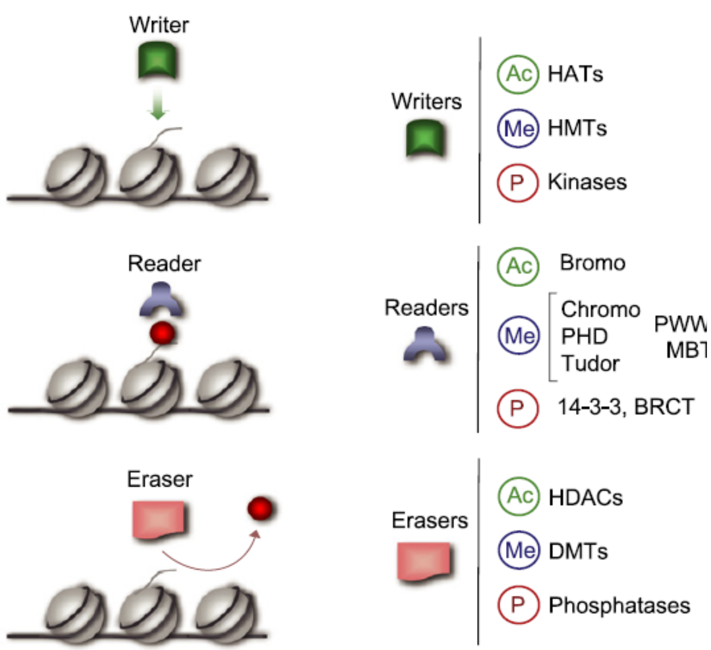
An Epigenetic Switch Involving NF-κB, Lin28, Let-7 MicroRNA, and IL6 Links Inflammation to Cell Transformation

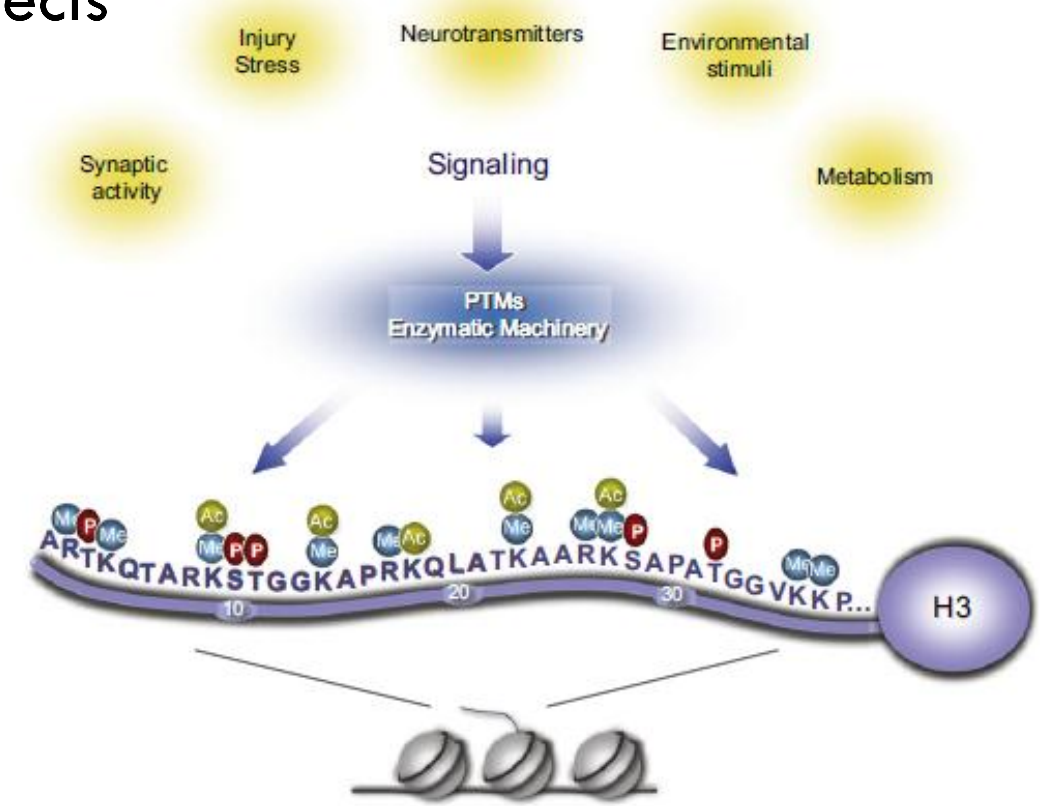
Dimitrios Iliopoulos,[1] Heather A. Hirsch,[1] and Kevin Struhl[1,*]
[1]Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: kevin@hms.harvard.edu
DOI 10.1016/j.cell.2009.10.014

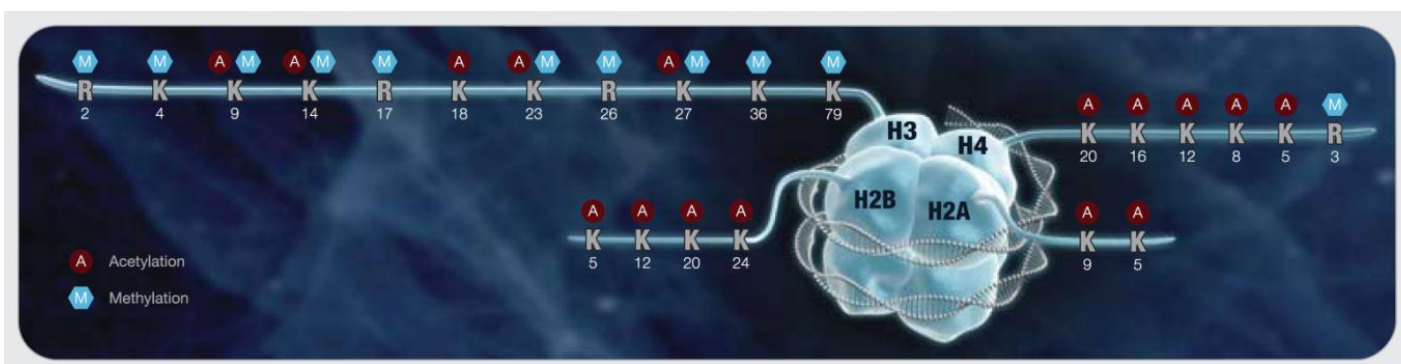
MicroRNA-Dependent Regulation of DNA Methyltransferase-1 and Tumor Suppressor Gene Expression by Interleukin-6 in Human Malignant Cholangiocytes

Chiara Braconi, Nianyuan Huang, and Tushar Patel

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects







3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects

Epigenetic dogma of cancer

Global hypomethylation

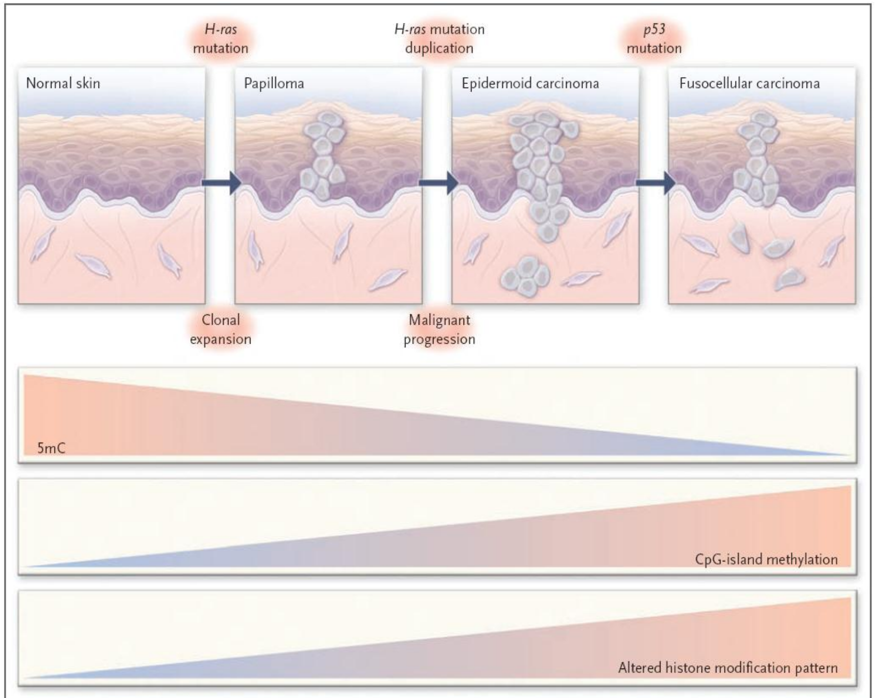


Figure 1. **Epigenetic Alterations in Tumor Progression.**
A multistage model of carcinogenesis in skin is shown. In conjunction with phenotypic cellular changes and the accumulation of genetic defects, there is a progressive loss of total DNA methylation content, an increased frequency of hypermethylated CpG islands, and an increased histone-modification imbalance in the development of the disease. *H-ras* denotes Harvey–ras oncogene, and 5mC 5-methyl-cytosine.

Hypermethylation of tumor suppressor genes

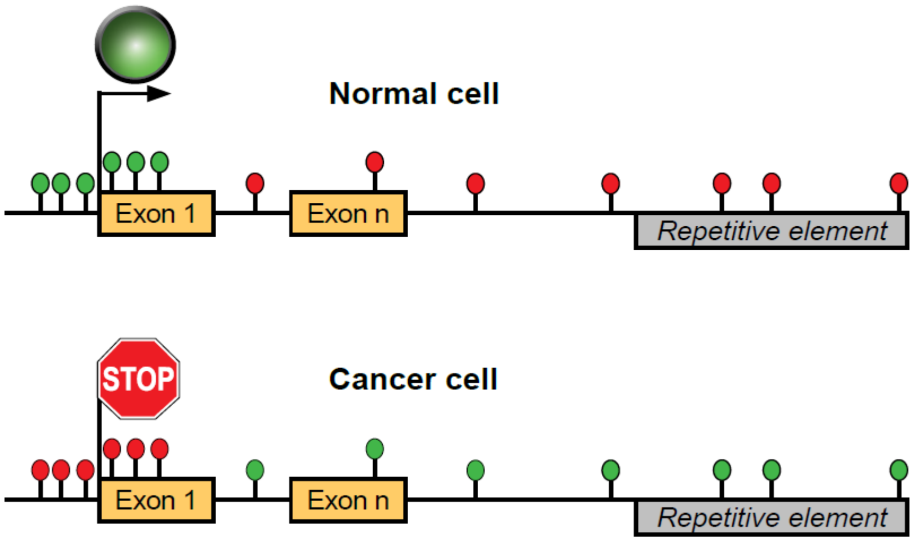
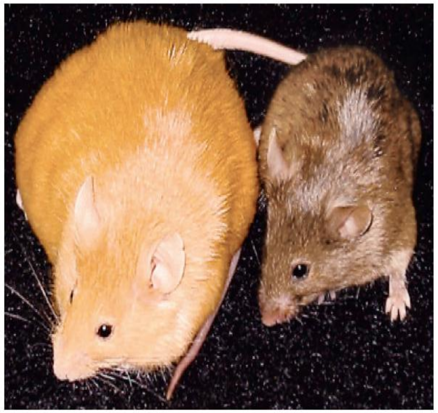


Figure 2. DNA methylation pattern in normal and cancer cells. CpG islands are protected from methylation in normal cells. CpG sites away from transcription start sites and in repetitive elements are typically methylated. The situation gets reversed in cancer resulting in focal hypermethylation and global hypomethylation. CpG islands flanking start sites of some genes may become methylated. Intragenic CpG sites and repeats are become unmethylated. Green lollipops show unmethylated, red lollipops methylated CpG sites.

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects - key experiments

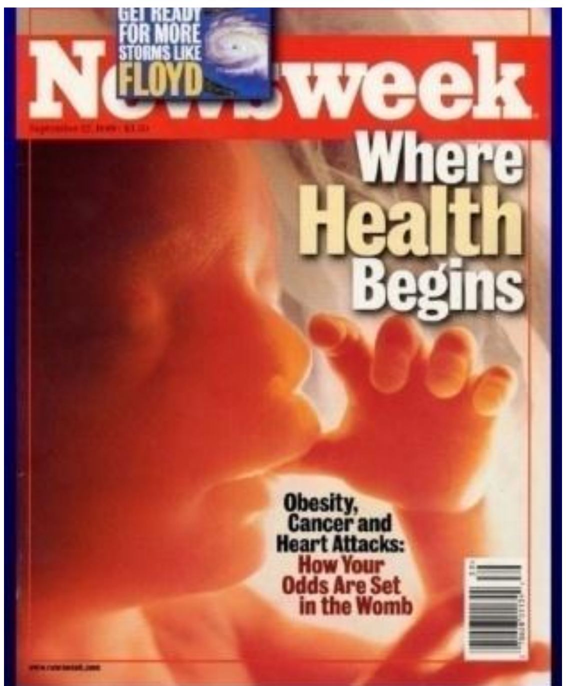
With no more than a change in diet, laboratory agouti mice (left) were prompted to give birth to young (right) that differed markedly in appearance and disease susceptibility. Recently, researchers showed that an epigenetic change in nematode worms can be inherited for 80 generations.



Agouti model: R. Waterland and R. Jirtle

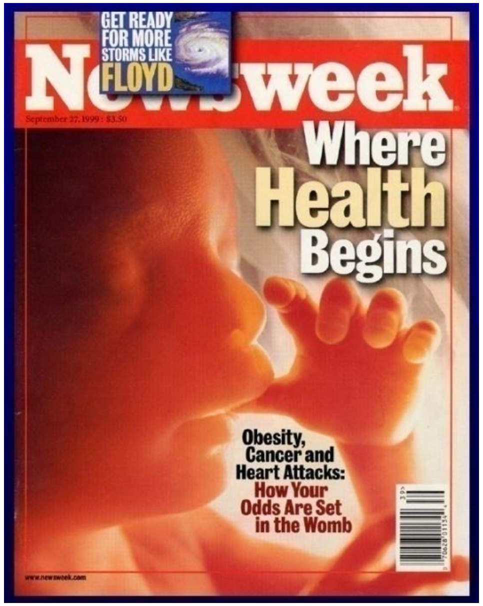
Germ cells carry the epigenetic benefits of grandmother's diet

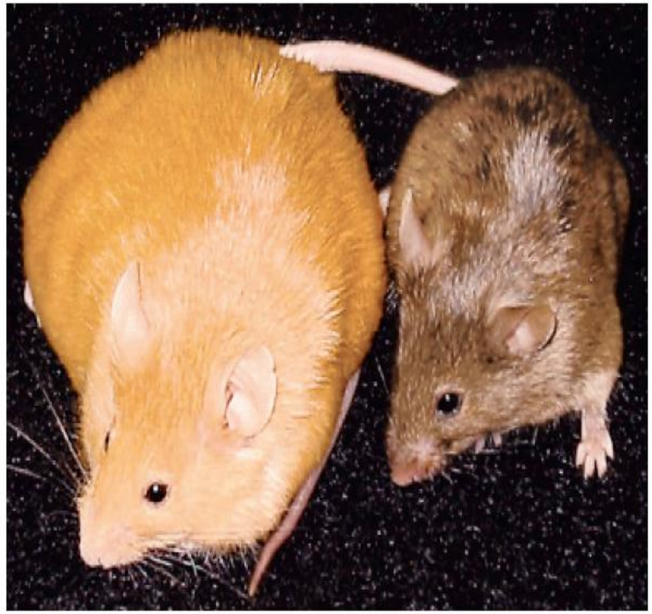
Craig A. Cooney*
Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR 72205

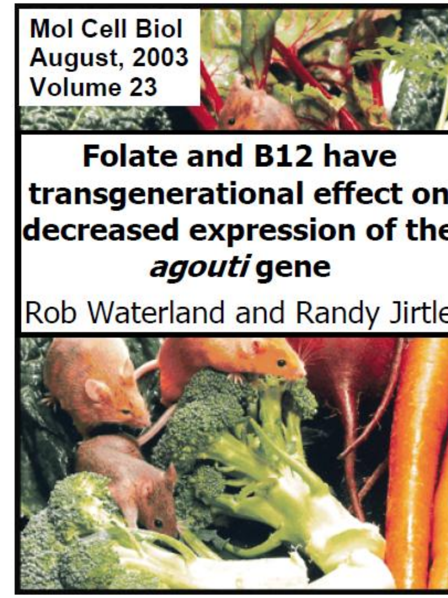


Maternal Supplements
With Genistein
Zinc methionine
Betaine choline,
Folate B_{12}

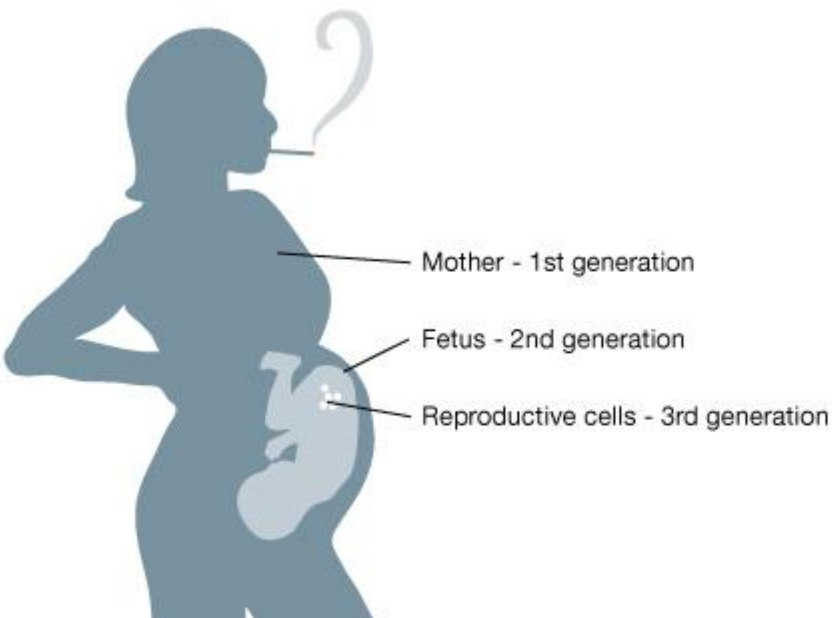
Lower risk of cancer, diabetes, obesity , CVD and prolonged life







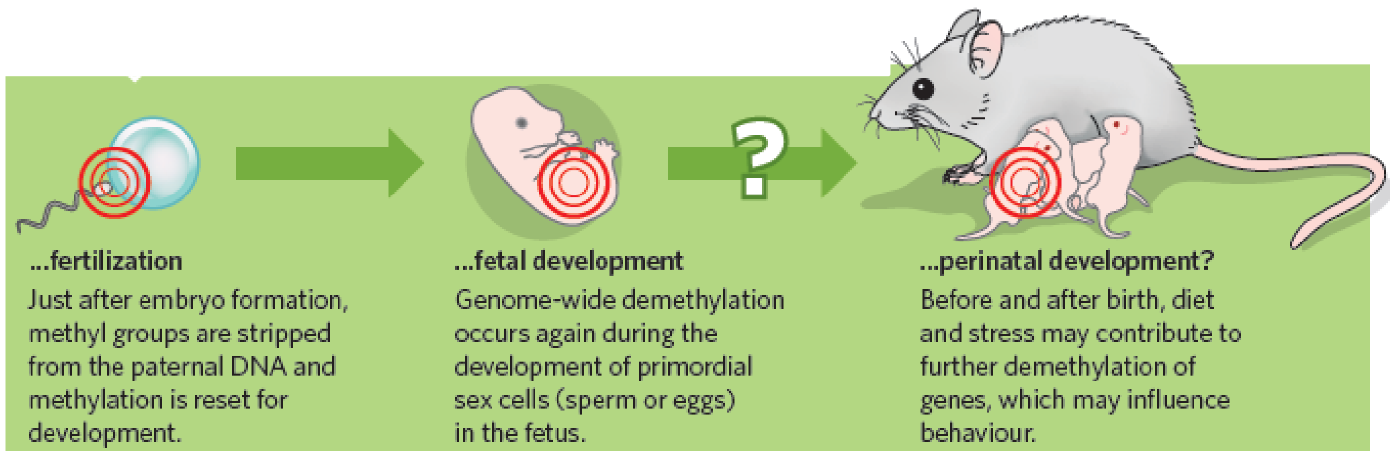
Agouti mouse model : Soy diet induces transgenerational changes in DNA methylation which protect 2 unexposed generations to obesity & cancer



Half of your DNA has been exposed to the environmental conditions in the uterus of your maternal grandmother

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects - key experiments

Timing of dietary exposure maybe critical to achieve chemopreventive effects



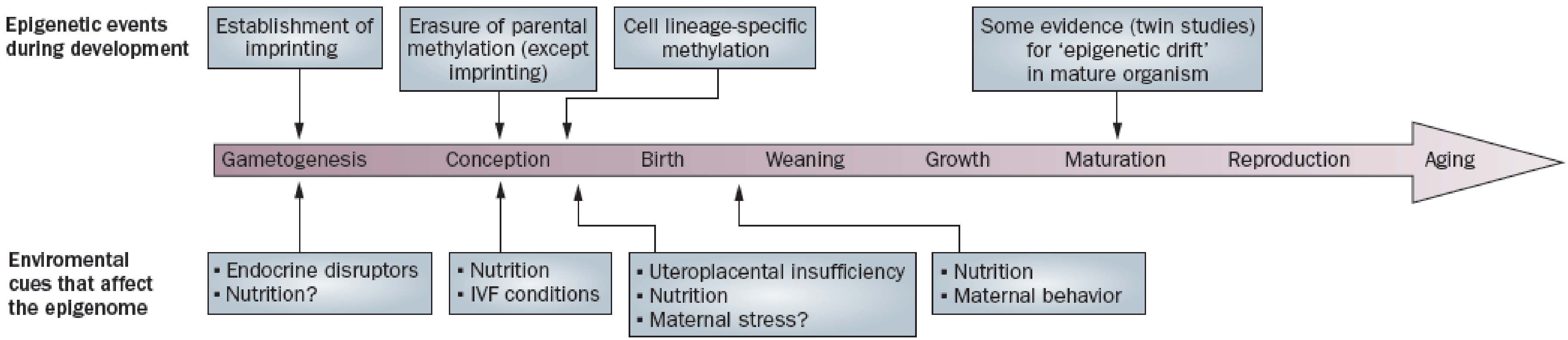


Figure 2 | Environmental sensitivity of the epigenome throughout life. The top row indicates normal reprogramming of the epigenome during gametogenesis, fertilization and development. The bottom row indicates the environmental cues that affect the epigenome and have late-life consequences, and the stages of life at which they act. Sensitivity of the epigenome to the environment (represented by shading of the arrow) is likely to decrease during life as growth slows. Abbreviation: IVF, *in vitro* fertilization.

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects - key experiments

OPEN ACCESS Freely available online PLoS one

Early Life Exposure to Famine and Colorectal Cancer Risk: A Role for Epigenetic Mechanisms

Laura A. E. Hughes[1], Piet A. van den Brandt[1], Adriaan P. de Bruïne[2], Kim A. D. Wouters[2], Sarah Hulsmans[2], Angela Spiertz[3], R. Alexandra Goldbohm[3], Anton F. P. M. de Goeij[2], James G. Herman[4], Matty P. Weijenberg[1], Manon van Engeland[2]*

1 Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands, 2 Department of Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands, 3 Department of Prevention and Health, TNO Quality of Life, Leiden, The Netherlands, 4 Sidney Kimmel Comprehensive Cancer Center, John Hopkins University School of Medicine, Baltimore, Maryland, United States of America

Gluckman *et al. Genome Medicine* 2010, 2:14
http://genomemedicine.com/content/2/2/14

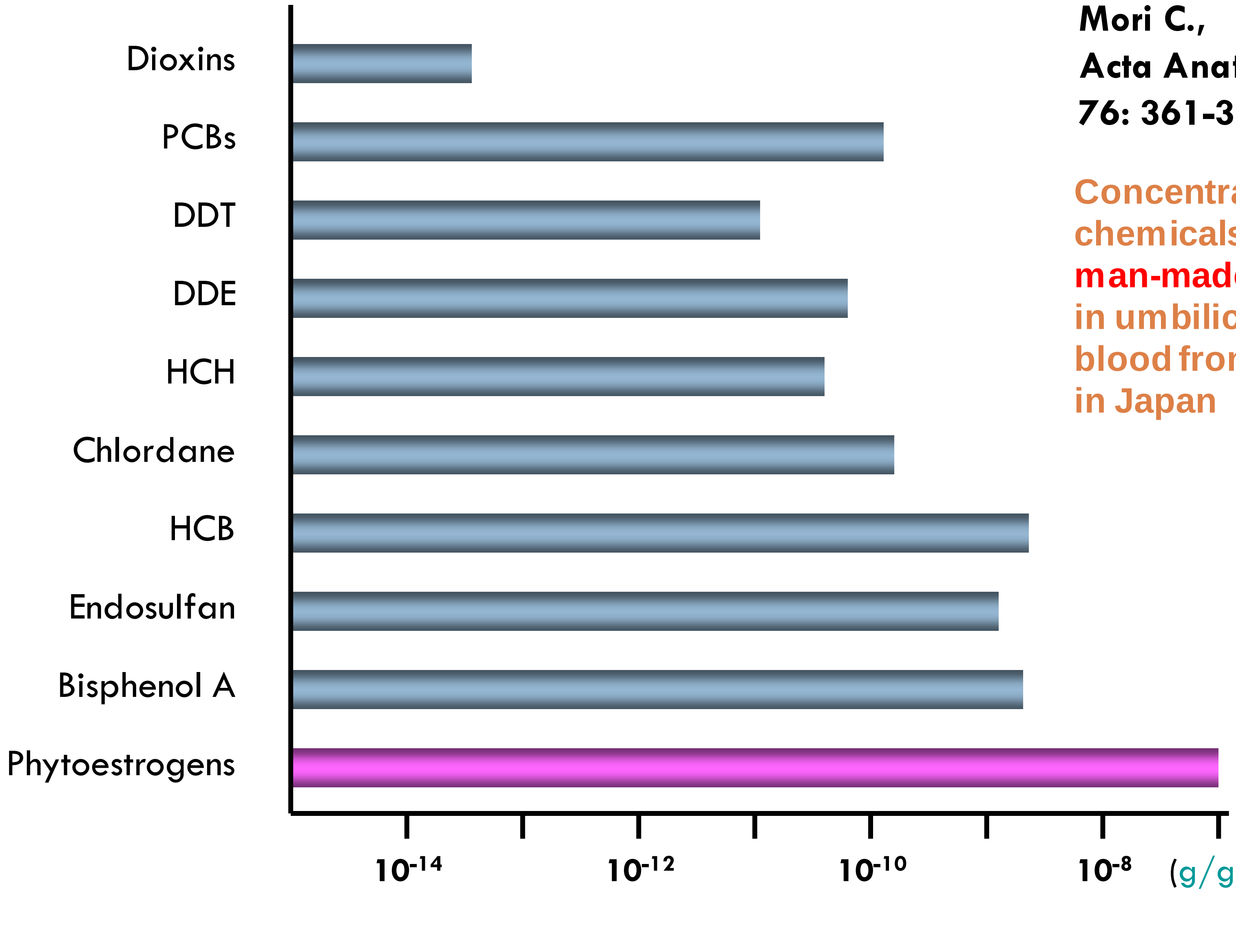
Genome Medicine

COMMENTARY

Developmental origins of health and disease: reducing the burden of chronic disease in the next generation

Peter D Gluckman[1,2], Mark A Hanson[3] and Murray D Mitchell[1*4]

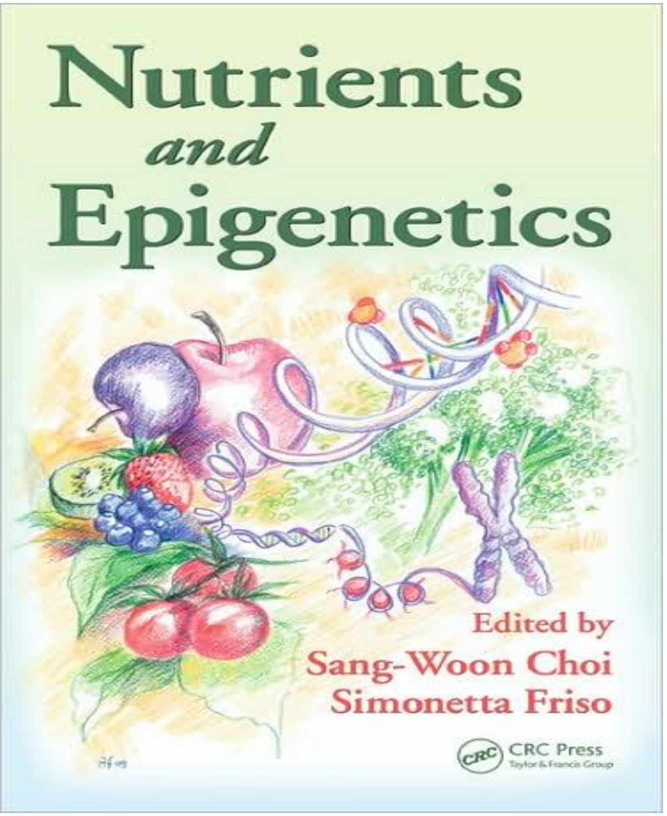
3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects?



Mori C., Acta Anat. Nippon. 76: 361-368 (2001)

Concentration of chemicals including man-made and natural in umbilical cords/cord blood from newborns in Japan

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects?



FOOD	CHEMICAL	EPIGENETIC ROLE
Sesame Seeds	Methionine	Methylates DNA (gene silencing)
Nuts	Folic Acid	Methylates DNA (gene silencing)
Sunflower Seeds	Folic Acid	Methylates DNA (gene silencing)
Peppers	Methionine	Methylates DNA (gene silencing)
Spinach and Other Leafy Vegetables	Methionine and Folic Acid	Methylates DNA (gene silencing)
Broccoli	Sulphoraphane	Acetylates Histones (activating genes)
Other Vegetables	Vitamin B6	Methylates DNA (gene silencing)
Garlic	Diallylsulphide (DADS)	Acetylates Histones (activating genes)
Soy or Soy Products	Choline, Genistein	Methylates DNA (gene silencing)
Milk	Vitamin B12	Methylates DNA (gene silencing)
Bakers Yeast	Folic Acid	Methylates DNA (gene silencing)
Whole Grain Products	Vitamin B6	Methylates DNA (gene silencing)
Fish	Methionine	Methylates DNA (gene silencing)
Shellfish	Vitamin B12	Methylates DNA (gene silencing)
Beef	Vitamin B12	Methylates DNA (gene silencing)
Veal	Choline	Methylates DNA (gene silencing)
Chicken	Choline	Methylates DNA (gene silencing)
Liver	Folic Acid	Methylates DNA (gene silencing)
Egg Yolk	Choline	Methylates DNA (gene silencing)

PNAS

Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development

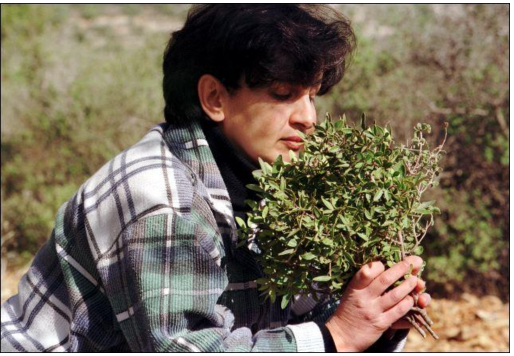
Dana C. Dolinoy*†‡, Dale Huang*, and Randy L. Jirtle*†‡§

*Department of Radiation Oncology and ‡University Program in Genetics and Genomics, Duke University, Durham, NC 27710; and †Integrated Toxicology and Environmental Health Program, Duke University, Durham, NC 27708

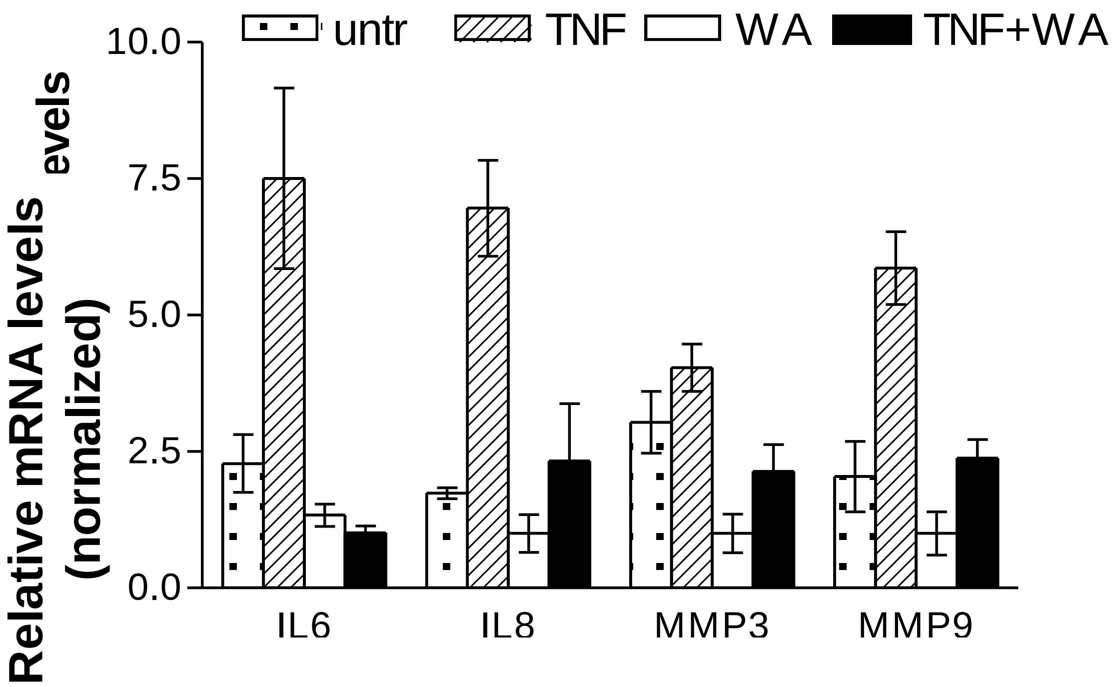
Edited by R. Michael Roberts, University of Missouri, Columbia, MO, and approved June 25, 2007 (received for review April 23, 2007)

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

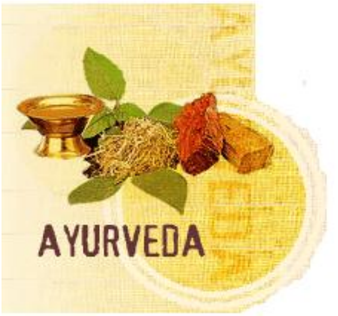
Withaferin A inhibits inflammatory gene expression in MDA-MB231 breast cancer cells in [nM] range



Kaileh, JBC 2007

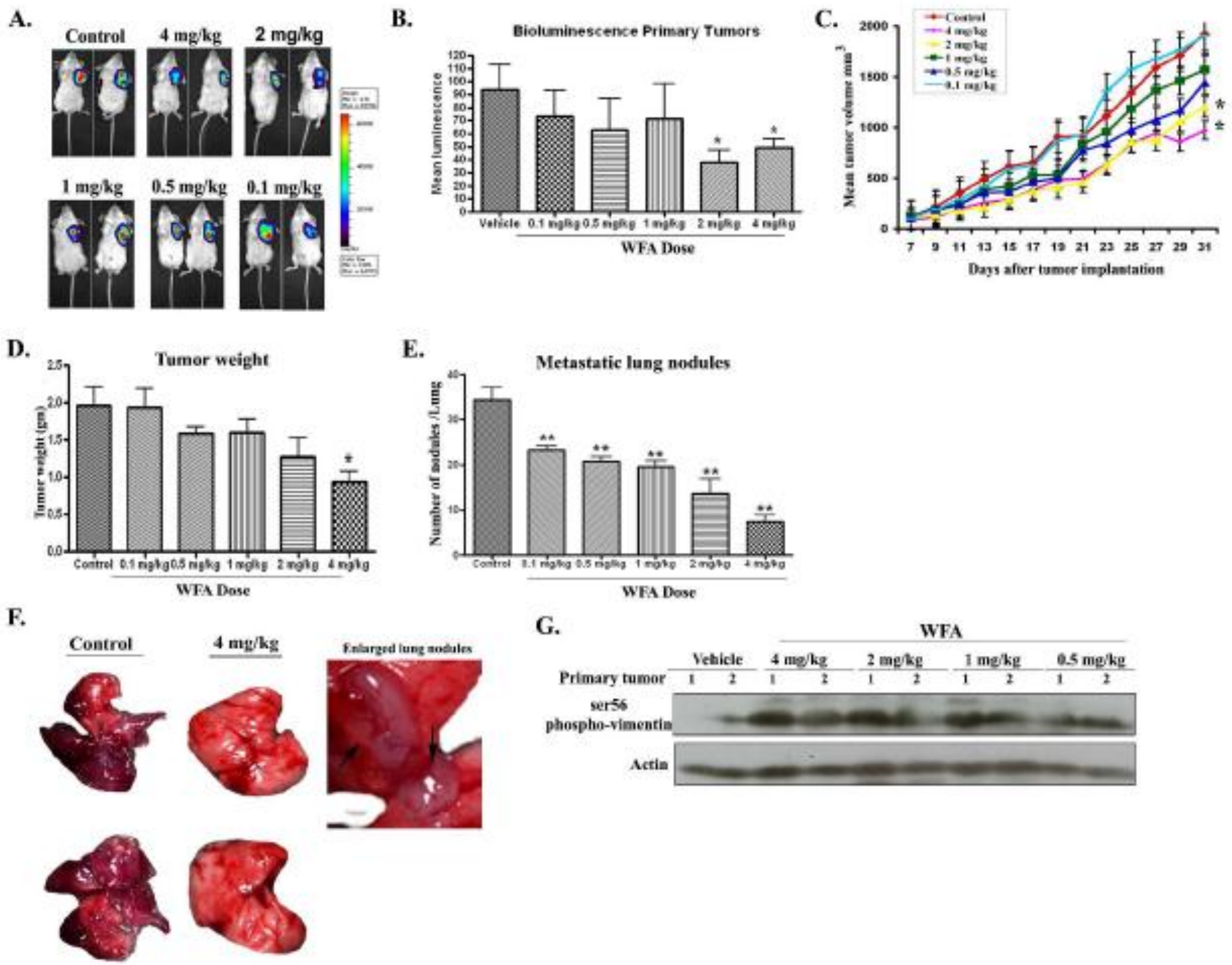


Widespread etnopharmacological use of *Withania Somnifera / Ashwagandha* (Ayurvedic) extracts for cancer chemotherapy and anti-inflammatory use



3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

Withaferin A blocks breast cancer metastasis in vivo in nM range

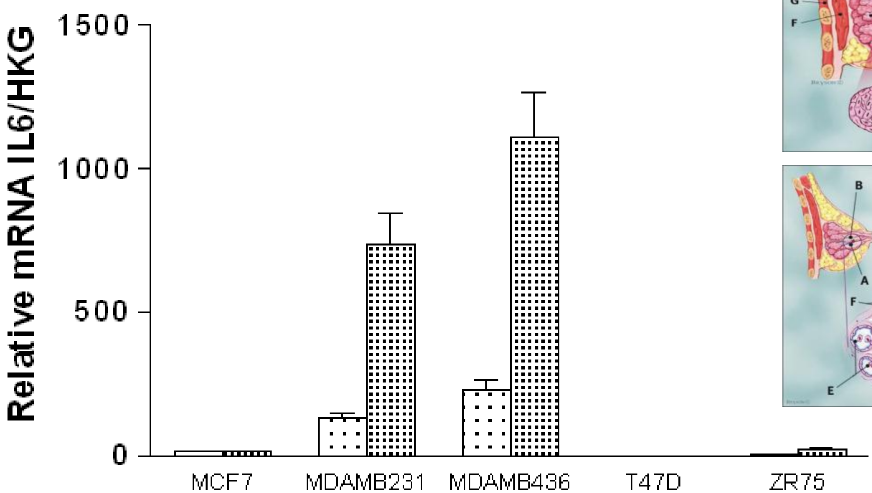


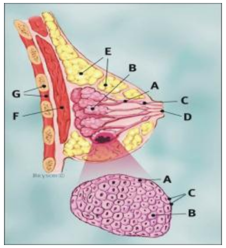
Thaiparambil et al. 2011, Int. J. Cancer, DOI: 10.1002/ijc.25938

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

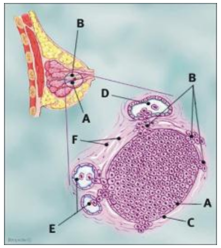
Differential IL6 gene expression in weak versus strong metastatic breast cancer cell types

A



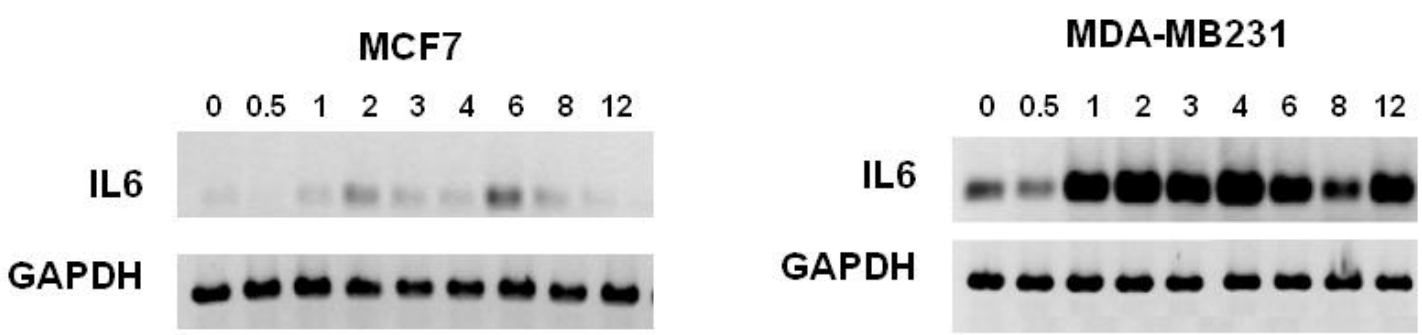


ERα-positive, low metastatic ,
Weak IL6 gene expression levels
MCF7, T47D, ZR75



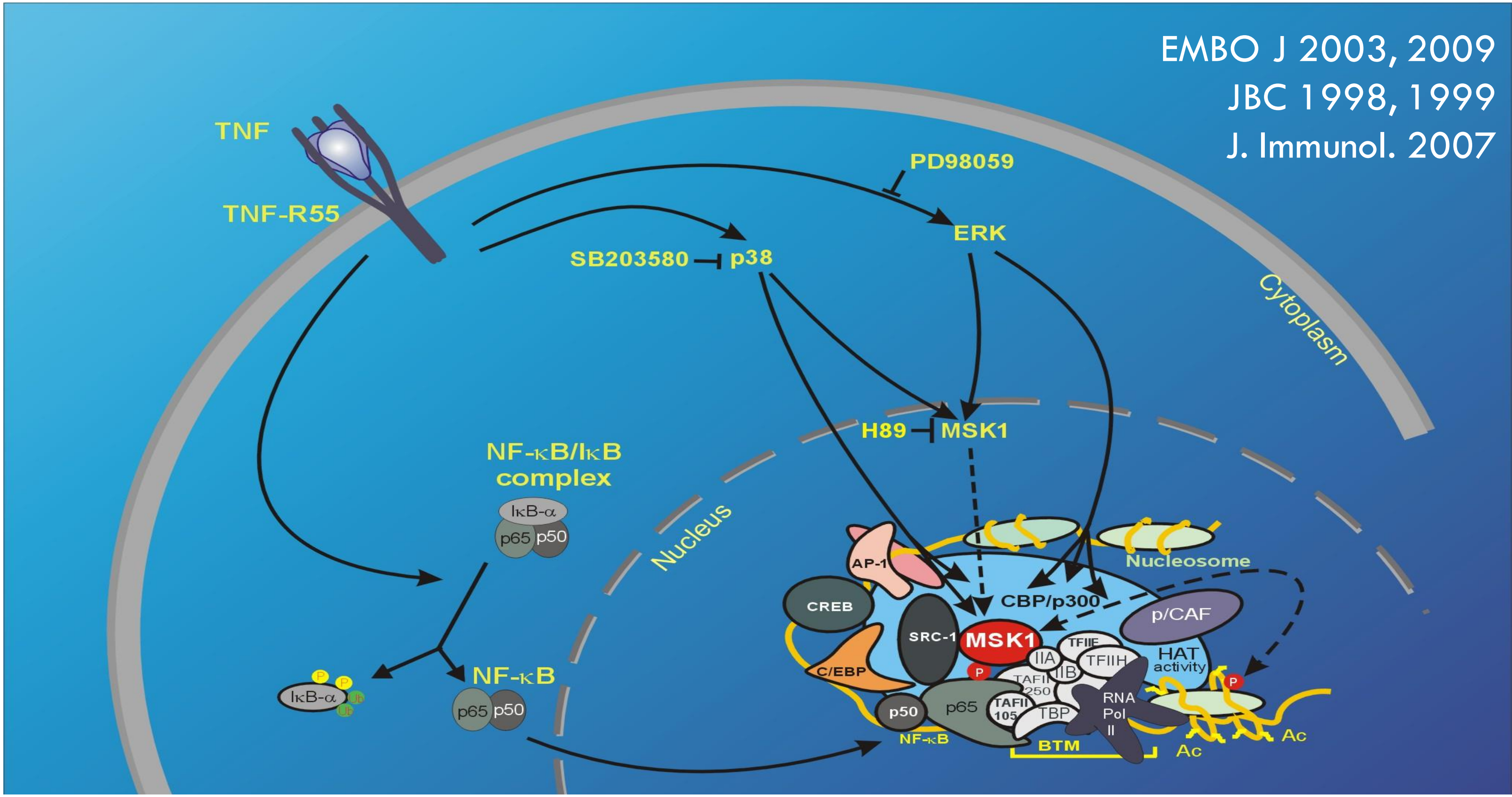
ERα-negative, strong metastatic, aggressive
Strong IL6 gene expression levels
MDA-MB231, MDA-MB468

B



3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

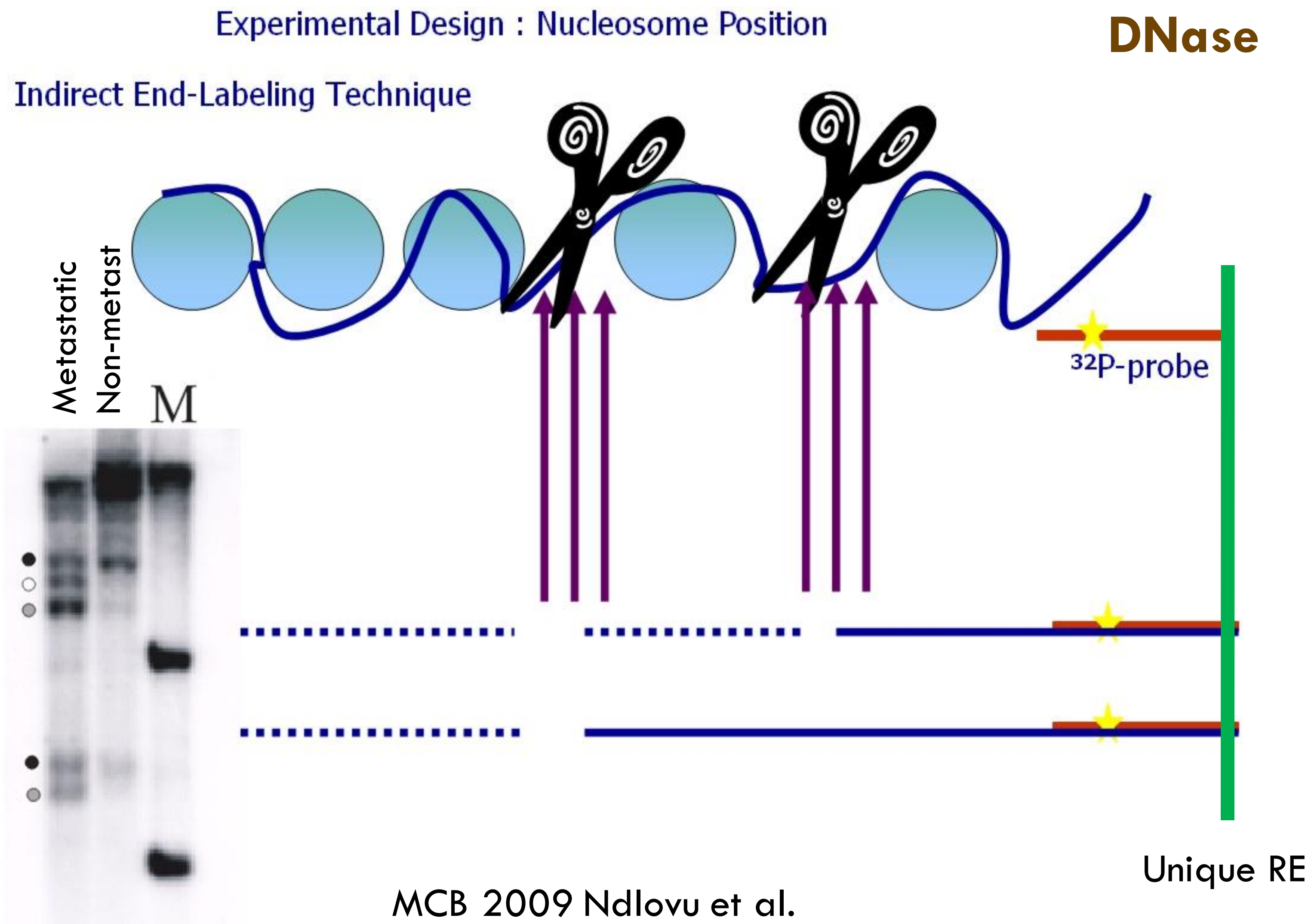
Differential IL6 gene expression in weak versus strong metastatic breast cancer cell types



Phytochemical effects on histone modifier enzymes selectively affects specific NFKB target genes

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

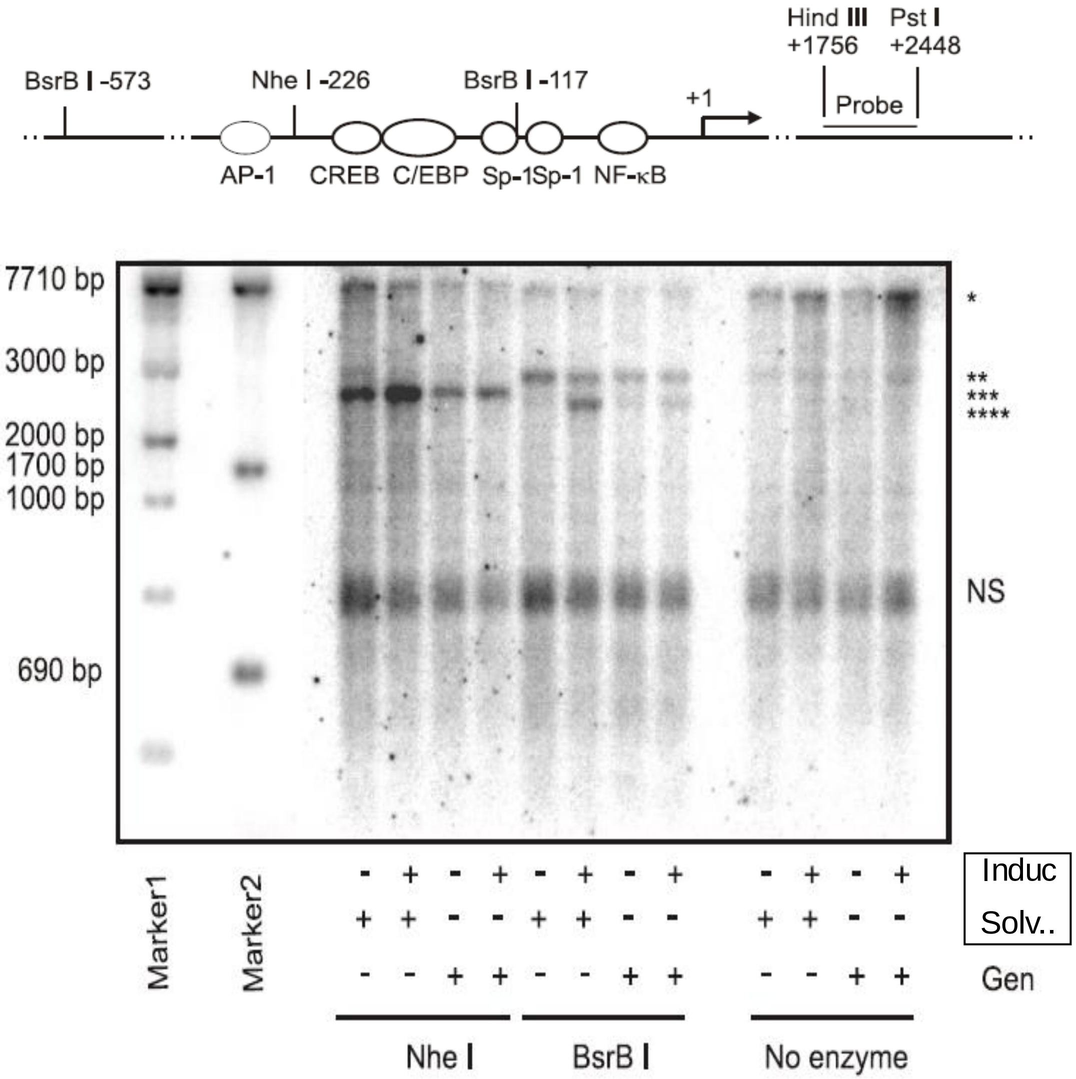
Oncogene chromatin opening involved in breast cancer metastasis



MCB 2009 Ndlovu et al.

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

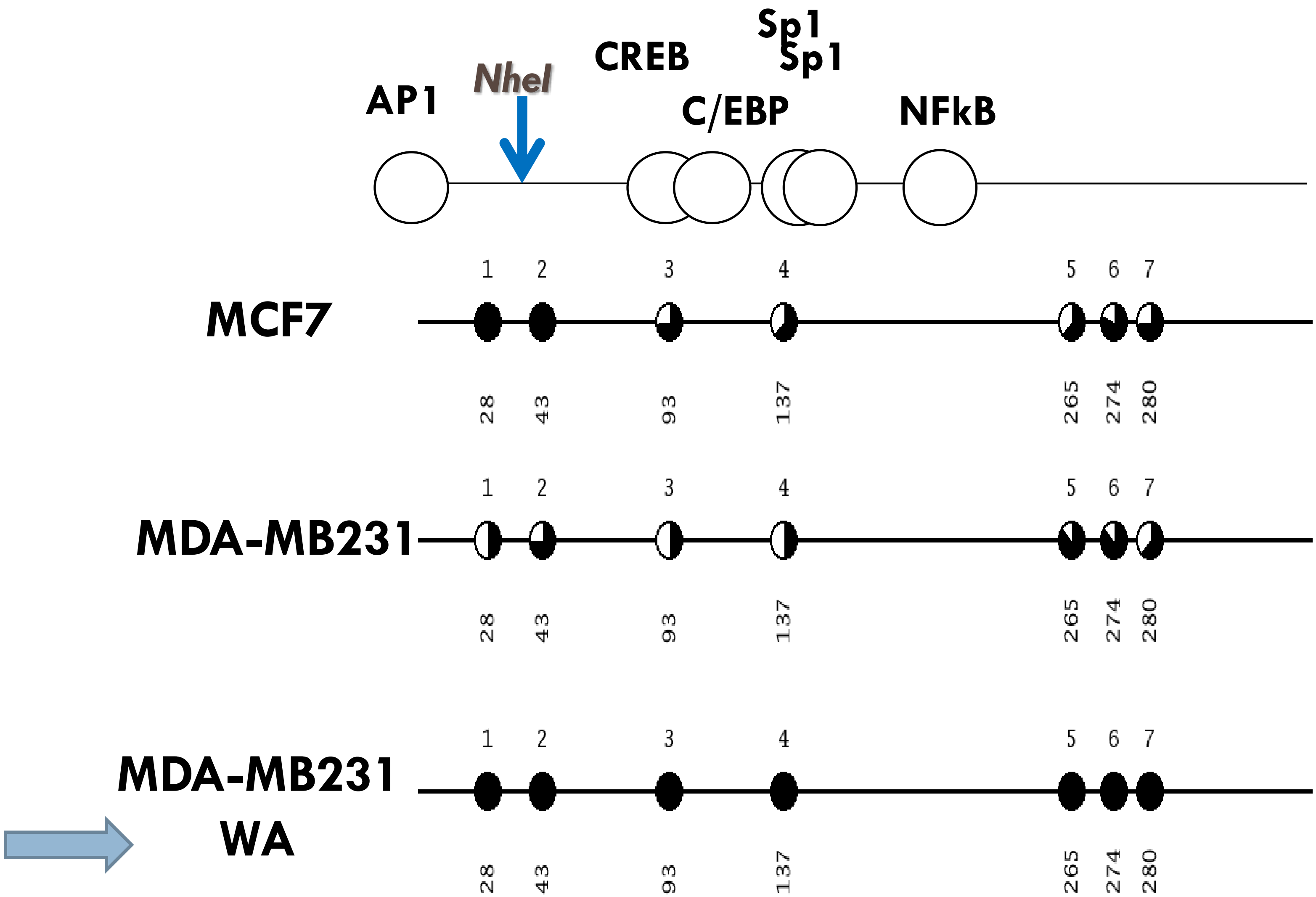
Phytochemicals also regulate chromatin dynamics of inflammatory cells (DC)



Dijsselbloem
J. Immunol. 2007

3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

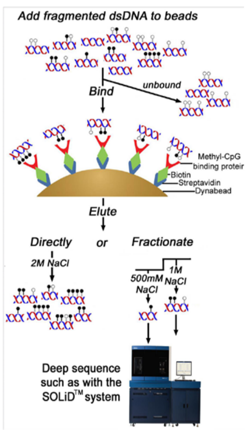
Reverse oncogenic gene expression by increased DNA methylation via dietary compounds ?

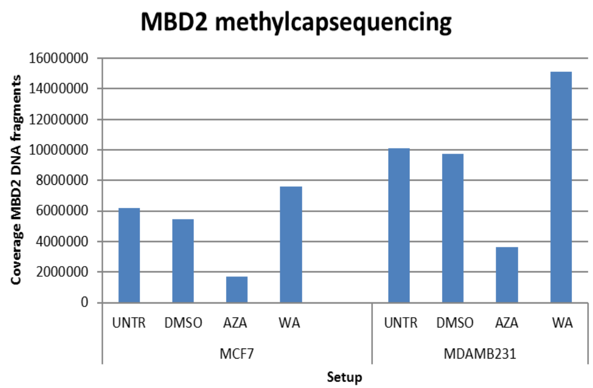


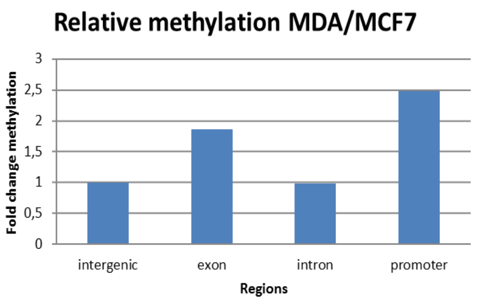
3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

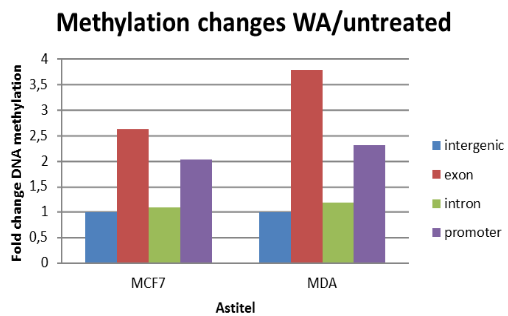
MBD2 seq based profiling of the cancer methylome/immune cell methylome

Principle MBD2 sequencing:

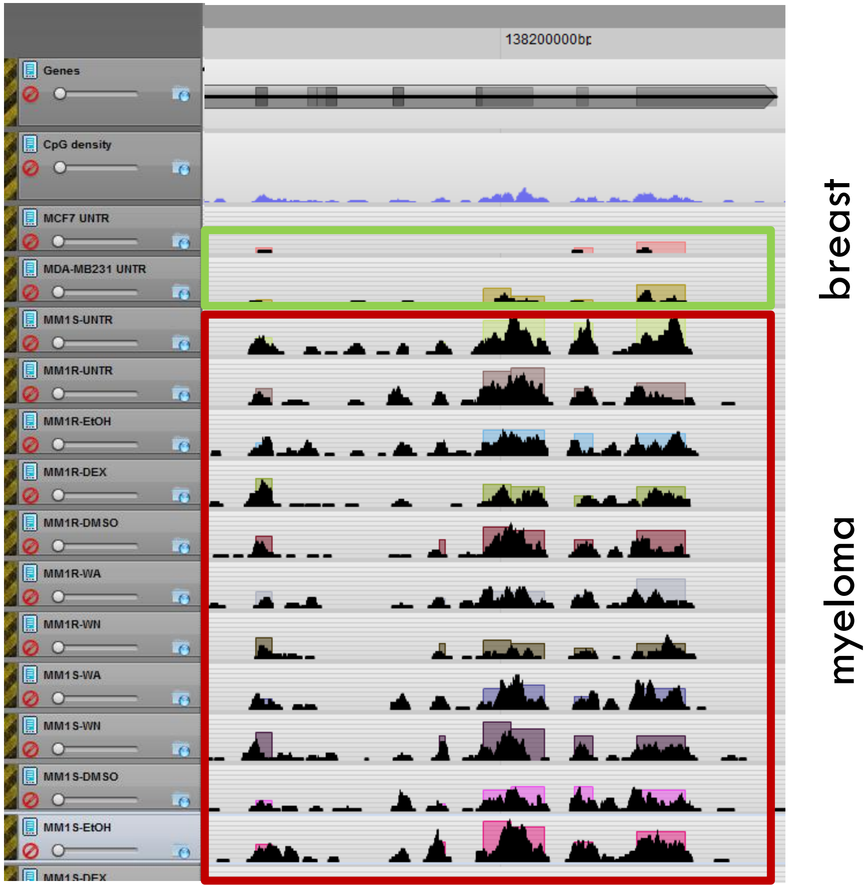






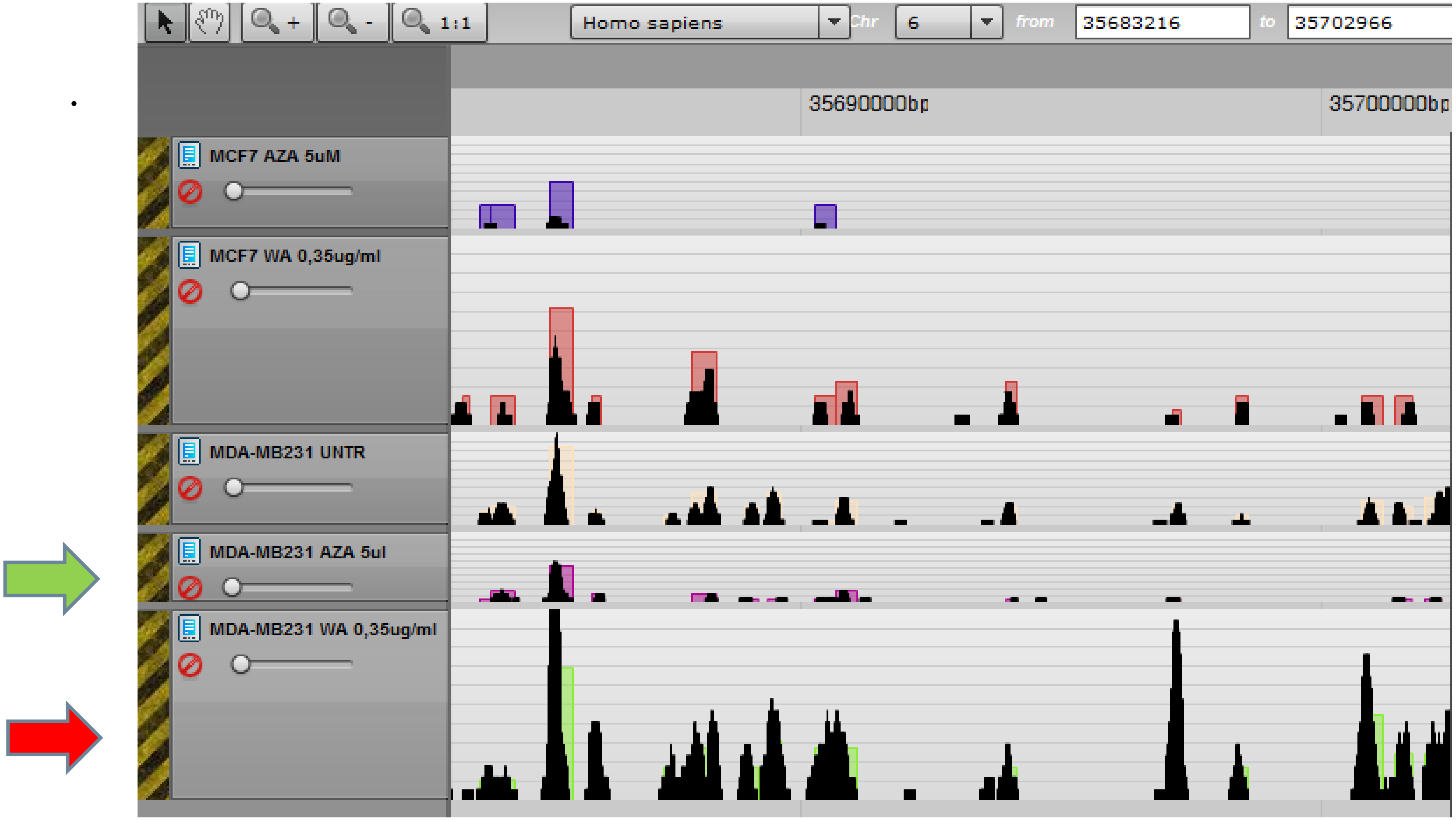


DNA methylation
Signature is cell specific



3. Can epigenetic effects of phytochemicals explain their potential anti-cancer effects? A case study

Complexity of methylation dynamics



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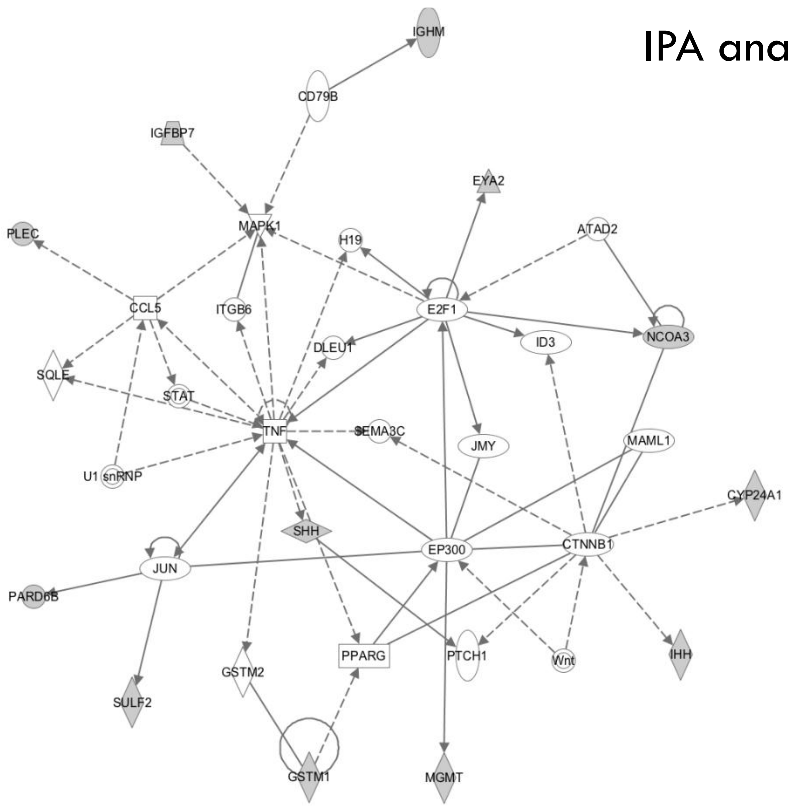
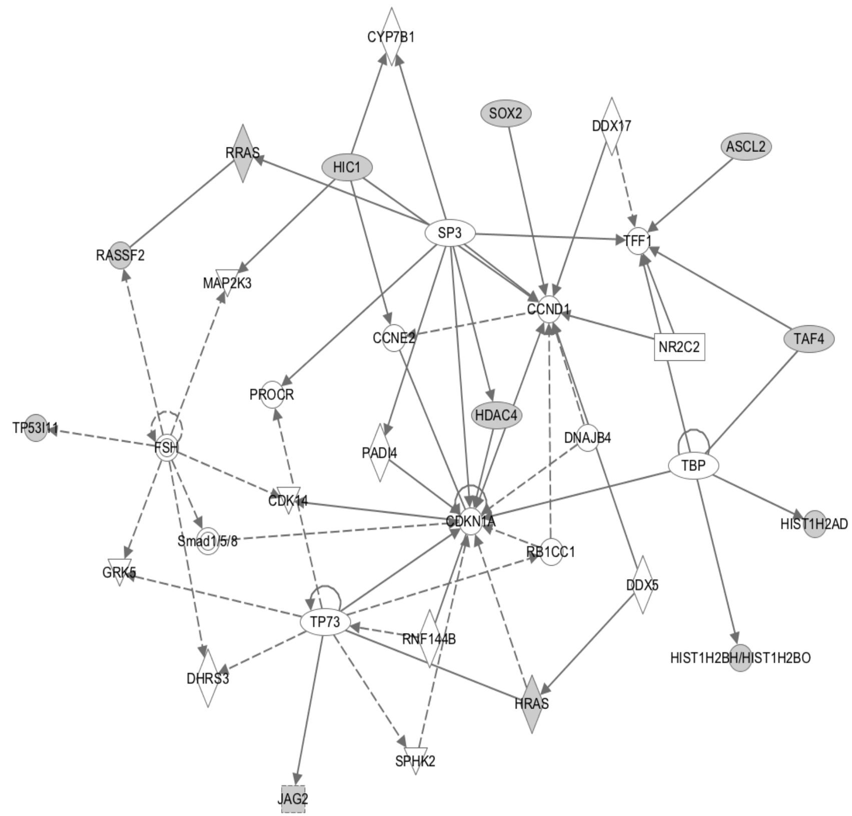
Dietary effects on methylation signature in breast cancer

IPA analysis





DNA methylation profiling reveals a predominant immune component in breast cancers, Dedeurwaerder et al. In press 2011

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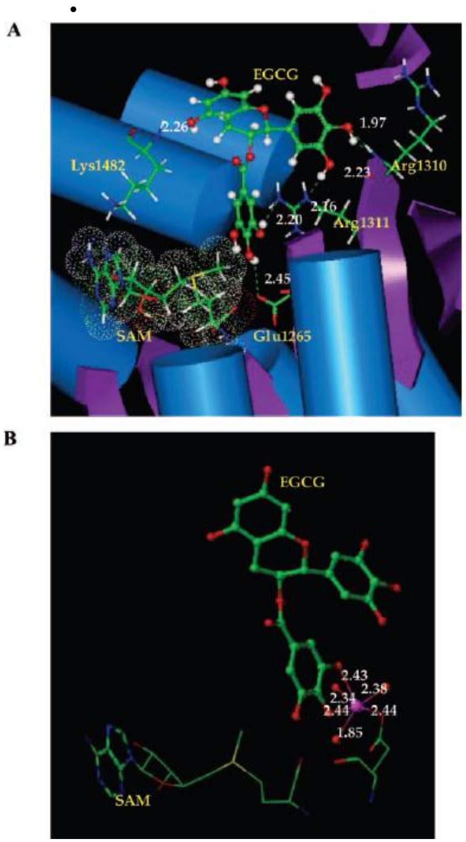
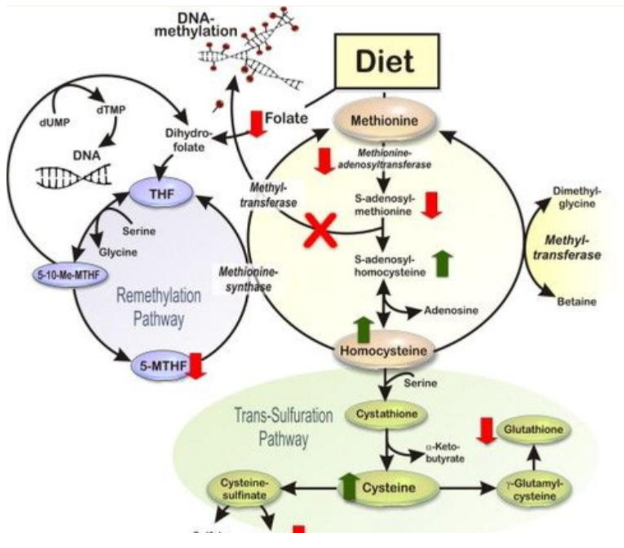
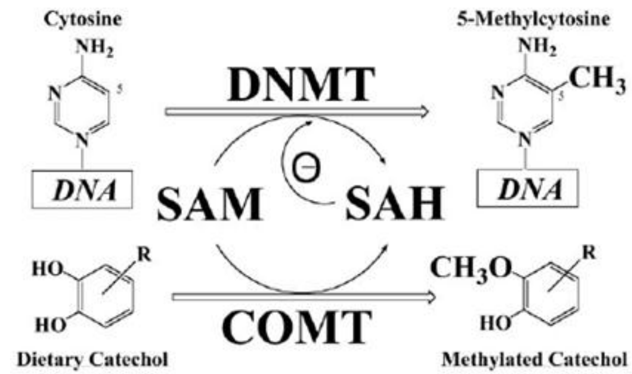
Possible mechanisms of diet dependent DNA (de)methylation dynamics

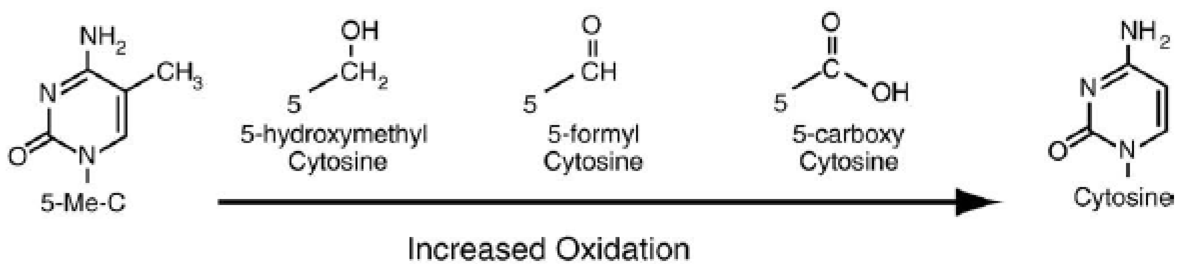


Inhibition Dnmt
Decreased CpG Me





Depletion methyl donors
Decreased CpG Me



Genotoxicity – oxidative damage
Decreased CpG Me

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Is epigenetic drift a consequence of aerobic life?

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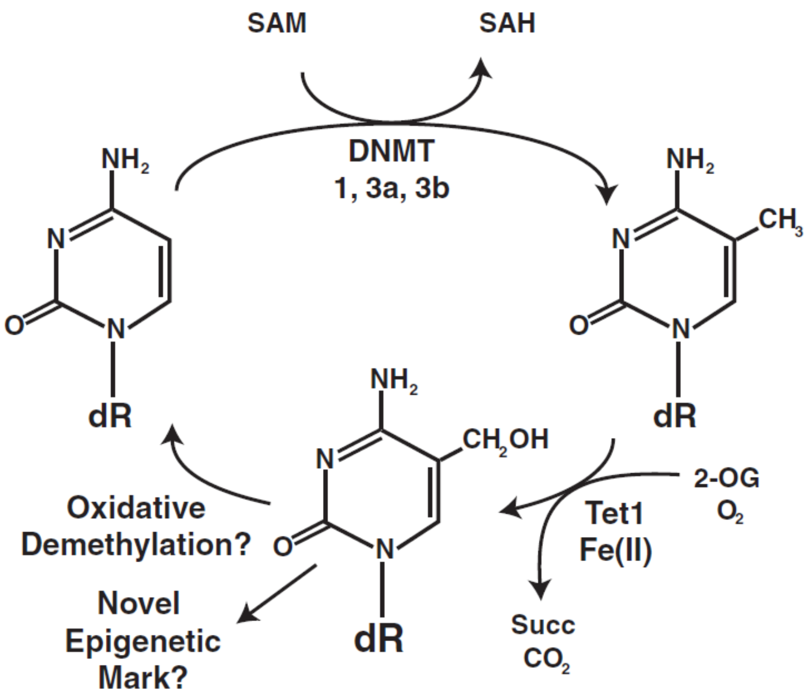

ANTIOXIDANTS & REDOX SIGNALING
Volume 15, Number 2, 2011

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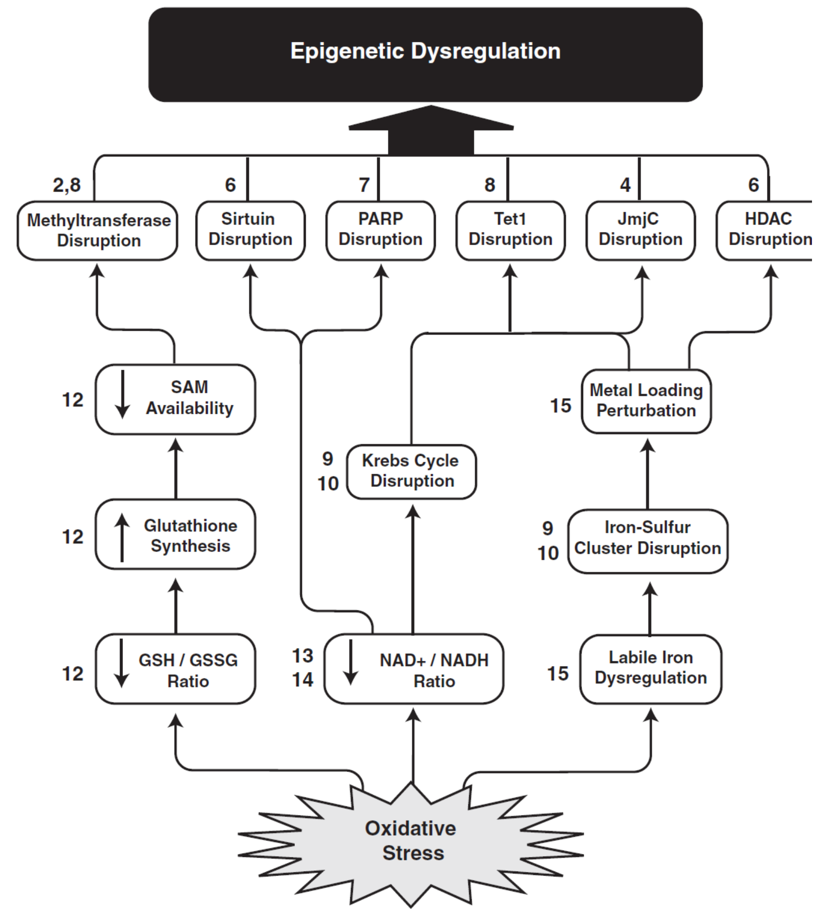
COMPREHENSIVE INVITED REVIEW

The Redox Basis of Epigenetic Modifications:
From Mechanisms to Functional Consequences

Anthony R. Cyr and Frederick E. Domann



Epigenetics 6:7, 1-4; July, 2011; © 2011 Landes Bioscience

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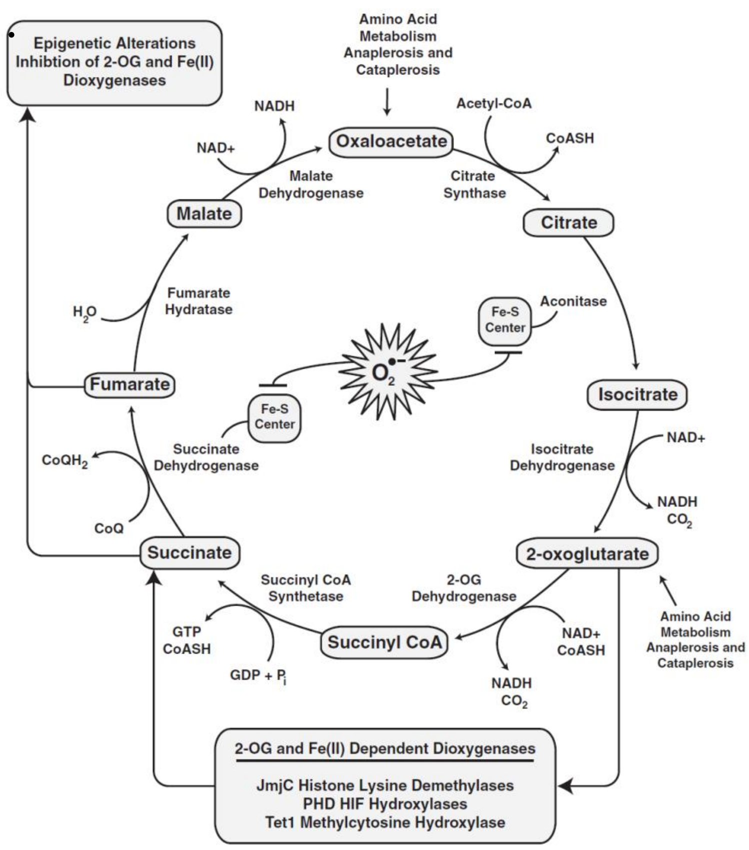
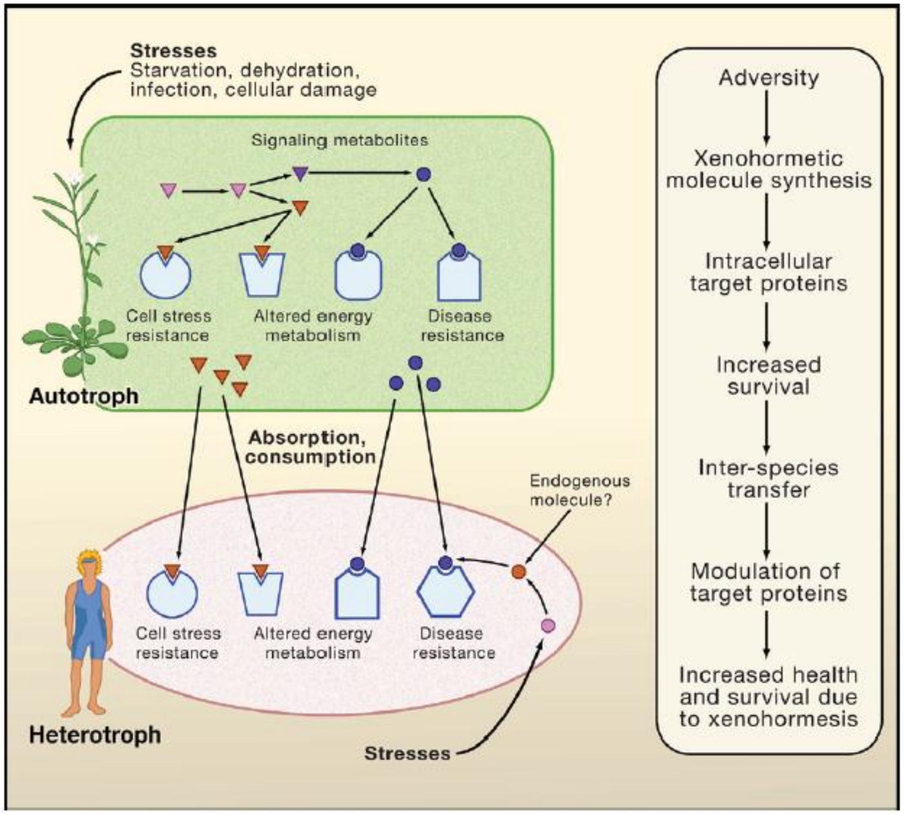
Xenohormesis: interspecies epigenetic stress response





Xenohormesis: Sensing the Chemical Cues of Other Species

Konrad T. Howitz[1,*] and David A. Sinclair[2,*]

Cell 133, May 2, 2008 ©2008 Elsevier Inc.

Conclusions

Epigenetic reprogramming of the cancer-immunomethylome may contribute in chemopreventive effects of early life exposure to physiological concentrations of dietary phytochemicals

Future:

Study methylation dynamics (turnover) in function of age (pregnant, neonatal, puberty, old) or single/repeated exposure

Compare methylation dynamics following exposure to dietary polyphenols versus bisphenols: rationale for benefecial/detrimental effects in cancer?

Study crosstalk metabolic pathways vs. dynamics DNA methylation/hydroxymethylation, histone methylation

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flaviola

Targeted delivery of dietary flavanols for optimal human cell function

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MARS incorporated

Universiteit Gent

Universiteit Antwerpen

SCIPROM Scientific Project Management

http://www.flaviola.org

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Carine Van Lint
Francois Fuks

University Montpellier Inserm U540
Dany Chalbos

Questions?

If they ask you anything you don't know, just
just say it's due to epigenetics.