Nutri-epigenetica e cancro

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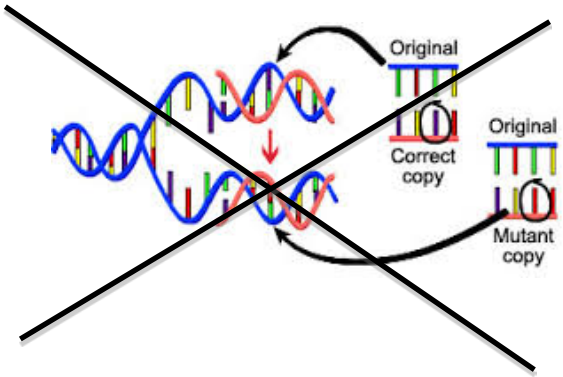
II Giornata Internazionale
Sensibilizzazione e Prevenzione del Tumore Ovarico



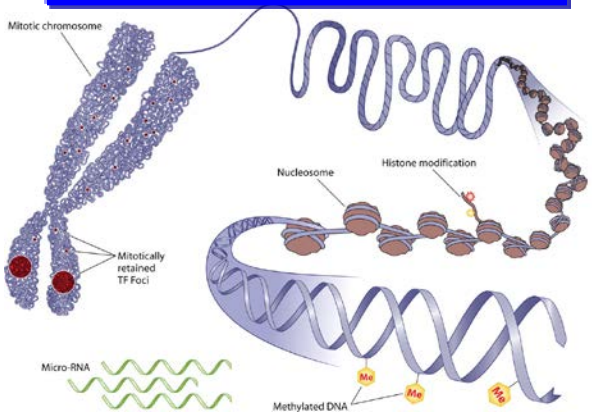
1) epi-mutazioni

2) tessuto specifiche → *imprinting genomico*

3) potenzialmente reversibili

4) trasferibili alla progenie

Stato di condensazione della cromatina



Metilazione del DNA

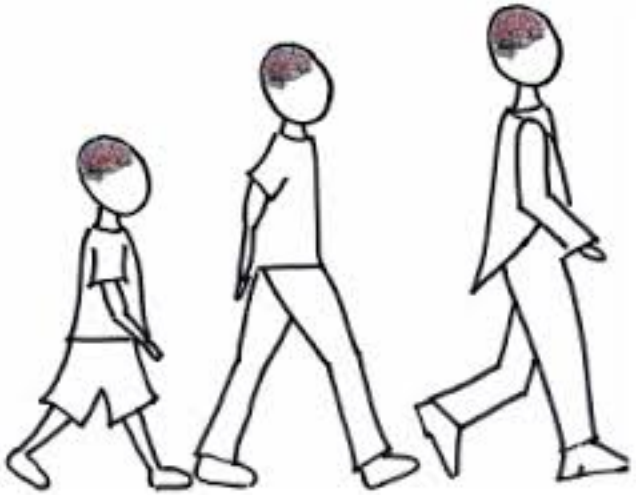
Variazione dell’espressione genica

Quali sono i fattori scatenanti e quando si verificano?

Xenobiotici

Nutrizione

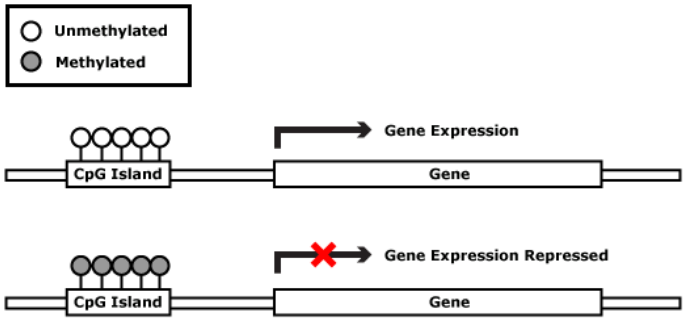
Stress

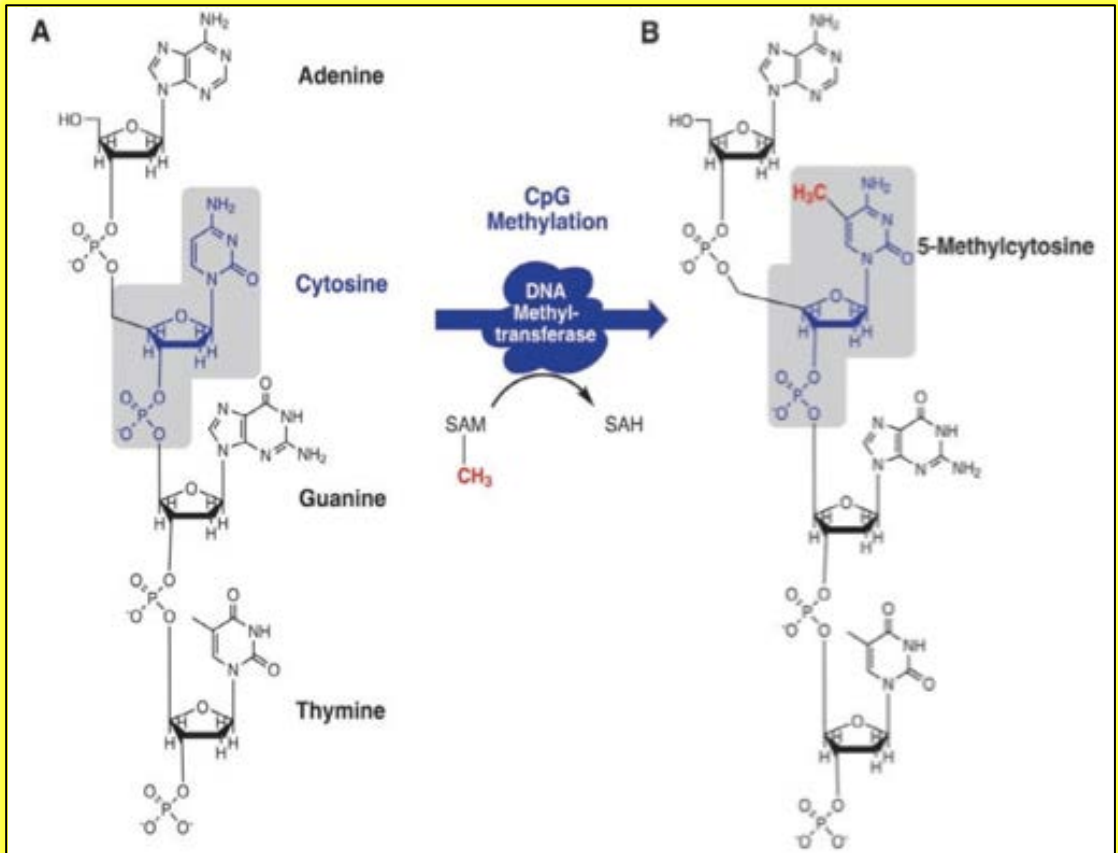


“fetal programming” of adult chronic diseases

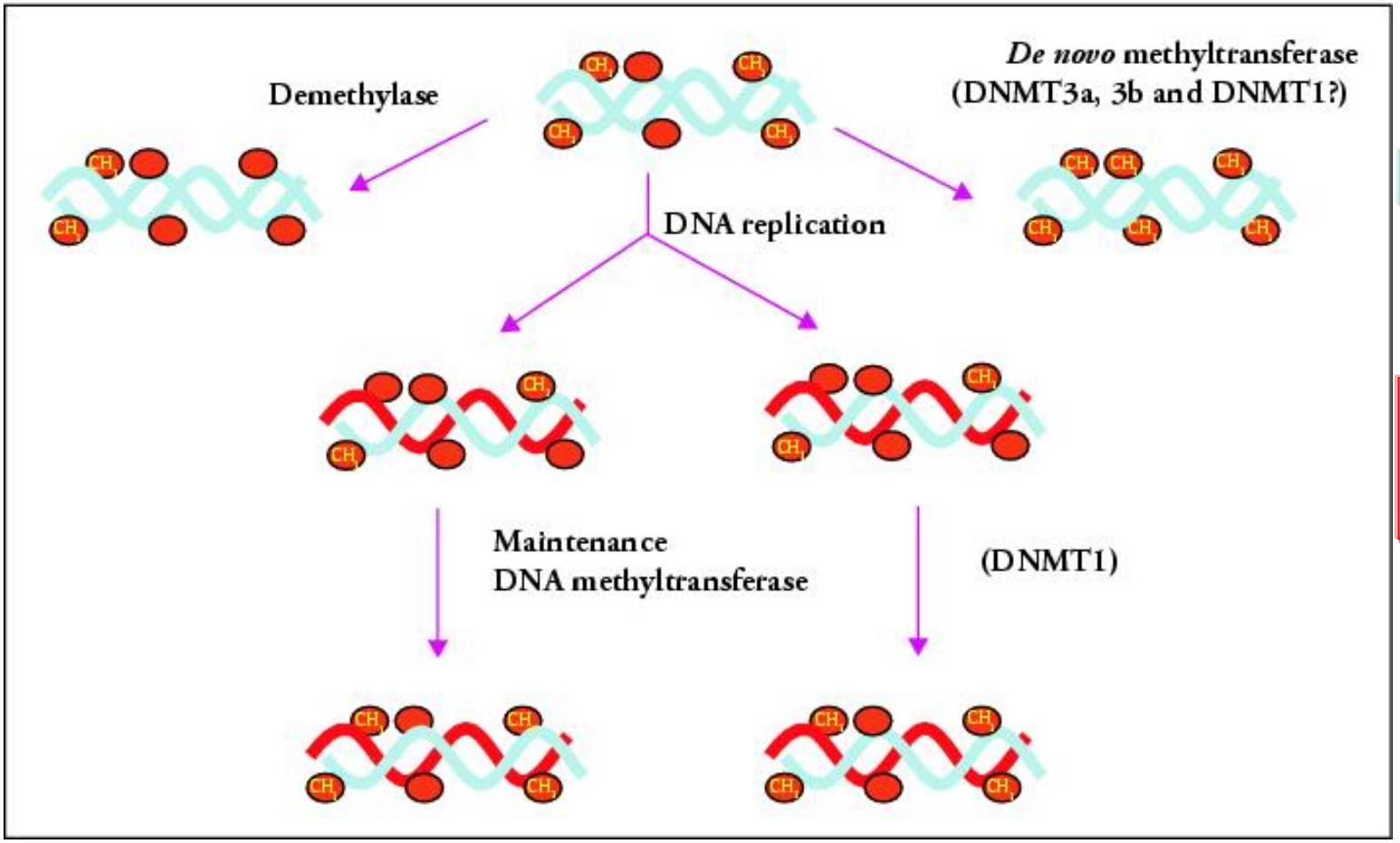
Stile di vita

DNA METHYLATION



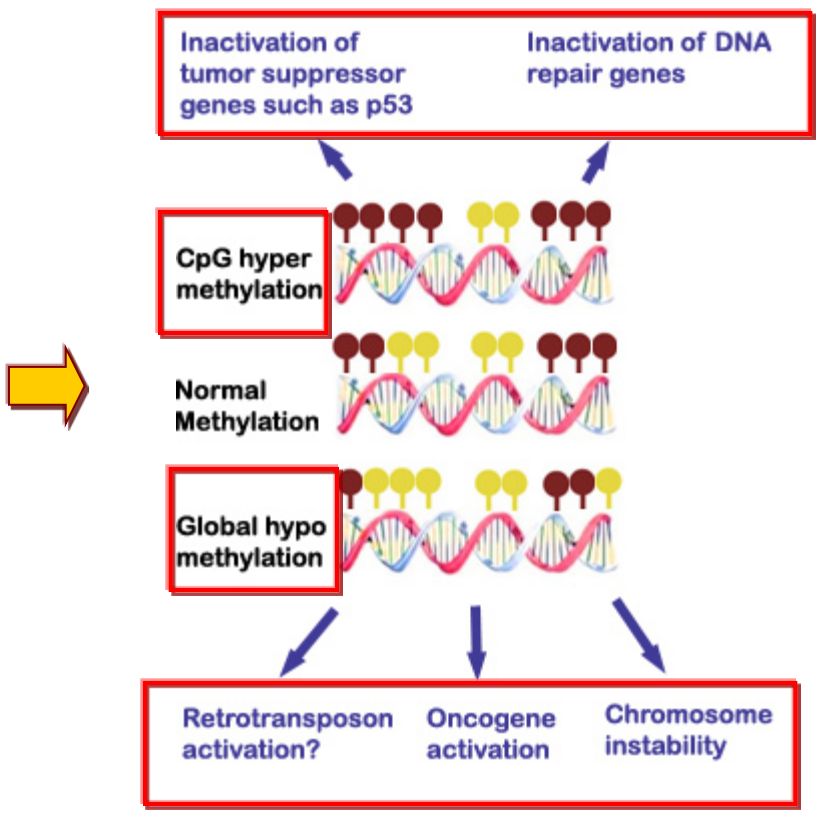


DNA METHYLATION



Le DNMT3b hanno un ruolo importante nella carcinogenesi

Ipermetilazione di specifici promotori genici e globale ipometilazione nel cancro

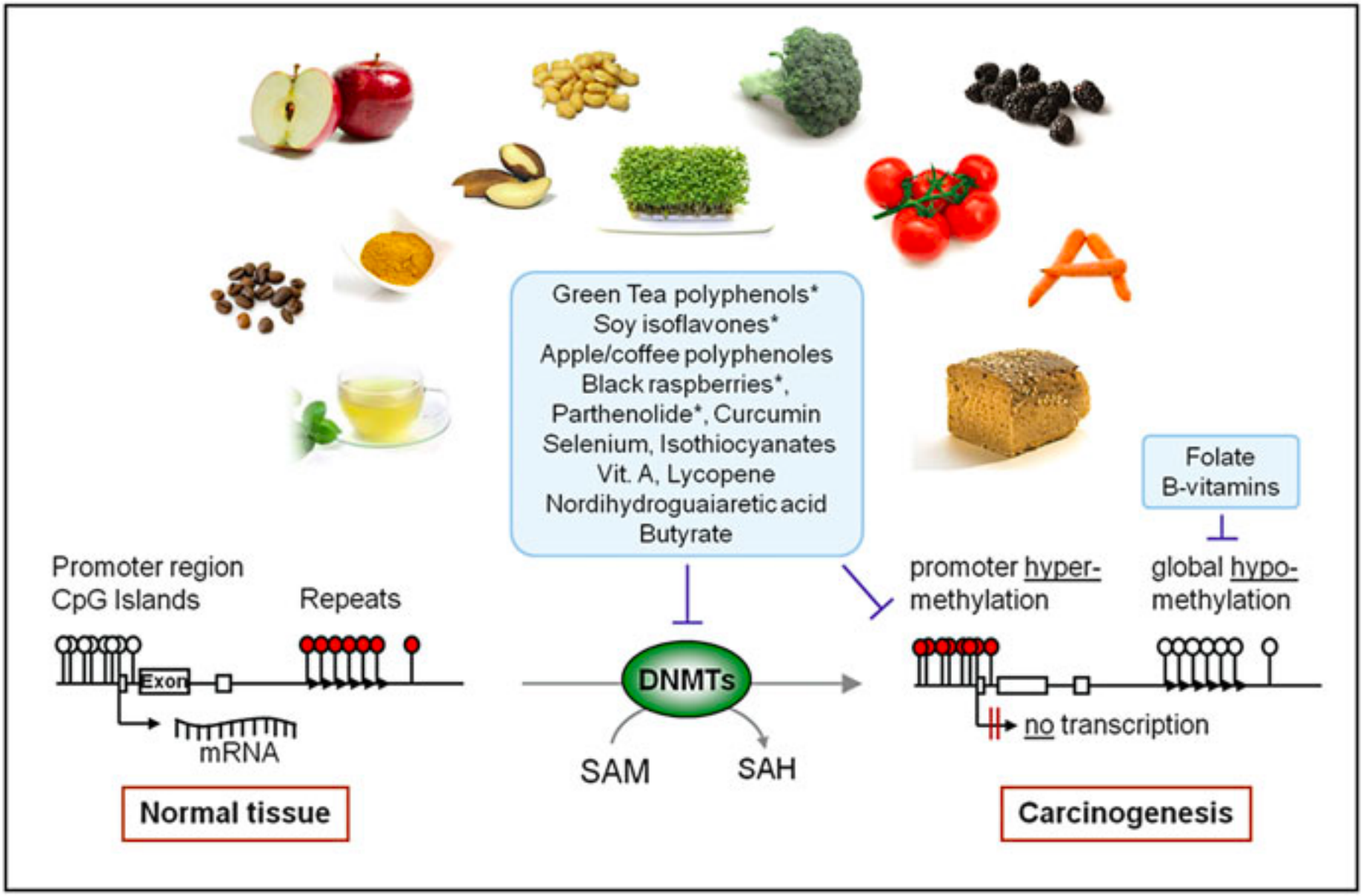


DNA methylation inhibitors

activate silenced tumor suppressor genes

arrest of tumor growth

as candidate anticancer drugs



Fonte C. Gerhauser. Cancer Chemoprevention and Nutri-Epigenetics: State of the Art and Future Challenges.
Top Curr Chem (2012) DOI: 10.1007/128_2012_360

Cancro ovarico ed effetto di phytochemicals sulla metilazione del DNA

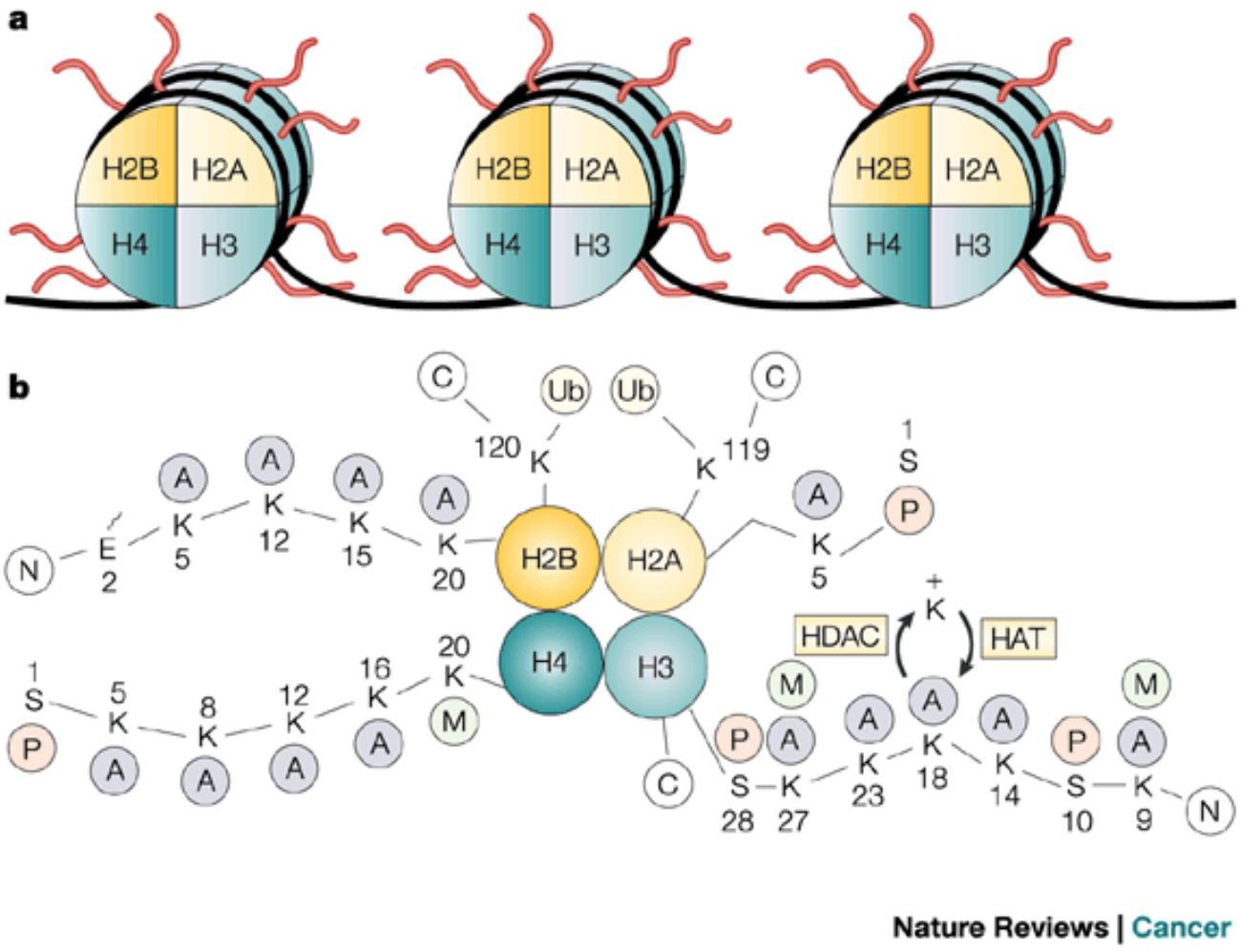
Genisteina ↓ nucleosome binding protein-1 (Nsbp1) promoter methylation

Early and permanent epigenetic mark of neonatal exposure to **estradiol/bisphenol A** that persists throughout life, unaffected by events during adulthood alters promoter methylation and expression of Nsbp1

(Endocrinology. 2012 Jan;153(1):42-55. doi: 10.1210/en.2011-1308. Epub 2011 Nov 22.)

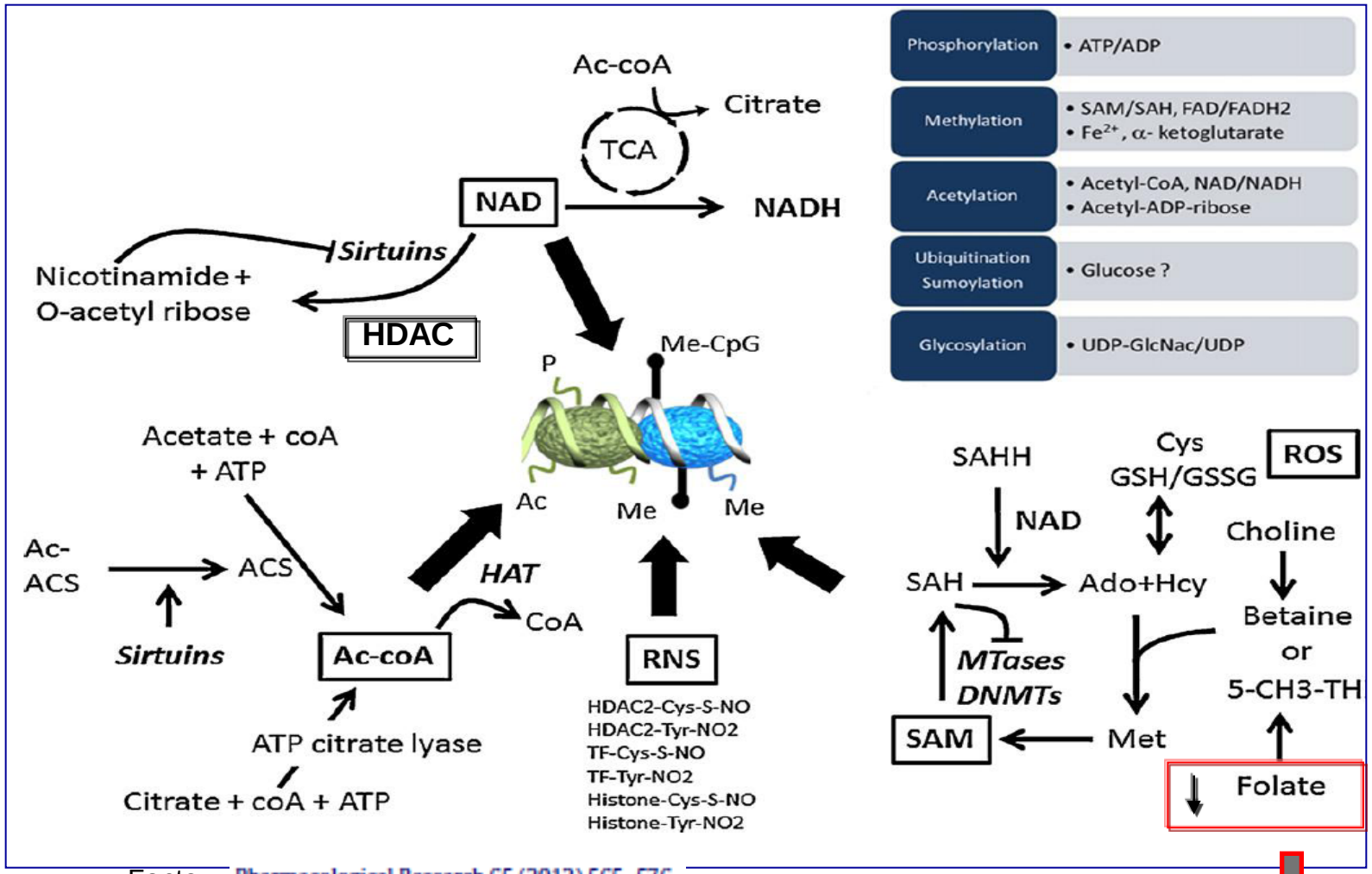
mahanine → Inibitore DNMT **Ras association domain-containing protein 1 (**RASSF1A)

HISTONE MODIFICATIONS



H3K4, H3K36, H3K79 ➡ modulazione trascrizionale positiva
H3K9, H3K27, H4K20 ➡ modulazione trascrizionale negativa

Modificazioni istoniche e metaboliti essenziali



Fonte: Pharmacological Research 65 (2012) 565–576

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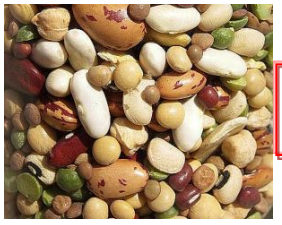


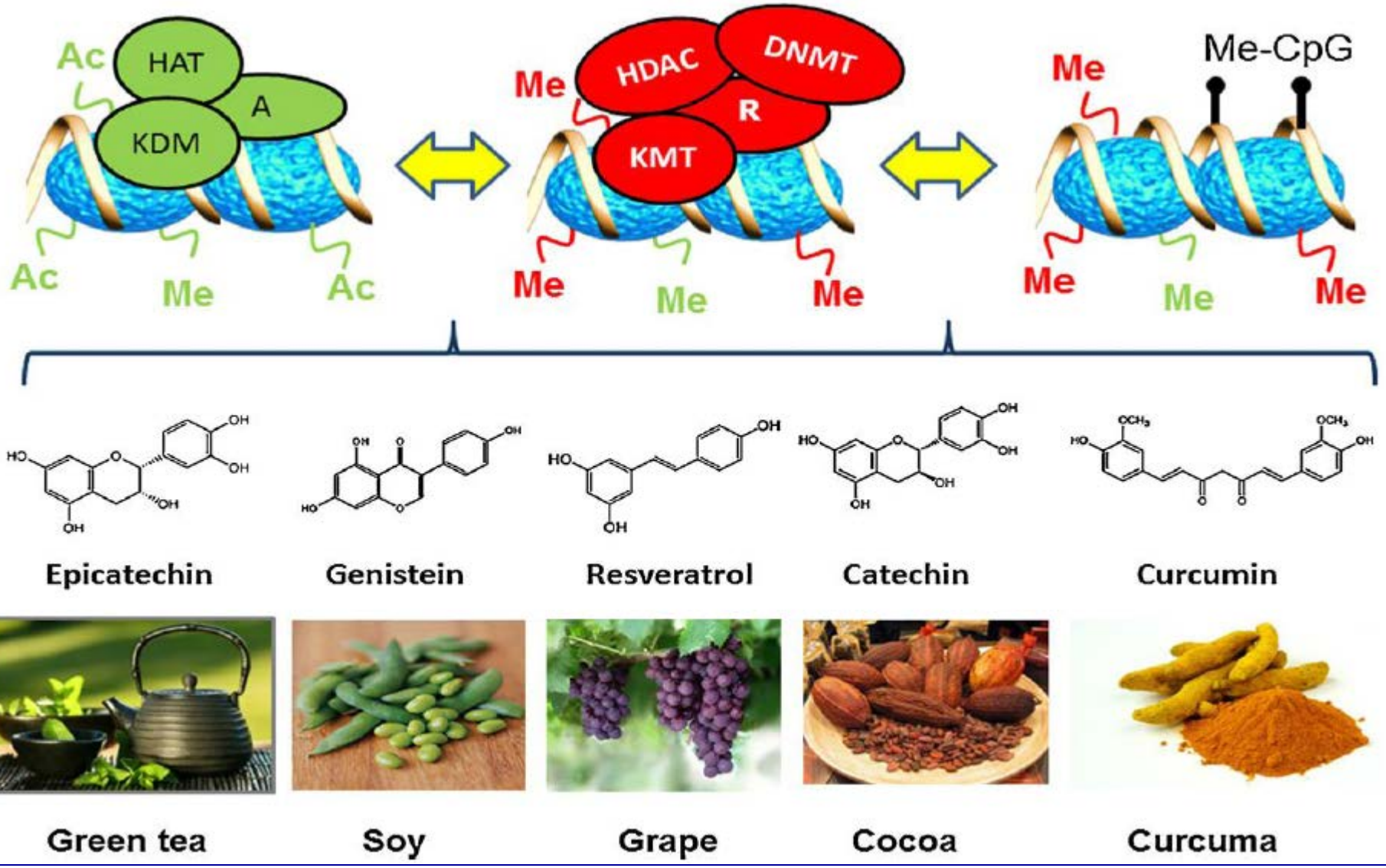
cancro ovarico

Folati: fonte e quantità?

• Excessive intake of synthetic folic acid (from high-dose supplements or fortified foods) may even increase human cancer risk by accelerating growth of precancerous lesions (Duthie SJ (2010) Folate and cancer: how DNA damage, repair and methylation impact oncolon carcinogenesis. J Inherit Metab Dis. doi:10.1007/s10545-010-9128-0).

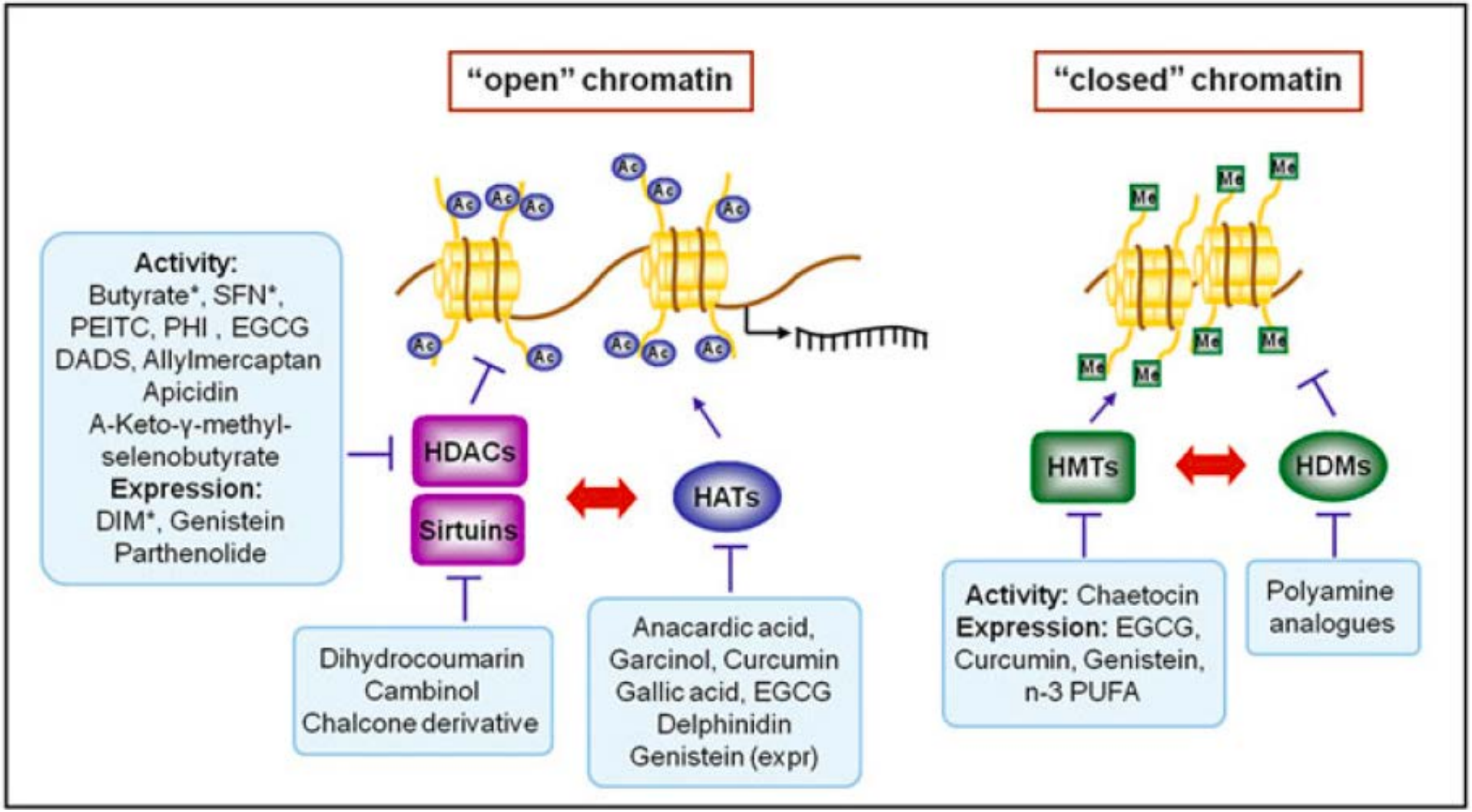
•Significant protection from DNA methylation (less than two genes methylated) was observed for regular consumption of folate [OR (odds ratio) ¼ 0.84 per 750 mg/day; CI (95% confidence interval), 0.72–0.99], leafy green vegetables (OR, 0.83 per 12 monthly servings; CI, 0.74–0.93), and multivitamin use (OR, 0.57; CI, 0.40–0.83)

Alimenti funzionali: modulatori epigenetici



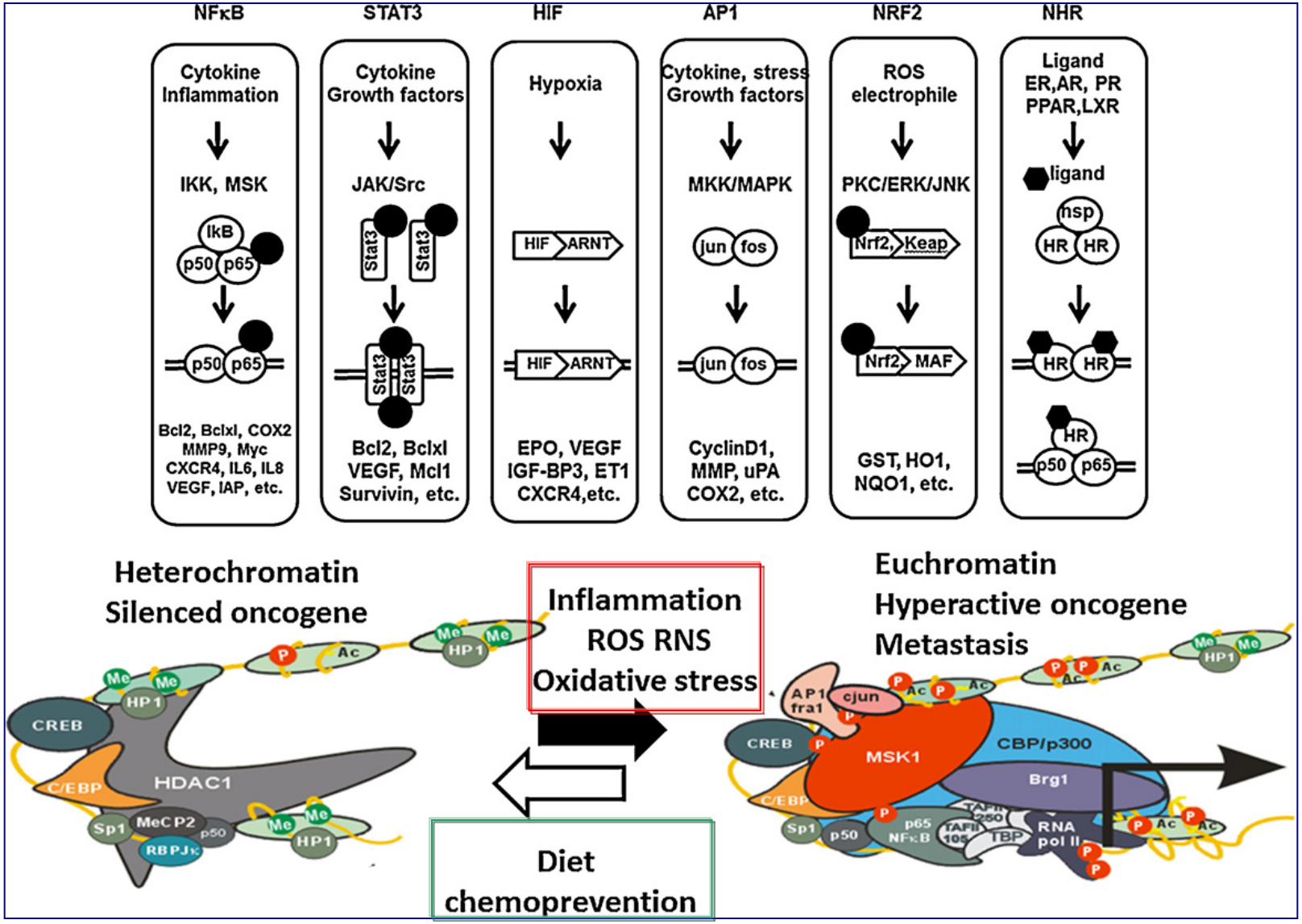
Fonte: Pharmacological Research 65 (2012) 565–576

Componenti naturali della dieta con attività chemioprotettiva



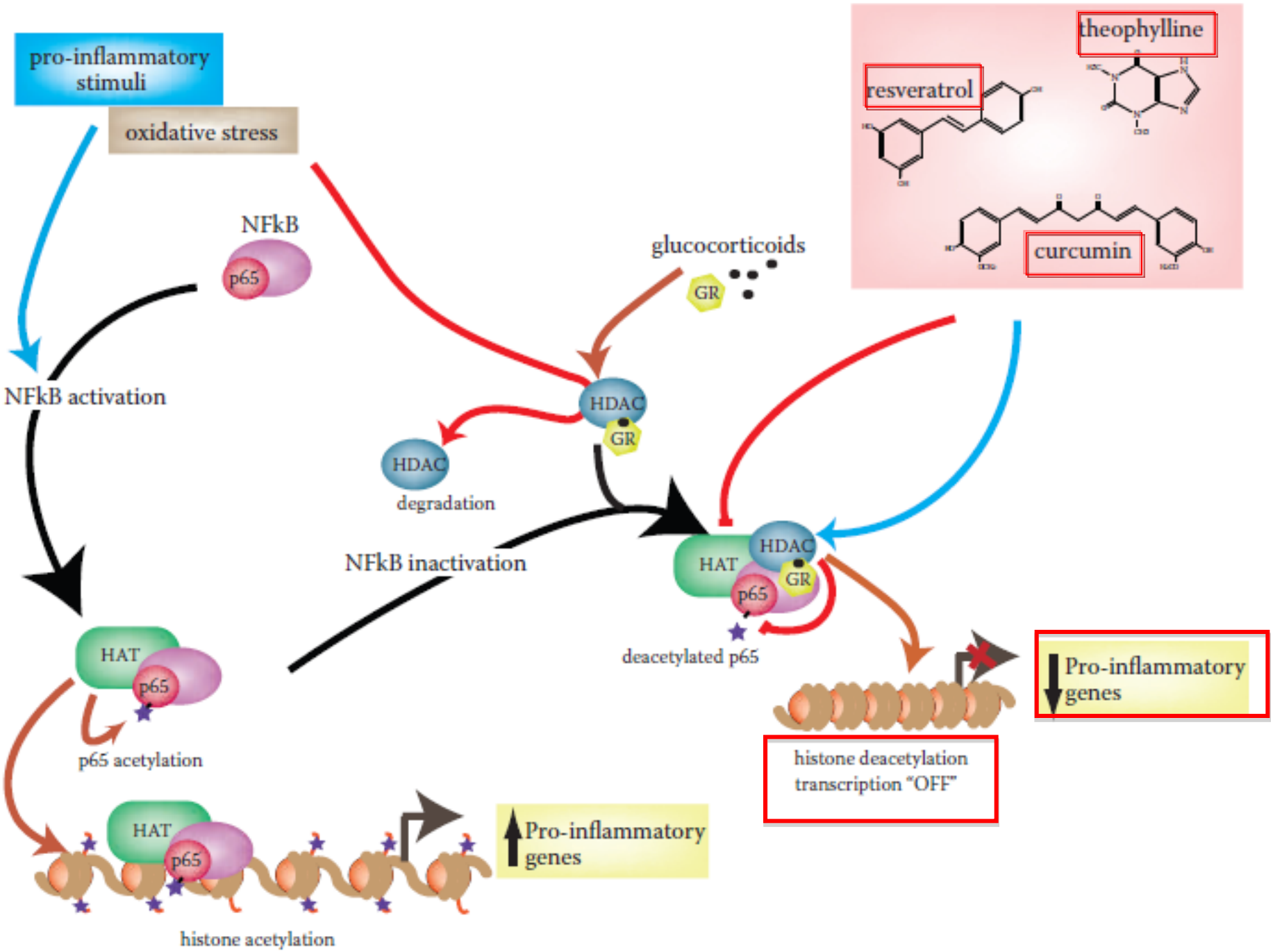
Fonte: C. Gerhauser. Cancer Chemoprevention and Nutri-Epigenetics: State of the Art and Future Challenges. Top Curr Chem (2012) DOI: 10.1007/128_2012_360

Modulazione dietetica dei pathways dei fattori di trascrizione che regolano l'"oscillazione" dinamica tra eucromatina ed etero cromatina a livello degli oncogeni e degli oncosoppressori.



Fonte: Pharmacological Research 65 (2012) 565–576

Fonte: Nutrient and Epigenetics, Sang-Woon Choi , Simonetta Friso, 2009; 13:978



Food Chemistry 145 (2014) 145–153

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journal homepage: www.elsevier.com/locate/foodchem

The fortification of tea with sweeteners and milk and its effect on *in vitro* antioxidant potential of tea product and glutathione levels in an animal model

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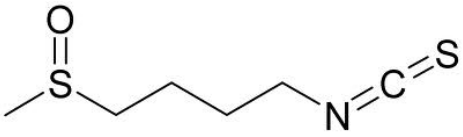
[a] Department of Bioche
[b] Association for Streng
[c] Tea Research Foundat

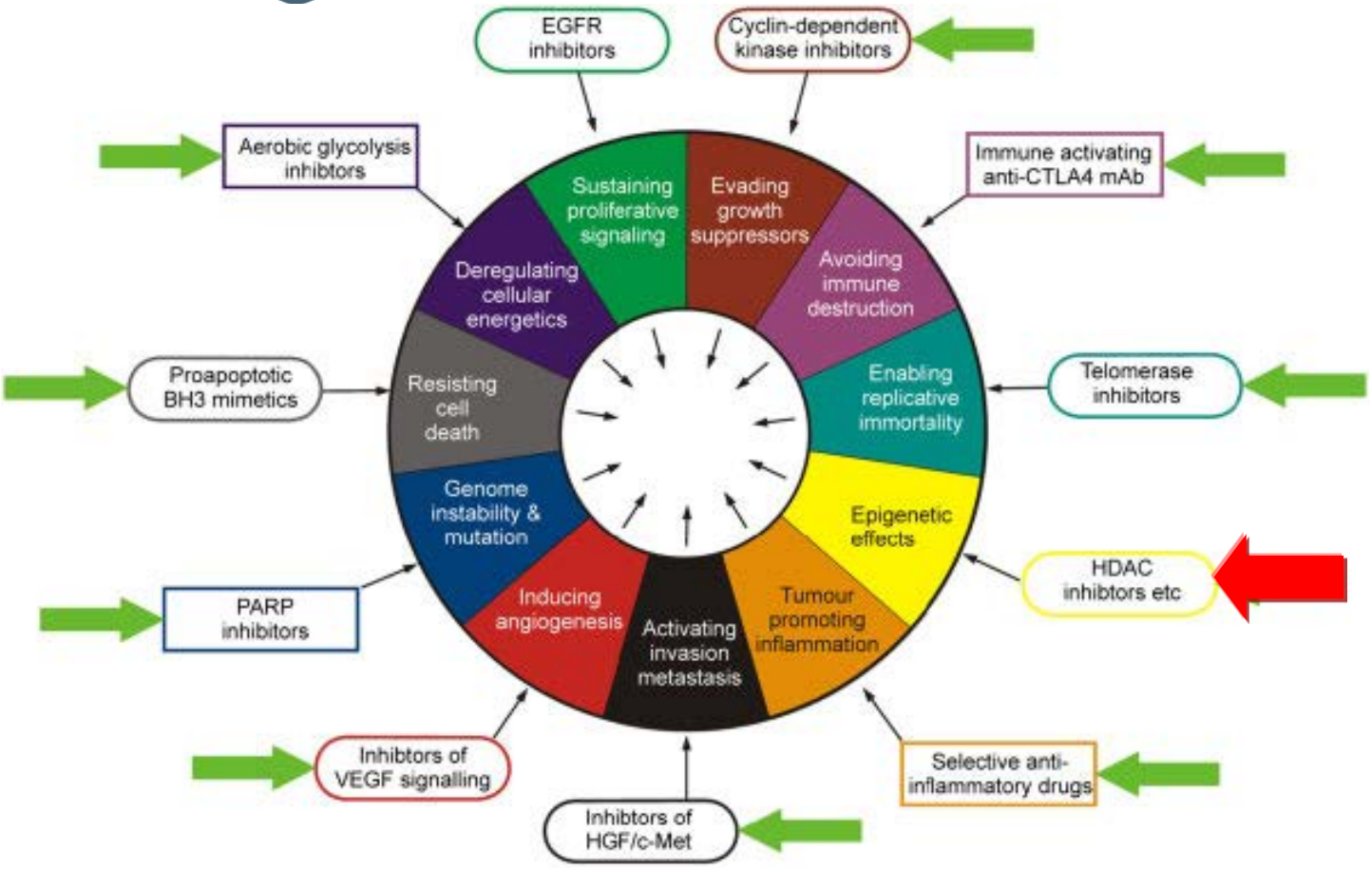
Table 4
Mean values of antioxidant activity of sweetened plain and milk-fortified black teas.

Tea treatment	Antioxidant activity	
	Plain tea	Milk fortified tea
No sweetener	91.6[a]	84.2[a]
0.1 g stevia/100 ml	91.6[a]	85.0[a]
0.3 g stevia/100 ml	90.5[a]	84.6[a]
3 g sugar/100 ml	84.1[b]	75.2[b]
10 g sugar/100 ml	46.5[d]	44.7[d]
3 g honey/100 ml	54.2[c]	46.5[c]
10 g honey/100 ml	37.1[e]	33.1[d]
C.V (%)	2.8	3.75
LSD	3.2	4.07

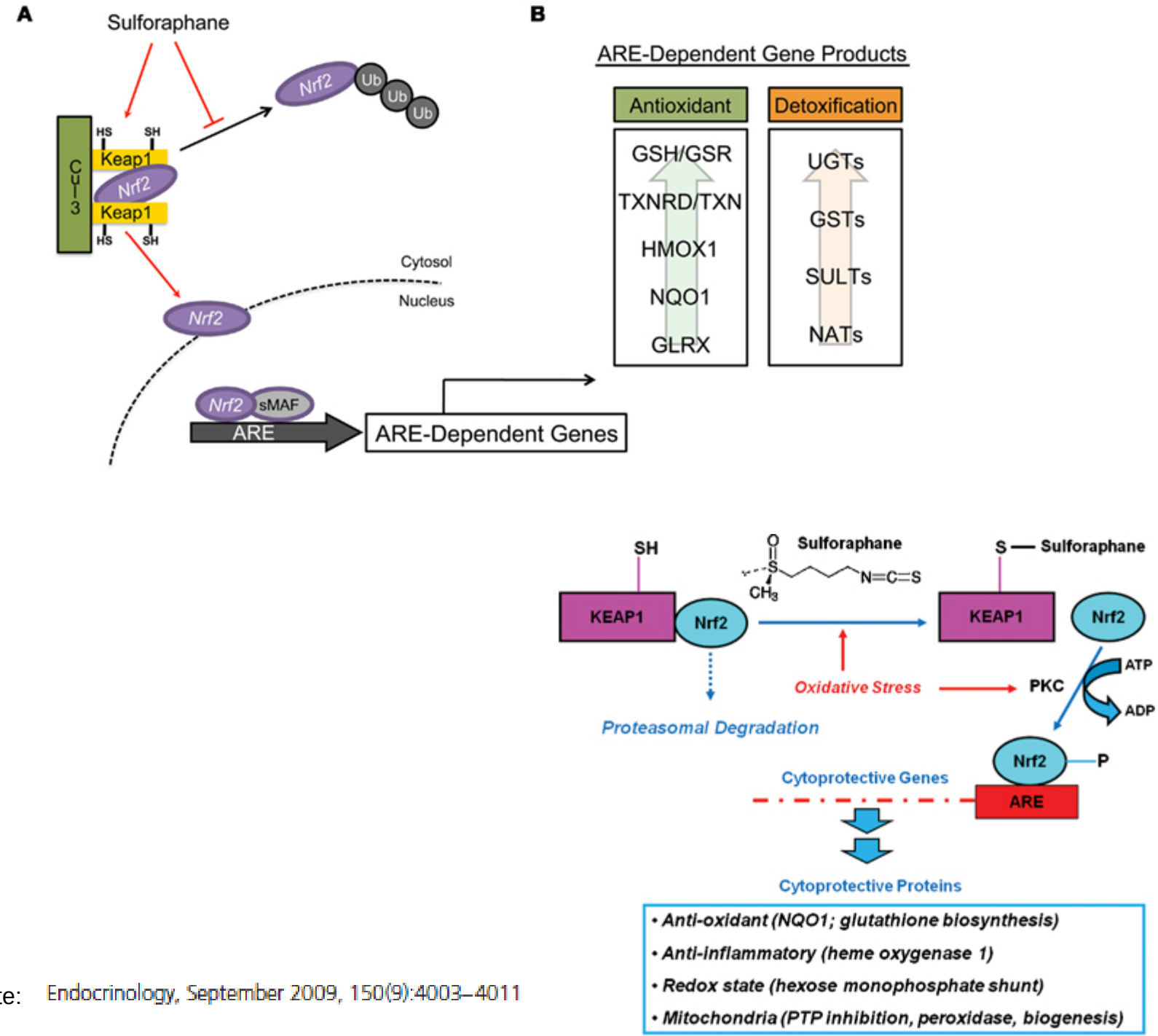
Means within a column followed by the same letters are not significantly different at $p < 0.05$ by LSD test.

Siti d'azione del sulforafano e dei composti biologicamente attivi presenti negli estratti dei broccoli





Fonte: *Mol. Nutr. Food Res.* 2012, *56*, 126–146



Fonte: Endocrinology, September 2009, 150(9):4003–4011

KEY POINTS
nel cancro ovarico

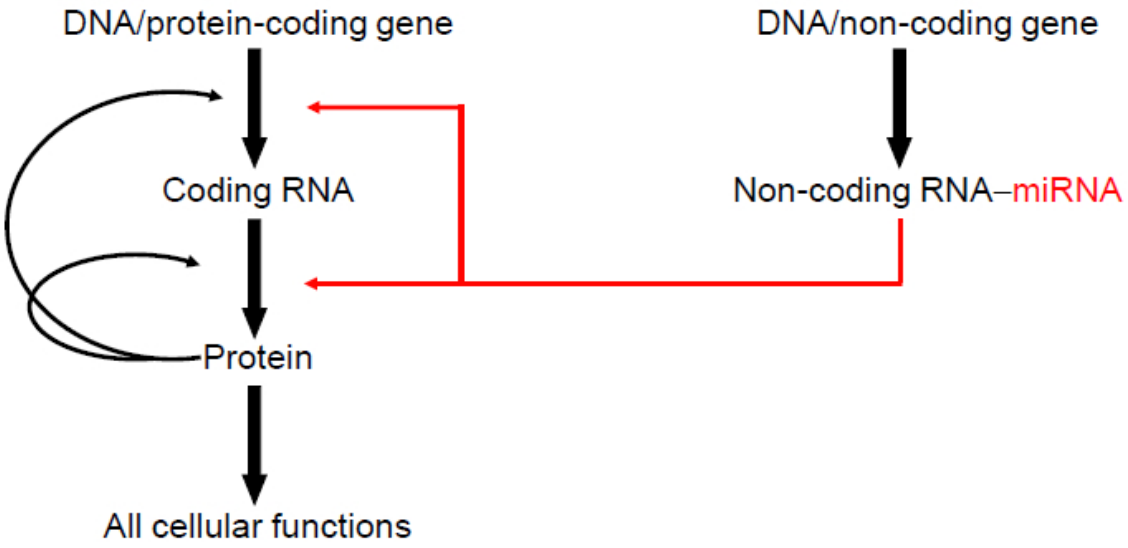
1. l'inibizione dell'attività di HDAC dei isotiocianati (sulforafano) è correlata con i livelli dei metaboliti urinari

2. La combinazione di isotiocianati con un agente demetilante (es. epigallocatechina gallato) aumenta l'attività antineoplastica con una riduzione dell'espressione delle DNMT1

3. La modulazione dell'espressione dei miRNA potrebbe essere coinvolta nella prevenzione neoplastica e delle metastasi, da parte dei isotiocianati

NON-CODING microRNAs

Sviluppo, differenziazione, apoptosi e proliferazione



miR-181 a implicato nel tumore ovarico (Nature Com.2014,5: 2977)

miR-484, 642 and 217 biomarkers di chemioresistenza nel tumore ovarico (PNAS 2013,24:9845)

TABLE 1. Altered epigenetic regulation in ovarian cancer

Epigenetic regulator	Modification	Type	Targets	Refs.
DNA methylation	Hypermethylation	Tumor suppressor genes	*BRCA1*	42
			p16	14
			hMLH1	15
			RASSF1A	16
			OPCML	17
			ARLTS1	87
			MYO18B	86
			SPARC	28
			CTGF	30
			ANGPTL2	29
		Imprinted genes	*ARH1*	18
			PEG3	18
		Cell adhesion genes	*ICAM-1*	22
			CDH1	23
		Proapoptotic genes	*LOT1*	19
			DAPK	15
			TMS1/ASC	21
			PAR-4	20
		Arylsulfatase gene	*Hsulf-1*	24, 25
		DNA damage repair gene	*PALB2*	26
		Class III β-tubulin	*TUBB3*	27
		Lipid phosphatase	*PTEN*	85
		Development genes	*HOXA10, HOXA11*	31
		Ribosomal genes	*18S, 28S rDNAs*	92
	Hypomethylation	Tumor promoter	*SNCG*	33
			MCJ	32
			IGF2	35
			BORIS	34
			Claudin-4	36
Histone modifications	Lysine acetylation (gene-activating)	Acetylated histones H3 and H4	*GATA4, GATA6*	46
			p21/WAF1	48
			Cyclin B1	47
	Lysine methylation (gene-activating)	Trimethylated H3K4	*GATA4, GATA6*	46
	Lysine methylation (gene-repressing)	Dimethylated H3K9	*GATA4, GATA6*	46
			Adam19	49
		Trimethylated H3K27	*GATA4, GATA6*	46
			Adam19	49
			RASSF1	50
miRNAs	Up-regulation	miR-200a	BAP1, SIP1, ZEB1/2	8, 54
		miR-299-5p	DLK1	8
		miR-135b	MSX2	8
		miR-141	BAP1	8
		miR-200c	BAP1, ZEB1/2, SIP1	8, 54
		miR-200b	BAP1, ZEB1/2, SIP1	8, 54
		miR-214	PTEN	8, 52
		miR-302d	VEGFA	88
		miR-373	VEGFA	88
	Down-regulation	miR-199a	c-SRK, MMP13, and FGF2	8
		miR-140	c-SRK, MMP13, and FGF2, VEGFA	8, 88
		miR-145	c-SRK, MMP13, and FGF2,PARP8, IRS1	8, 89, 90
		let-7i	Unknown	53
		miR-15/16	BCL2	91

Fonte: Endocrinology, September 2009, 150(9):4003–4011

Molteplicità di fattori

Fattori stocastici

Nutrizione
Stress
xenobiotici

Fattori pleiotropici

Polimorfismi genetici

Epigenetica

espressione genica

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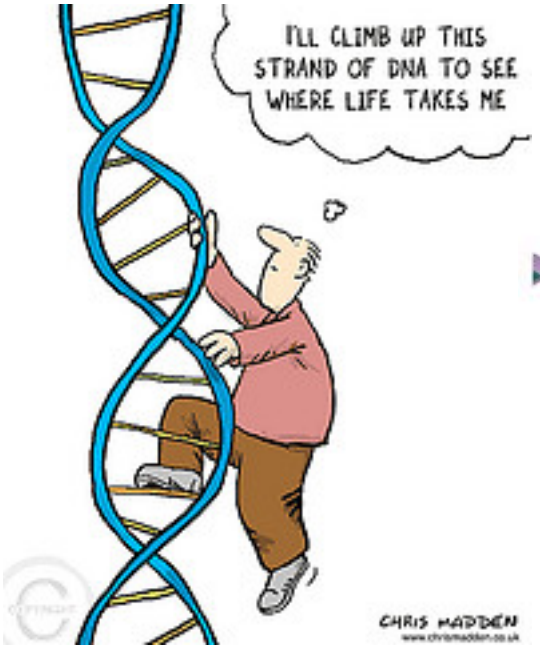
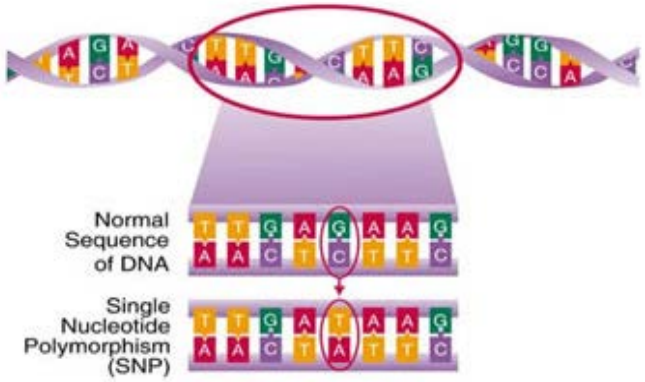
Nutrigenomica





Nutrigenetica

Conclusioni e riflessioni

1. Diversa risposta nutri-epigenetica tra gli studi in vitro e in vivo

2. Effetto nutri-epigenetico tessuto specifico

3. “Critical time of window” e prevenzione

4. Correlazione tra consumo di nutrienti contenenti HDACi e durata dell’effetto epigenetico

5. Maggiore effetto dell’efficacia di associazioni rispetto ai composti isolati

6. Complessità dei networks coinvolti: analisi bioinformatica dei dati ottenuti dalle “omiche”

Nutri-epigenetica

modulazione espressione genica → Scelta alimentare appropriata

University of Camerino

Summer School on
NUTRIGENOMICS

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GRAZIE PER L'ATTENZIONE

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