NUTRIZIONE ED EPIGENETICA

Prof. Calogero Caruso

UNIVERSITÀ DEGLI STUDI DI PALERMO

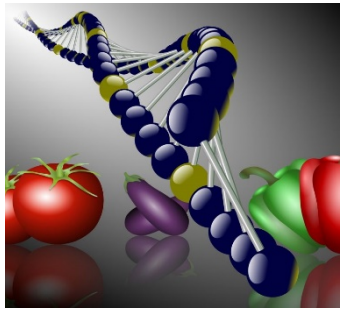
Joint Meeting with AACE Italian Chapter

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Alcune definizioni…

Il termine **EPIGENETICA** si riferisce a modifiche ereditarie dell'espressione genetica che non comportano alterazioni a carico della sequenza stessa del DNA (Waterland & Michels, 2007).



Il termine **EPIGENOMA** indica l'insieme delle modifiche epigenetiche sul genoma che regolano la struttura della cromatina e la sua accessibilità da parte del macchinario che regola l'espressione genica.

Tra i possibili meccanismi che possono provocare effetti epigenetici si annoverano:

- modifiche del DNA (metilazione delle citosine da parte delle metiltrasferasi);
- modifiche della cromatina (modificazioni degli istoni, quali acetilazione, metilazione etc).

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Le **modifiche epigenetiche** alterano l'accessibilità fisica alle regioni del genoma sulle quali si legano proteine ed enzimi deputati all'espressione genica e quindi alterano l'espressione del gene

Alcune definizioni…

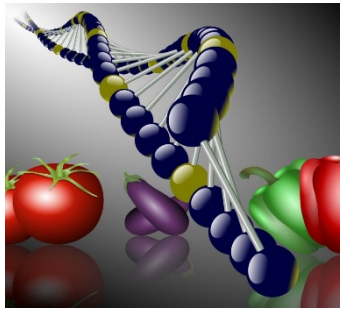
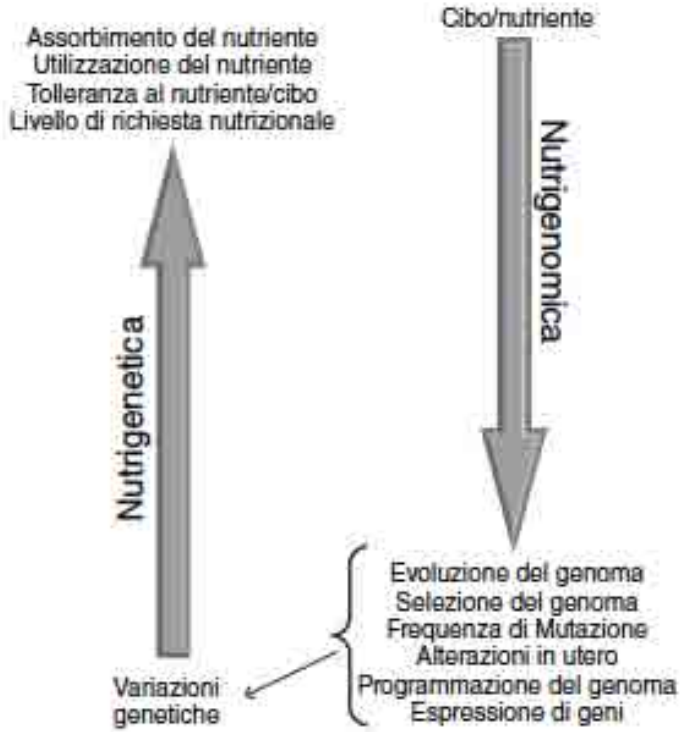
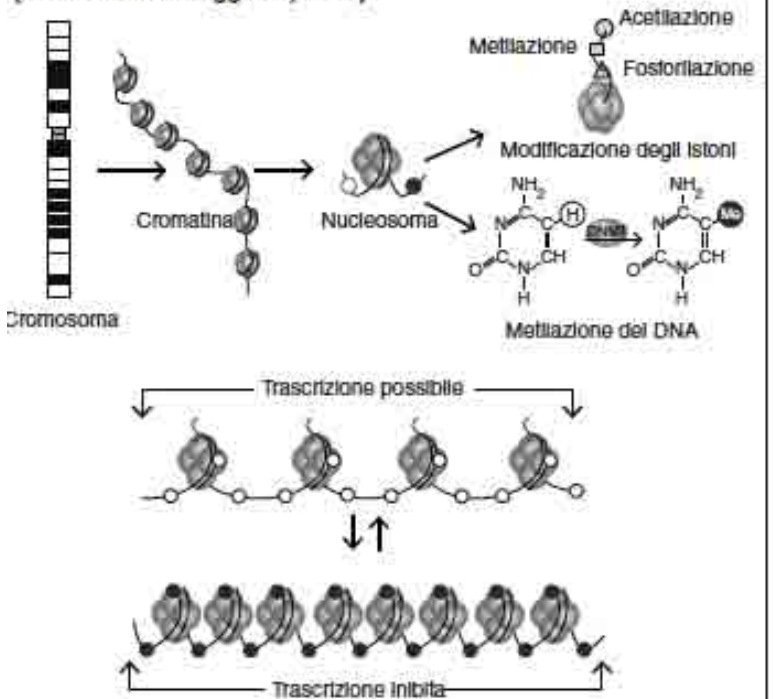


Figura 1 – Interazioni nutrienti-Genoma. Tratta da Stover e Caudill (2008).



Nella figura sono presentati due processi: la nutrigenetica e la nutrigenomica. Su questi due termini non vi è necessariamente accordo nel mondo scientifico. Chi scrive, mutuando le definizioni dai termini farmacogenetica e farmacogenomica, da più tempo discussi, intende questi due termini come di seguito definito. Nutrigenetica: influenza di varianti genetiche su assorbimento/utilizzazione/ metabolismo, tolleranza e necessità di determinati nutrienti (cioè su come, a causa di un differente corredo genetico, l'organismo agisce sul nutriente). Nutrigenomica: effetto dei nutrienti sulla evoluzione del genoma, le mutazioni, la programmazione e l'espressione dei geni.

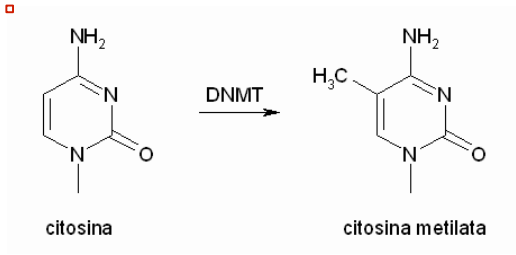
Figura 2 – La figura illustra alcuni aspetti della moderna visione del controllo dell'espressione di un gene in una cellula somatica (modificata da Waggoner, 2007)

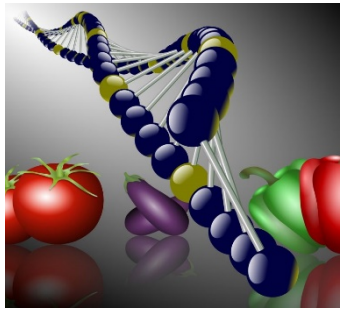


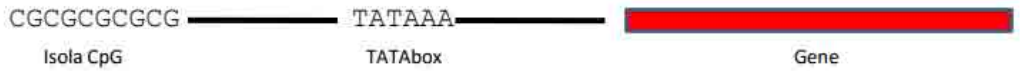
L'espressione di un gene in una data cellula è la risultante di una complessa serie di reazioni intracellulari, in risposta a stimoli esterni, che la controllano. L'arrivo di un segnale può avviare l'attivazione e la traslocazione al nucleo di fattori proteici che si possono legare al DNA e promuoverne o inibirne la lettura. Il DNA a sequenza immutata può essere oggetto di reazioni di metilazione che ne alterano la capacità di associarsi a tali fattori proteici. Inoltre il materiale genetico è normalmente superavvolto e possono essere duplicate solo quelle porzioni che vengono "svolte". Il superavvolgimento si avvale di alcune proteine nucleari, gli istoni, che permettono questa configurazione. L'attività degli istoni è a sua volta controllata da modificazioni postraduzionali della proteina (acetilazione, biotinilazione, fosforilazione, ubiquitinazione) controllate da reazioni enzimatiche (ad esempio acetilazione-deacetilazione). Questi processi sono sensibili a patologie, farmaci e principi nutritivi (si veda il testo per maggiori dettagli).

Metilazione del DNA

- La metilazione dei residui di citosina a livello del carbonio 5 è un marcatore epigenetico comune a molti eucarioti e viene spesso osservato nel contesto delle isole CpG o CpHpG;
- la metilazione delle citosine nei promotori è generalmente associata a repressione della trascrizione;
- avviene ad opera dell'enzima metiltransferasi in seguito all'aggiunta di un gruppo metilico (CH3) a livello del C5 della citosina.







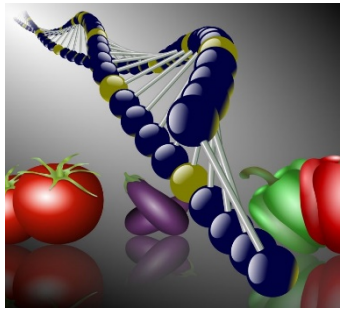
Metilazione isola CpG

Silenziamento del gene

Modifiche della cromatina

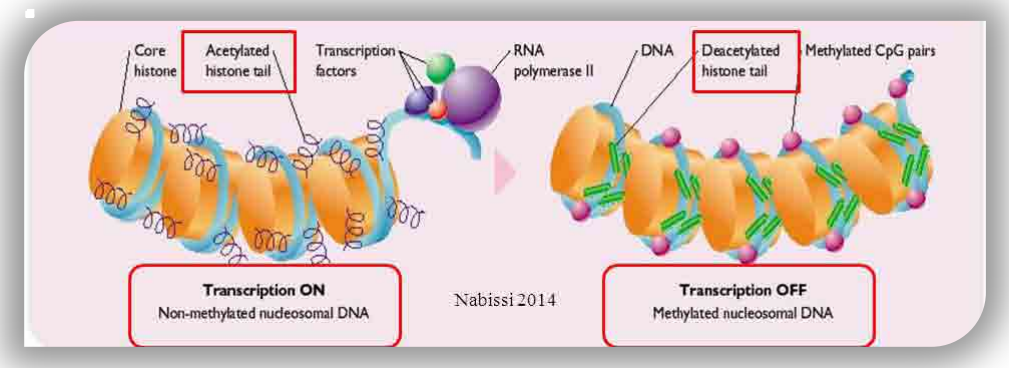
Modifiche covalenti a carico degli istoni

- **Acetilazione** (influenza la condensazione della cromatina), **fosforilazione**; **monoubiquitinazione**. Si tratta di modifiche reversibili;
- **metilazione** (è parzialmente reversibile e pare ci sia corrispondenza tra la metilazione degli istoni e del DNA).



Rimodellamento degli istoni

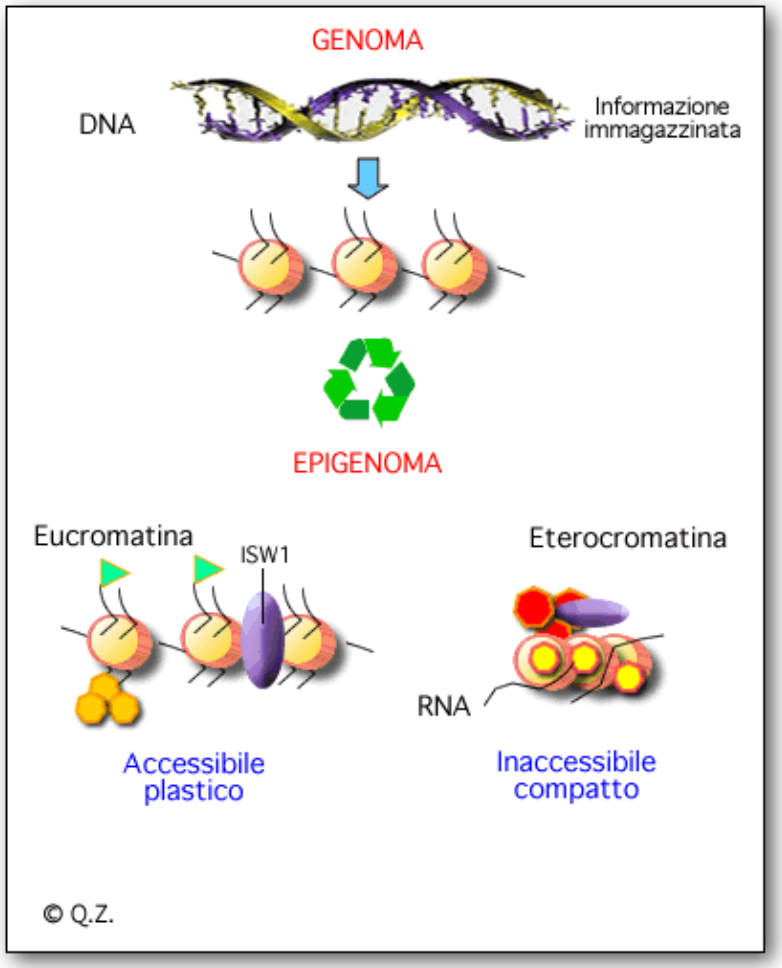
- Complessi proteici ATP-dipendenti;
- omologie con elicasi, ma non hanno attività elicasica
- deformano temporaneamente il DNA



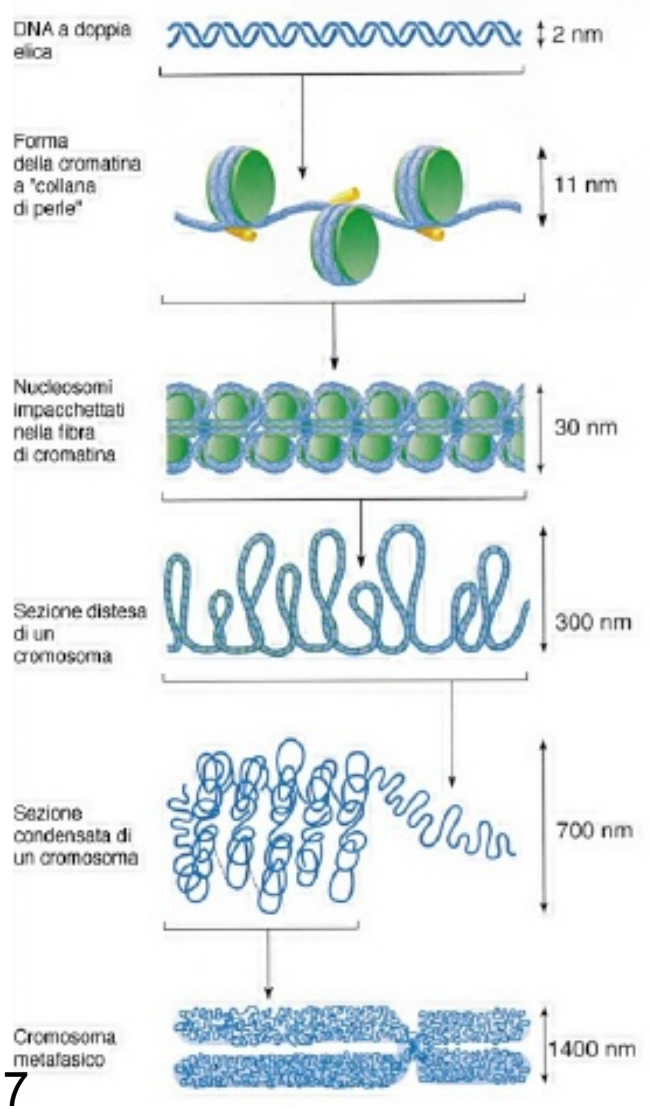
Le modifiche degli istoni corrispondono a segnali per il reclutamento o l'esclusione di proteine della cromatina

Rimodellamento della cromatina

Le modificazioni istoniche servono a definire particolari stati della cromatina.

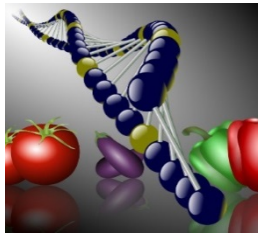


L'accessibilità alla cromatina è regolata principalmente a livello di modificazioni post-traduzionali che definiscono il grado di compattamento della cromatina da «aperto» (**eucromatina**) a «chiuso» (**eterocromatina**).

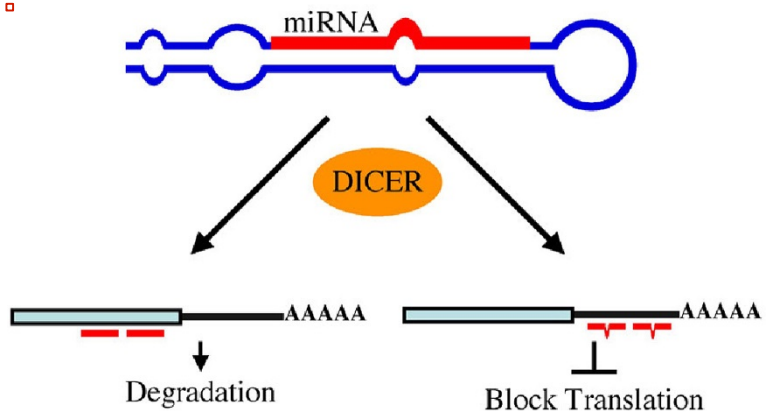


Epigenetica e miRNA

miRNA



- Piccole molecole di RNA (20-22 nt) con caratteristica forma a forcina
- Prodotte da precursori di 90-100 nt trascritti autonomamente o maturati da introni
- Si legano a mRNA che hanno sequenze complementari
- Presenti in tutti gli eucarioti



I miRNA agiscono mediante il riconoscimento di specifici mRNA targets al fine di determinarne la degradazione o la repressione della traduzione. La funzione di molti miRNA non è nota, ma per alcuni è stata provata la partecipazione a processi fisiologici e patologici: hanno un ruolo in proliferazione, apoptosi e differenziazione cellulare.
Possono essere deregolati in malattie umane e possono essere coinvolti nella tumorigenesi.

Epigenetica e miRNA

È stato dimostrato che esiste un link tra i meccanismi epigenetici e il controllo dell'espressione dei miRNAs.

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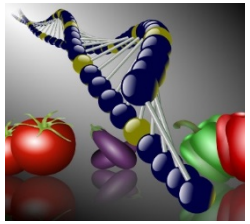
Epigenetics and MicroRNAs

JODY C. CHUANG, AND PETER A. JONES

Department of Biochemistry and Molecular Biology [J.C.C., P.A.J.], Department of Urology [P.A.J.], USC/Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California 90089



ABSTRACT: Epigenetics is defined as mitotically and meiotically heritable changes in gene expression that do not involve a change in the DNA sequence. Two major areas of epigenetics—DNA methylation and histone modifications—are known to have profound effects on controlling gene expression. DNA methylation is involved in normal cellular control of expression, and aberrant hypermethylation can lead to silencing of tumor-suppressor genes in carcinogenesis. Histone modifications control the accessibility of the chromatin and transcriptional activities inside a cell. MicroRNAs (miRNAs) are small RNA molecules, ~22 nucleotides long that can negatively control their target gene expression posttranscriptionally. There are currently more than 460 human miRNAs known, and the total number is predicted to be much larger. Recently, the expression of miRNAs has been definitively linked to cancer development, and miRNA profiles can be used to classify human cancers. miRNAs are encoded in our genome and are generally transcribed by RNA polymerase II. Despite the growing evidence for their importance in normal physiology, little is known about the regulation of miRNA expression. In this review, we will examine the relationship between miRNAs and epigenetics. We examine the effects of miRNAs on epigenetic machinery, and the control of miRNA expression by epigenetic mechanisms. Epigenetics is defined as heritable changes in gene expression that do not involve a change in DNA sequence.
(*Pediatr Res* 61: 24R–29R, 2007)

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Epigenetica e miRNA

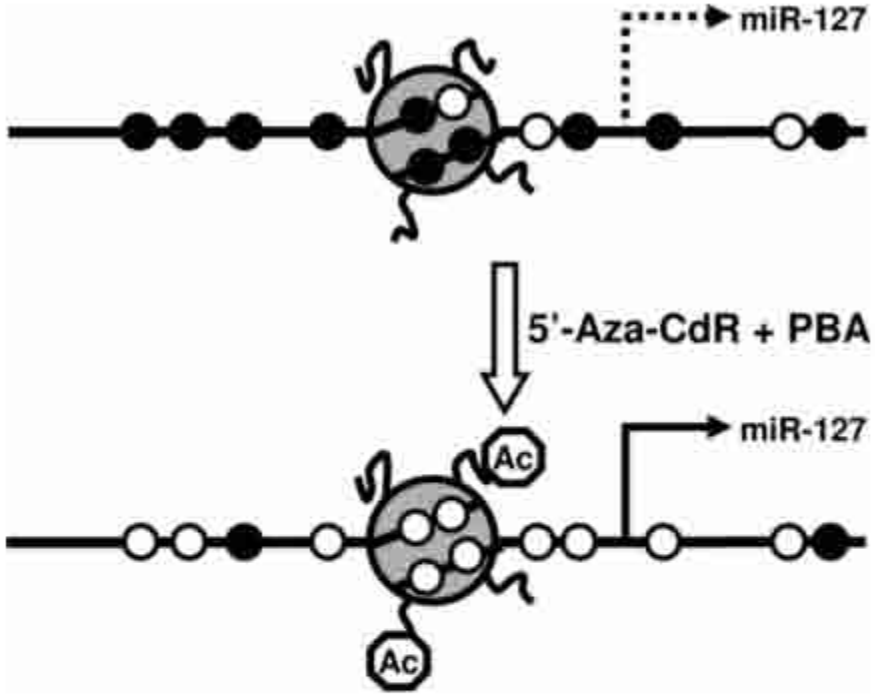


Figure 5. The expression of miRNAs can be controlled by epigenetic mechanisms. Epigenetic mechanisms such as DNA methylation and histone modifications can contribute to the transcriptional control of miRNA expression. In the case of miR-127, methylation of the CpG sites and deacetylation of the histones around its promoter region contribute to its silencing in tumor cell lines. Treatment with 5′-Aza-CdR and PBA leads to reduced DNA methylation and increased histone acetylation, allowing the miRNA to be expressed. The *gray circle* depicts a nucleosome with histone tails. *Open circles* on the DNA strand represent unmethylated CpG sites, and the *filled circles* methylated CpG sites. *Octagons* on the histone tails represent acetyl groups.

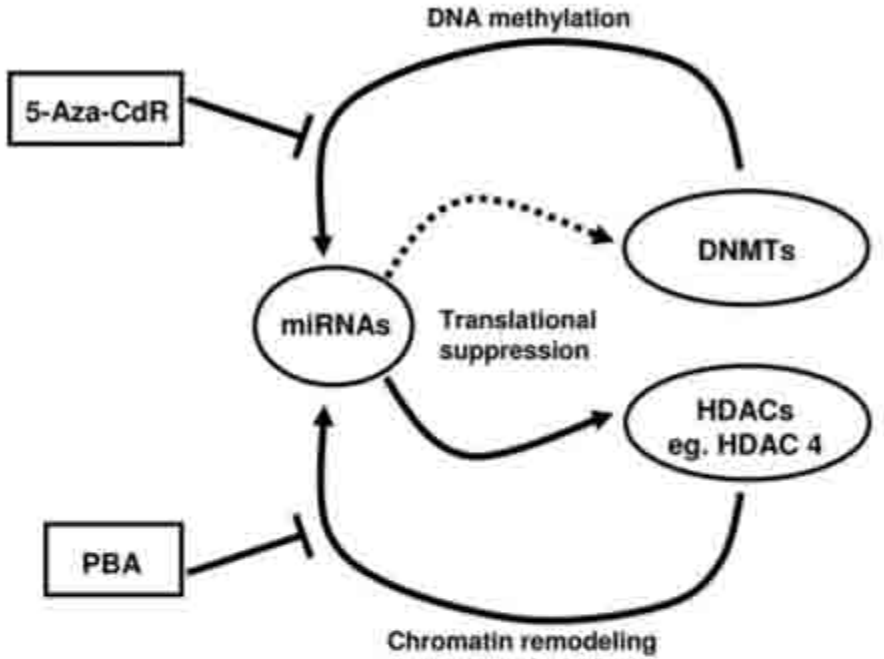
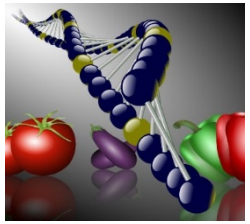


Figure 6. The interplay of epigenetics and miRNAs. Recent evidence has shone light on the relationship between miRNAs and epigenetics. miRNAs can affect the epigenetic mechanisms by targeting key enzymes involved in establishing epigenetic memory. For example, miR-140 has been shown to target HDAC4. It is likely that miRNAs can target other epigenetic players such as DNMTs. On the other hand, epigenetics can control the expression of miRNAs. DNMTs and HDACs can affect the expression of some miRNAs, and DNA methylation and histone modifications have been shown to control the expression of miR-127. Epigenetic drugs such as 5-Aza-CdR and PBA can reverse the changes done by DNMTs and HDACs, and this adds a new layer of understanding to the pharmacological actions of these drugs.



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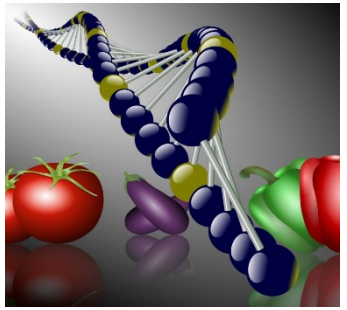
Chuang JC, Jones PA. Epigenetics and microRNAs. Pediatr Res. 2007 May;61(5 Pt 2):24R-29R.

Epigenetica e «ambiente»

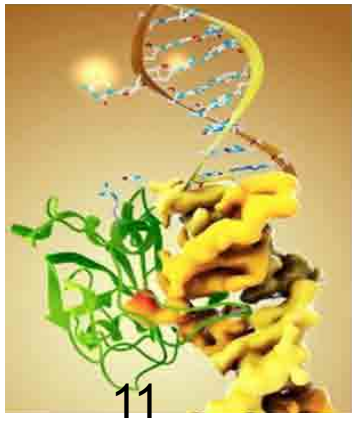
- Stress comportamentale
- Metalli pesanti
- Inquinanti e pesticidi
- Fattori nutrizionali
- Eventi stocastici

Alterazioni del pattern epigenetico

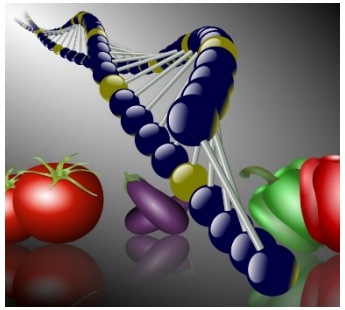


Alterazione dell'espressione genica

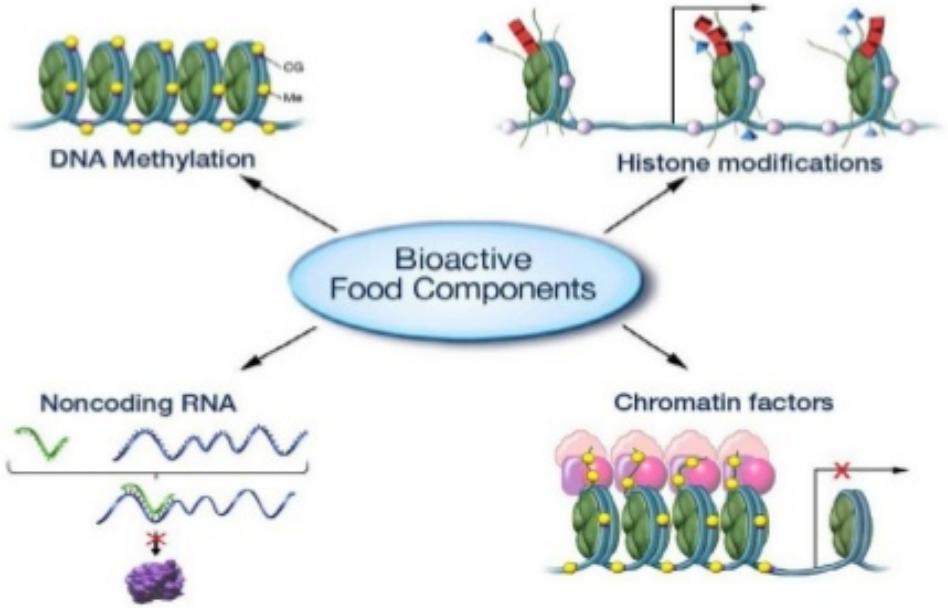
Patologia



Nutrizione ed epigenetica



L'epigenetica della nutrizione studia in che modo l'alimentazione o alcuni alimenti regolano l'espressione genica



miRNA e nutrizione

Review

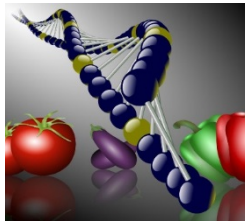
Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12372

The role of microRNA in nutritional control

E. N. M. Nolte-'t Hoen[1], E. Van Rooij[2], M. Bushell[3], C.-Y. Zhang[4], R. H. Dashwood[5], W. P. T. James[6], C. Harris[7] & D. Baltimore[8]

From the [1]Department of Biochemistry and Cell Biology, Faculty of Veterinary Medicine, Utrecht University; [2]Hubrecht Institute, Koninklijke Nederlandse Academie van Wetenschappen (KNAW), University Medical Center Utrecht, Utrecht, The Netherlands; [3]Medical Research Council (MRC) Toxicology Unit, University of Leicester, Leicester, UK; [4]Jiangsu Engineering Research Center for microRNA Biology and Biotechnology, State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, China; [5]Center for Epigenetics and Disease Prevention, Institute of Biosciences & Technology, Texas A&M Health Science Center, Houston, TX, USA; [6]London School of Hygiene and Tropical Medicine, London, UK; [7]Laboratory of Human Carcinogenesis, National Cancer Institute, Center for Cancer Research, National Institutes of Health, Bethesda, MD; and [8]Department of Biology, California Institute of Technology, Pasadena, CA, USA

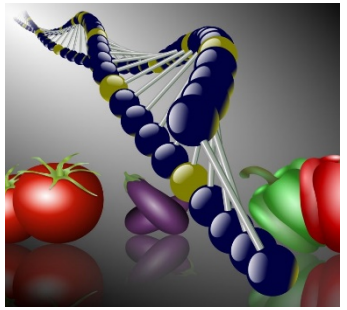


Role in metabolism and nutritional responses

The results of numerous studies indicate that miRNAs control metabolism and that miRNA levels change in response both to diet and to subsequent changes in nutritional state (Table 1). Moreover, it is becoming apparent which component of the metabolic pathways in any regulatory mechanism is regulated by a particular miRNA (Table 2). miR-122, for example, has been implicated in the biosynthesis, metabolism and transport of cholesterol [26] with the cholesterol transporter for high-density lipoprotein levels being modulated by miR-33 which also affects fatty acid synthesis and plasma triglyceride levels [27]. miRNAs also participate in the regulation of glucose metabolism [28] by modifying the activity of caveolin-1, a critical regulator of the insulin receptor, whereas miR-143, which is overexpressed in obesity, impairs insulin-stimulated AKT protein kinase activity, thereby also affecting glucose homoeostasis and insulin resistance [29]. Let-7, which is normally associated with the regulation of oncogenes, has recently been found to be involved also in multiple pathways affecting insulin sensitivity [30]. Obesity is known to impair insulin sensitivity and acts by inducing the hepatic overexpression of miR-802, which silences hepatocyte nuclear factor 1 homeobox B (Hnf1b) activity and then leads to glucose intolerance, impaired insulin signalling and promotion of hepatic gluconeogenesis [31].

Nutrizione ed epigenetica

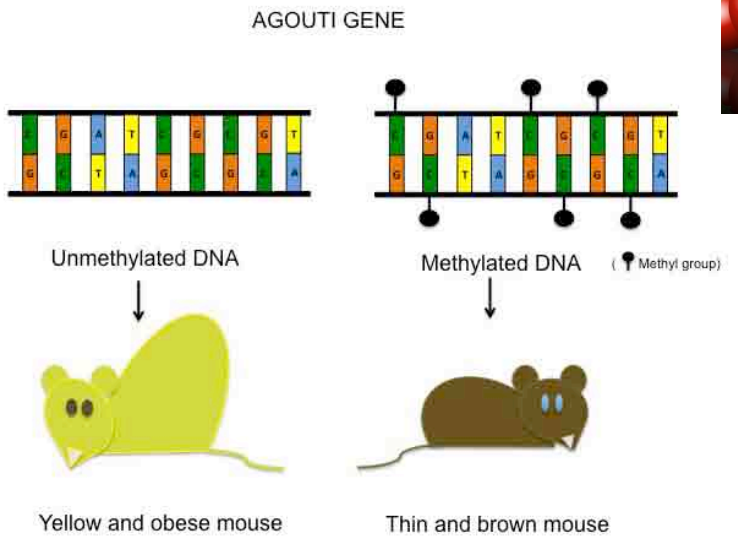
Il topo agouti



Il primo dato che ha mostrato come l'ambiente, e specificamente la dieta, poteva modificare il fenotipo, è stato ottenuto in un modello murino.

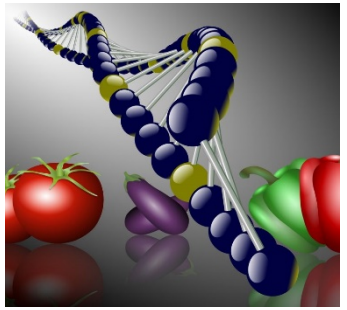
In questo modello, l'animale mostrava un colore di pelliccia dipendente, a livello genetico, da un'inserzione di un trasposone a monte di un gene, detto **agouti**, responsabile del colore marrone del manto.

Quando alla femmina gravida veniva somministrata una dieta ricca di sostanze donatrici di gruppi metile, il manto della progenie risultava di colore giallo per la ipo-regolazione del gene agouti in seguito alla sua metilazione.



Nutrizione ed epigenetica

Le api e l'epigenetica



Le modifiche epigenetiche hanno ruolo chiave nei cambiamenti nei ruoli sociali delle api

Com'è noto, nelle società di api, a partire da uno stesso genotipo possono manifestarsi fenotipi differenti: un embrione di sesso femminile può diventare una regina in seguito a una dieta a base di pappa reale e passare la vita a deporre uova, oppure può diventare un'ape operaia sterile.

A differenza delle regine, che non possono convertirsi in altri ruoli, le api operaie esibiscono una flessibilità di comportamenti molto elevata, passando metà della vita adulta come ape di alveare e l'altra metà come ape di campo, con compiti e comportamenti molto differenziati

La pappa reale modifica l'espressione dei geni

Nutrizione ed epigenetica

Le api e l'epigenetica

While royalty is typically heritable in humans and in some social insects, this is not so in honeybees. The honeybee queen and workers might be genetically identical but what seals their respective fates is that queen larvae get fed a special diet—royal jelly—in large quantities and over extended periods. This richly nutritious substance's chemical composition is only partially understood and is produced by glands in the mouths of young nurse bees. All larvae are initially fed with royal jelly, although worker larvae are soon weaned and switched to a diet of pollen and nectar, whereas queen larvae are bathed in royal jelly throughout their larval development and feed on it into adulthood. This differential rearing procedure results in striking morphological, behavioural, and physiological differences between these different castes.

It seems possible that DNA methylation results in repression of gene expression in workers. DNA methylation requires the enzyme DNA methyltranferase DNMT3. It was recently shown that silencing DNMT3 expression in newly hatched honeybee larvae mimics the effect of royal jelly, namely, the larvae destined to become workers develop into queens with fully developed ovaries This was a direct demonstration that royal jelly provides the external information interpreted by the developing larva to create and maintain the epigenetic state necessary to generate a queen. Royal jelly also contains a family of proteins , which are thought to be crucial in reproductive maturation. Intriguingly, one of the components of royal jelly is phenyl butyrate, a known histone deacetylase inhibitor. Histone deacetylases catalyse the removal of acetyl groups from histones, which may allow for chromatin to become more compacted, so repressing transcription.

Chittka A, Chittka L (2010) Epigenetics of Royalty. PLOS Biology 8(11): e1000532. https://doi.org/10.1371/journal.pbio.1000532
http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000532

Nutrizione ed epigenetica

Le api e l'epigenetica

	Worker	Queen
Mass at emergence	81–151mg	178–292mg
Development egg->adult	16–24 days	14–17 days
Age	15–38 days (summer bees) 140 days (winter bees)	1–3 years normally (up to 8 yrs in some cases)
Facets in compound eye	5,000–6,000	3,500
Placoid olfactory sensillae	2,700	1,600
Pollen basket	Yes	No
Wax glands	Yes	No
Spermatheca	Rudimentary	Large
Ovarioles	2–12	150–180
Sting barbs	Yes	Rudimentary
Mandibular glands	Large	Very large
Nasonov glands	Yes	No
Dance communication	Yes	No

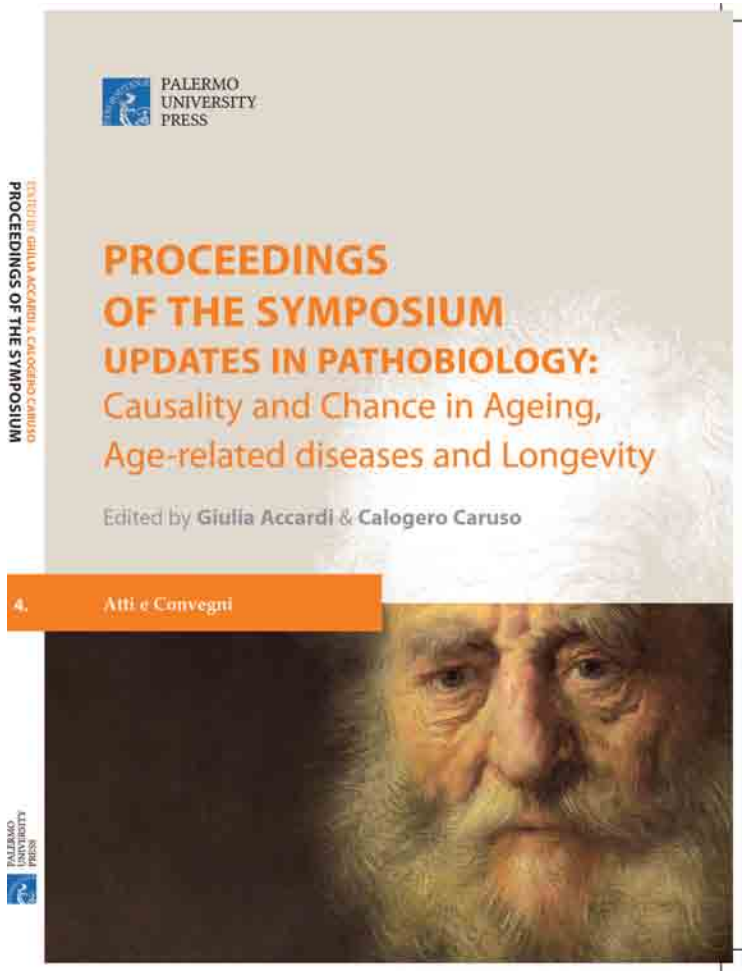
Note: there is no intention of completeness; there are many more anatomical, neurobiological, and hormonal and behavioural differences between these castes [4,17,18,25].
doi:10.1371/journal.pbio.1000532.t001

Chittka A, Chittka L (2010) Epigenetics of Royalty. PLOS Biology 8(11): e1000532. https://doi.org/10.1371/journal.pbio.1000532
http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000532

Nutrizione ed epigenetica

Carestia olandese del 1944/45

Accardi, G., Caruso, C., 2017. In: Accardi, G., Caruso, C. (Eds.), Updates in Pathobiology: Causality and Chance in Ageing, Age-related Diseases and Longevity In Updates in Pathobiology: Causality and Chance in Ageing, Age-related Diseases and Longevity. Palermo University Press, pp. 13–23.



The stochastic epigenetic model has important implications for evolutionary biology considering environmental effects that may be consistent for many generations but can then change stochastically, for example in response to an environmental crisis such as drought or famine. At this regard, during the winter of 1944–1945, a famine affected the western Netherlands. It was the result of an embargo on transport of food supplies imposed by the German occupying forces in early October 1944 in reprisal for a wave of partisan activity. It lasted for approximately 5 months and ended abruptly with the liberation by allied forces in May 1945. Several studies addressed the effects of maternal malnutrition during the different periods of gestation on health in adult life. Individuals conceived in Holland occupied by the Nazis showed at a distance of sixty years a higher incidence of diabetes, obesity and other diseases when compared to subjects age and sex matched whose mothers followed a non-famine dietary regimen in Holland occupied by allied armies. The association was present in subjects, whose exposure to famine occurred around the time of conception, proving the strict relation between causality and chance intrinsic to epigenetic changes. So, research over the past 3 decades has shown that exposure to famine during gestation has life-long effects on health, and that these effects vary depending on the timing of exposure as well as evolution of the recovery period. The effects of famine during gestation thus differ from those of adult exposure, which has only short-term effects

Nutrizione ed epigenetica

Carestia olandese del 1944/45

Glucose tolerance in adults after prenatal exposure to famine

THE LANCET • Vol 351 • January 17, 1998

A C J Ravelli, J H P van der Meulen, R P J Michels, C Osmond, D J P Barker, C N Hales, O P Bleker

	Exposure to famine					Total (SD) (n=702)	p	Missing observations
	Born before famine (n=202)	Late gestation (n=116)	Mid gestation (n=100)	Early gestation (n=63)	Conceived after famine (n=221)			
Fasting								
Glucose (mmol/L)	5·8	5·8	5·7	5·8	5·6	5·7 (1·1)	0·2	0
Insulin (pmol/L)	46·7	48·9	45·4	52·6	47·0	47·5 (1·7)	0·3	7
Proinsulin (pmol/L)	5·8	6·3	5·9	6·6	5·9	6·0 (1·9)	0·05	9
32–33 proinsulin (pmol/L)	6·2	6·9	6·1	7·5	6·6	6·5 (2·1)	0·1	14
30 min								
Glucose (mmol/L)	9·0	8·8	8·7	9·2	8·8	8·9 (1·2)	0·8	12
Insulin (pmol/L)	314	285	303	327	319	310 (1·8)	0·3	19
Relative insulin increment*	3·4	3·3	3·4	3·4	3·4	3·4 (0·7)	0·3	26
120 min								
Glucose (mmol/L)	5·7	6·3	6·1	6·1	5·9	6·0 (1·4)	0·006	0
Insulin (pmol/L)	160	200	190	207	181	181 (2·4)	0·04	8
Prevalence of IGT or type 2 diabetes	15%	21%	14%	16%	15%	16%	0·4	0

*Not geometric.

Table 2: **Geometric means of plasma glucose and insulin concentrations**

They included 702 people born between Nov 1, 1943, and Feb 28, 1947, in Amsterdam, for whom they had detailed prenatal and birth records. Glucose concentrations were increased 2 h after a standard glucose load among exposed participants (p=0·006), and were highest in men and women exposed during mid and late gestation. Prenatal exposure to famine was related to increased fasting proinsulin (p=0·05) and 2 h insulin concentrations (p=0·04), which suggests an association with insulin resistance.

Nutrizione ed epigenetica

Carestia olandese del 1944/45

Obesity at the age of 50 y in men and women exposed to famine prenatally[1–3]

Anita CJ Ravelli, Jan HP van der Meulen, Clive Osmond, David JP Barker, and Otto P Bleker

TABLE 2

Effect of prenatal exposure to famine on adult body size expressed as differences between participants prenatally exposed to famine (in late, mid, or early gestation) and nonexposed people (those born before or conceived after the famine pooled together)[1]

Sex and body characteristic	Time of gestational exposure to famine		
	Late	Mid	Early
Men			
Body size at age 50 y			
Weight (kg)	0.8 (−3.1, 4.7)	−2.3 (−6.6, 1.9)	1.5 (−3.5, 6.6)
Height (cm)	0.5 (−1.4, 2.5)	−1.5 (−3.7, 0.6)	0.9 (−1.7, 3.4)
Head circumference (cm)	0.2 (−0.3, 0.7)	−0.3 (−0.8, 0.2)	−0.1 (−0.7, 0.6)
BMI (% of nonexposed mean)	0.4 (−3.5, 4.5)	−1.2 (−5.5, 3.3)	0.5 (−4.6, 6.0)
Waist circumference (cm)	1.8 (−1.4, 4.9)	−1.0 (−4.5, 2.5)	1.8 (−2.4, 6.0)
Waist-to-hip ratio (×100)	1.3 (−0.5, 3.1)	−0.4 (−2.4, 1.6)	1.5 (−0.9, 3.9)
Weight recalled for age 20 y			
Weight (kg)	−1.0 (−3.8, 1.7)	−1.5 (−4.6, 1.6)	3.6 (0.0, 7.2)
BMI (% of nonexposed mean)	−1.9 (−5.2, 1.6)	−0.2 (−4.0, 3.9)	3.8 (−0.8, 8.5)
Women			
Body size at age 50 y			
Weight (kg)	−1.8 (−6.1, 2.5)	−1.5 (−5.7, 2.8)	7.9 (2.5, 13.2)
Height (cm)	0.1 (−1.6, 1.8)	−0.6 (−2.3, 1.0)	0.9 (−1.2, 2.9)
Head circumference (cm)	0.2 (−0.3, 0.6)	0.0 (−0.4, 0.5)	0.2 (−0.3, 0.7)
BMI (% of nonexposed mean)	−2.1 (−7.0, 3.1)	−1.3 (−6.3, 3.9)	7.4 (0.7, 14.5)
Waist circumference (cm)	−0.7 (−4.4, 3.0)	0.4 (−3.2, 4.1)	5.7 (1.1, 10.3)
Waist-to-hip ratio (×100)	0.8 (−1.2, 2.8)	0.9 (−1.1, 2.9)	2.2 (−0.3, 4.7)
Weight recalled for age 20 y			
Weight (kg)	−3.1 (−6.0, −0.1)	−1.3 (−4.2, 1.5)	1.8 (−1.7, 5.4)
BMI (% of nonexposed mean)	−5.0 (−9.1, −0.8)	−0.9 (−5.0, 3.4)	2.2 (−3.1, 7.8)

[1] $\bar{x}$, 95% CI in parentheses.

ABSTRACT

Background: It was shown that men who were conceived during the Dutch famine of 1944–1945 had higher rates of obesity at age 19 y than those conceived before or after it.

Objective: Our objective was to study the effects of prenatal exposure to the Dutch famine on obesity in women and men at age 50 y.

Design: We measured the body size of 741 people born at term between November 1943 and February 1947 in Amsterdam. We compared people exposed to famine in late, mid, or early gestation (exposed participants) with those born before or conceived after the famine period (nonexposed participants).

Results: The body mass index (BMI; in kg/m^2) of 50-y-old women exposed to famine in early gestation was significantly higher by 7.4% (95% CI: 0.7%, 14.5%) than that of nonexposed women. BMI did not differ significantly in women exposed in mid gestation (−2.1%; −7.0%, 3.1%) or in late gestation (−1.3%; −6.3%, 3.9%). In 50-y-old men, BMI was not significantly affected by exposure to famine during any stage of gestation: BMI differed by 0.4% (−3.5%, 4.5%) in men exposed to famine in late gestation, by −1.2% (−5.5%, 3.3%) in those exposed in mid gestation, and by 0.5% (−4.6%, 6.0%) in those exposed in early gestation compared with nonexposed men.

Conclusions: Maternal malnutrition during early gestation was associated with higher BMI and waist circumference in 50-y-old women but not in men. These findings suggest that pertubations of central endocrine regulatory systems established in early gestation may contribute to the development of abdominal obesity in later life. *Am J Clin Nutr* 1999;70:811–16.

Nutrizione ed epigenetica

Carestia olandese del 1944/45

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline Slagboom[a], and L. H. Lumey[e,1]

Departments of [a]Molecular Epidemiology, [c]Medical Statistics, and [d]Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands; [b]Hubert Department of Global Health, Rollins School of Public Health, Emory University Atlanta, GA 30322; [e]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032; and [f]New York State Psychiatric Institute, New York, NY 10032

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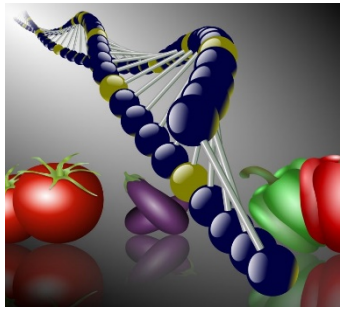

Extensive epidemiologic studies have suggested that adult disease risk is associated with adverse environmental conditions early in development. Although the mechanisms behind these relationships are unclear, an involvement of epigenetic dysregulation has been hypothesized. Here we show that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–45 had, 6 decades later, less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings. The association was specific for periconceptional exposure, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks. These data are the first to contribute empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life.

IGF2 gene

insulin like growth factor 2

Normal Function

The *IGF2* gene provides instructions for making a protein called insulin-like growth factor 2. This protein plays an essential role in growth and development before birth. Studies suggest that insulin-like growth factor 2 promotes the growth and division (proliferation) of cells in many different tissues. Although the *IGF2* gene is highly active during fetal development, it is much less active after birth.

Nutrizione ed epigenetica

Carestia olandese del 1944/45

IMPRINTING GENOMICO

Durante lo sviluppo dei Mammiferi i genomi dei genitori sono funzionalmente non equivalenti, in quanto alcuni *loci* omologhi subiscono l'effetto di modificazioni epigenetiche specifiche per la linea germinale, quando i cromosomi si separano nelle linee maschili e femminili. Questo processo conferisce a una sottoclasse di *loci*omologhi, definiti 'geni imprinted', un'espressione dipendente dal genitore d'origine. Alcuni di questi geni sono espressi se ereditati dal padre, altri se ereditati dalla madre. L'altro allele parentale viene, infatti, mantenuto in uno stato in parte represso mediante la metilazione del DNA, una delle più importanti modificazioni epigenetiche ereditabili. Alcuni geni sottoposti a imprinting sono raggruppati in particolari domini cromosomici e controllati da un elemento regolativo, definito 'centro di imprinting'. Tali geni svolgono un ruolo significativo nello sviluppo: un errato imprinting o un'espressione non appropriata di questi geni sono alla base di diverse malattie genetiche umane.

Nutrizione ed epigenetica

Carestia olandese del 1944/45

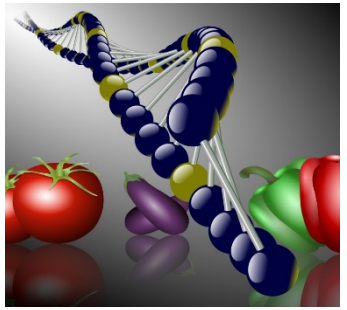

Table 1. *IGF2* DMR methylation among individuals periconceptionally exposed to famine and their unexposed, same-sex siblings

IGF2 DMR methylation	Mean methylation fraction (SD)				Relative change exposed	Difference in SDs	*P*
	Exposed (n = 60)		Controls (n = 60)				
Average	0.488	(0.047)	0.515	(0.055)	−5.2%	−0.48	5.9×10^{-5}
CpG 1	0.436	(0.037)	0.470	(0.041)	−6.9%	−0.78	1.5×10^{-4}
CpG 2 and 3	0.451	(0.033)	0.473	(0.055)	−4.7%	−0.41	8.1×10^{-3}
CpG 4	0.577	(0.114)	0.591	(0.112)	−2.3%	−0.12	.41
CpG 5	0.491	(0.061)	0.529	(0.068)	−7.2%	−0.56	1.4×10^{-3}

P values were obtained using a linear mixed model and adjusted for age.

Table 2. *IGF2* DMR methylation among individuals exposed to famine late in gestation and their unexposed, same-sex siblings

IGF2 DMR methylation	Mean methylation fraction (SD)				Relative change exposed	Difference in SDs	*P*
	Exposed (n = 62)		Controls (n = 62)				
Average	0.514	0.045	0.519	0.036	−0.9%	−0.12	.64
CpG 1	0.460	0.044	0.464	0.048	−0.9%	−0.09	.68
CpG 2 and 3	0.462	0.039	0.471	0.039	−1.7%	−0.21	.46
CpG 4	0.602	0.085	0.612	0.073	−1.5%	−0.12	.30
CpG 5	0.529	0.060	0.531	0.060	−0.3%	−0.02	.77

P values were obtained using a linear mixed model and adjusted for age.

Table 3. Timing of famine exposure during gestation, *IGF2* DMR methylation, and birth weight

	Periconceptional exposure	Late gestational exposure	All controls
n	60	62	122
Males, %	46.7	45.2	45.9
Mean age, years	58.1 (SD, 0.35)	58.8 (SD, 0.4)	57.1 (SD, 5.5)
Birth weight, g	3612 (SD, 648)	3126 (SD, 408)	—
IGF2 DMR methylation			
Average	0.488 (SD, 0.047)	0.514 (SD, 0.045)	0.517 (SD, 0.047)
$P_{\text{vs all controls}}$	1.5×10^{-5}	.69	
$P_{\text{interaction}}$			4.7×10^{-3}

P values were obtained using a linear mixed model and adjusted for age.

Nutrizione ed epigenetica

Carestia olandese del 1944/45

The current study presents a first example of an association between a periconceptional exposure and DNA methylation in humans. It will be of prime interest to investigate whether other exposures during early development that are more common in modern societies, including overnutrition (3) and assisted reproductive technologies (27), give rise to similar associations. In addition, the extent to which epigenetic marks at other genomic regions are vulnerable to such exposures remains to be established. A key area to explore in future studies will be to assess the phenotypic consequences of changes in epigenetic marks. Diseases that have been associated with early gestational exposure to famine, such as schizophrenia (28) and coronary heart disease (29), are of particular interest in this respect. Analogous to current studies in genetic epidemiology (30), such epigenetic epidemiologic studies may need to be large and to include replication. Understanding how epigenetic control depends on early exposure may shed light on the link between development and health over the lifespan and ultimately suggest new ways to prevent human disease.

Nutrizione ed epigenetica

Dieta e ambiente

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Archives of Pharmacal Research

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REVIEW

Epigenetic modifications of gene expression by lifestyle and environment

Qudeer Ahmed Abdul[1] · Byung Pal Yu[2] · Hae Young Chung[3] · Hyun Ah Jung[4,5] · Jae Sue Choi[1]

Dietary nutrients and bioactive food components contribute to epigenetic phenomena either by directly suppressing DNA methylation or histone catalyzing enzymes or by changing the availability of substrates required for enzymatic reactions.

Diets that contain catechol-dominant polyphenols are reported to suppress enzyme activity and activate epigenetically silenced genes.

Furthermore, several dietary nutrients play a crucial role in one-carbon metabolism including folate, cobalamin, riboflavin, pyridoxine, and methionine by directly affecting *S*-adenosyl-l-methionine.

Soy polyphenols block DNA methyltransferases and histone deacetylases to reverse aberrant CpG island methylation.

Organosulfur-rich compounds such as the sulforaphane found in broccoli appear to normalize DNA methylation and activate miR-140 expression, which represses SOX9 and ALDH1 and decreases tumor growth.

Epigenetic modifications of gene expression by lifestyle and environment

Table 1 Environmental epigenetic factors and their effects on gene expression

Agent	Active component	Epigenetic and gene expression modifications	References
Polyphenols	Curcumin	Histone deacetylase inhibitor	Bora-Tatar et al. (2009)
		Inhibits the expression of class I HDACs (HDAC1, HDAC3, and HDAC8)	Liu et al. (2005)
		Upregulates acetylated histone H4	
		Suppresses p300, HDAC1, and HDAC3	Chen et al. (2007)
	Resveratrol	Represses epigenetic silencing of the BRCA-1 gene	Papoutsis et al. (2010)
		Decreases sodium/iodide symporter RNA and protein expression as a function of time	Giuliani et al. (2014)
		Inhibits sodium/iodide symporter gene expression in vivo	
	Soy polyphenols	Blocks DNA methyltransferases and histone deacetylases	Qin et al. (2009)
		Reverses aberrant CpG island methylation	
Flavonoids	Herbimycin A	Downregulates LPS-activated NF-κB	Geng et al. (1993)
	Genistein	Inhibits LPS-induced NF-κB	Geng et al. (1993)
		Downregulates DNMT1, DNMT3a, and DNMT3b	Li et al. (2009)
	Apigenin	Blocks GSK-3β/NF-κB	Johnson and de Mejia (2013)
		Arrests cell cycle at the G2/M phase	
		Reduces the expression of cyclin B1	
		Upregulates expression of cytokine genes IL17F, LTA, IL17C, IL17A, and IFNB1	
Flavonoids	Kaempferol, fisetin	Suppresses TNF-α-induced IL-8 promoter stimulation and gene expression	Lee et al. (2009)
	Chrysin, quercetin	Inhibits phosphorylation and degradation of IκBα	
		blocks translocation of NF-κB p65	
	Quercetin	Reduces mRNA and protein expression levels of survivin	Deng et al. (2013)
		Arrests cell cycle at the G0/G1 phase	
		Reduces TSH-regulated RNA level of the thyroid-restricted gene Sodium/iodide symporter (NIS)	Giuliani et al. (2008)
		Downregulates transcriptional activation of the MDR1 gene	Kioka et al. (1992)
		Downstream signaling of Hsp90 expression	Muthu Altundag et al. (2016)
	Kaempferol, rhamnocitrin (kaempferol-7-methyl ether)	Induces heme oxygenase (HO)-1 gene expression	Hong et al. (2009)
		Attenuates p38 phosphorylation (MAPK signaling pathway)	
	Berberine	Represses the expression of constitutive androstane receptor and its target genes CYP2B6 and CYP3A4	Zhang et al. (2016a)
		Upregulates DNA methylation levels in the entire genome	
		Reduces elevated DNA methylation in the promoter CpG regions of CYP2B6 and CYP3A4 genes	
Diet and dietary nutrients	Folate, cobalamin, riboflavin, pyridoxine and methionine	Affects the methyl donor *S*-adenosyl-L-methionine AdoMet	Stefanska et al. (2012)
	Folate deficiency	Modifies components of DNA methylation	Ghoshal et al. (2006)
		Enhances DNMT1, DNMT3B, MBD2, and MBD4 mRNA and protein levels	
	Beta carotene, arachidonic acid	Induces modifications in CpG island methylation of the KDR pro-angiogenic gene promoter	Kiec-Wilk et al. (2009)

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Recommendations for good epigenetic practices

1. Avoid toxins:
   - Use organic fruits and vegetables
   - Limit all processed foods
   - Avoid eating fast foods
   - Avoid GMO foods
   - Avoid eating too much, which is probably the most important factor for the protection of genes, to avoid cellular exposure to toxic substances
2. Antioxidant rich foods:
   - Consume plenty of fresh fruits and vegetables rich in vitamins
   - Consume raw almonds to intake vitamin E
   - Consume antioxidant rich sea food
3. Take essential minerals regularly:
   - Selenium
   - Chromium picolinate
   - Magnesium
   - Zinc
   - Potassium
   - Calcium
4. Practice stress reduction:
   - Exercise daily
   - Be positive to dramatically reduce stress and stay happy

Table 1 continued

Agent	Active component	Epigenetic and gene expression modifications	References
Diet and dietary nutrients	Broccoli sprouts	Inhibits HDAC activity in circulating peripheral blood mononuclear cells	Chen and Xu (2010)
		Activates histone H3 and H4 acetylation	Myzak et al. (2007)
	Sulforaphane	Normalizes DNA methylation	Li et al. (2014)
		Activates miR-140 expression	
	Phenethyl isothiocyanate and curcumin	Reduces COX-2 in Nrf2(+/+) macrophages	Boyanapalli et al. (2014)
		Increases HO-1 expression in Nrf2(+/+) macrophages	
		Suppresses IL-6 and TNF-α expression levels	
Lifestyle	Lifestyle modifications	Gene expression profiling during intensive cardiovascular lifestyle modifications	Blackburn et al. (2015)
	Stress reduction	Enhances telomerase gene expression with reduced blood pressure	Duraimani et al. (2015)
	Lifestyle pattern	Effects on genome methylation and gene expression	Zhang et al. (2016a)
Exercise	Exercise practice	Regulates muscle growth and metabolic adaptation by DNA methylation	Kanzleiter et al. (2015)
		Genome-wide changes in DNA methylation in human adipose tissues	Rönn et al. (2013)
		Modulates muscle myostatin (MSTN) protein	Bassi et al. (2015)
Metals	Cadmium	Decreases genome methylation	Takiguchi et al. (2003)
		Inhibits DNA methyltransferases	
	Low arsenic doses	Decreases AdoMet level	Zhao et al. (1997)
		Induces DNA hypomethylation	
	Long-term low arsenic doses	Reduces AdoMet	Reichard et al. (2007)
		Suppresses expression of DNA methyltransferase genes DNMT1 and DNMT3A	
Metals	Nickel	Modifies gene expression by enhancing DNA methylation and compaction	Lee et al. (1995)
	Sodium arsenite	Upregulates genomic hypomethylation	Okoji et al. (2002)
	Methyl-deficient diet and sodium arsenite	Upregulates genomic hypomethylation	Okoji et al. (2002)
		Downregulates the incidence of oncogenic gene Ha-ras methylation	
	Arsenic	Reduces uptake of (3)H methyl groups	Majumdar et al. (2010)
	Metal-rich particulate matter (contamination with lead and cadmium)	Modifies miRNA expression	Bollati et al. (2010)
	Diethyl phosphate, mercury, cotinine, selenium and octachlorodipropyl ether (S-421)	Induces nuclear staining modifications	Arai et al. (2011)
	Mercury and selenium	Induces aberrant DNA methylation	Arai et al. (2011)
	Aluminum sulfate	Increases miRNA-146a	Pogue et al. (2009)
Pesticides	Vinclozolin and methoxychlor	Decreases spermatogenic ability	Anway et al. (2005)
		Enhances the frequency of male infertility in the F1 generation	
	Trichloroethylene, dichloroacetic acid, trichloroacetic	Downregulates methylation in the promoter regions of c-jun and c-myc genes	Tao et al. (2000)
		Upregulates the expression of respective mRNA and proteins	
	Dieldrin	Upregulates the acetylation of histones H3 and H4	Song et al. (2010)
Air pollution	Ambient air	1.6-fold increase in sperm mutation frequency	Yauk et al. (2008)
	Diesel exhaust particles	Hypermethylates the IFN-γ enhancer	Liu et al. (2008)
		Hypomethylates IL-4	
		Changes in miRNA expression in human airway epithelial cells	Jardim et al. (2009)

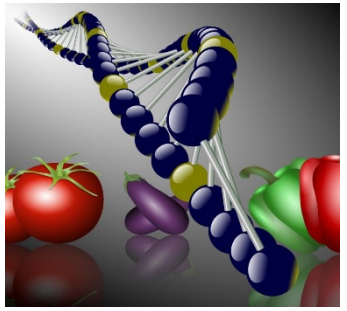
Epigenetica e nutrizione

I centenari come modello

Centenarians as a model to discover genetic and epigenetic signatures of healthy ageing

Annibale Alessandro Puca[a,b,*], Chiara Spinelli[a], Giulia Accardi[c], Francesco Villa[a], Calogero Caruso[c]

[a] Cardiovascular Research Unit, IRCCS MultiMedica, 20138 Milan, Italy
[b] Department of Medicine and Surgery, University of Salerno, 84084 Salerno, Italy
[c] Department of Pathobiology and Medical Biotechnologies, University of Palermo, 90134 Palermo, Italy



Centenarians are a model of successful ageing. The data favours the theory that, in order to live to 100, it is mandatory to inherit the right genetic variants from parents or acquire epigenetic variants through the environment. Therefore, the study of epigenetic signatures of healthy ageing is becoming an important aspect to identify the role of chromatin modification in ageing and understand how manage this fine-tuning system. So, according to the concept of developmental plasticity, establishment of a longevity phenotype requires a combination of stochastic and non-stochastic events that modulate the genetic substrate and leads to a different outcome. It can be concluded that centenarians have a more powerful "engine" shaped by evolution, and that the environment, through epigenetic system, is a component influencing outcome.

Fig. 1. Longevity elixir's recipe. Diet, smoking, stress, air pollution, physical exercise and other environmental factors, together with genetic background, epigenetic mechanisms, and stochastic factors influence ageing process. Will there be a way to manage and control all these ingredients toward healthspan?

Epigenetica e nutrizione

I centenari come modello

Centenarians as a model to discover genetic and epigenetic signatures of healthy ageing

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[a] Cardiovascular Research Unit, IRCCS MultiMedica, 20138 Milan, Italy
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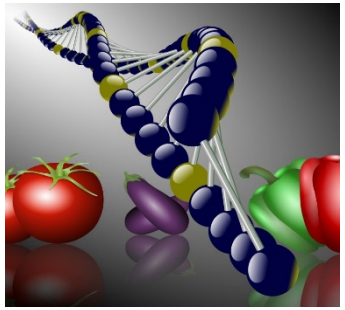


Table 1
The table shows the epigenetic effect of some phytochemicals on ageing (in different model organisms, in human beings and in vitro).

Phytochemicals	Sources	Epigenetic targets	Findings	References
Anthocyanins	Red fruits, red onion, aubergine	NF-κB	Decrease of the plasma concentrations of several NF-κB-regulated pro-inflammatory mediators.	Karlsen et al., 2007
Curcumin	Curry, turmeric	DNMT, HDAC and HAT inhibitor and miRNA modulator	Inhibition of the expression of pro-inflammatory mediators by affecting histone acetylation of transcription factors and methylation pattern of gene promoters associated with inflammatory response.	Boyanapalli and Tony Kong, 2015; Kang et al., 2006
Resveratrol	Grapes, peanuts, mulberries, cranberries, blueberries	Inhibition of HDAC inhibitor	Activation of SIRT-1 leading to deacetylation of p53, NF-κB, HSF-1, FOXO 1,3,4 and PGC-1 alpha, influencing replicative senescence, inflammation, apoptosis, metabolism and stress resistance.	Barger et al., 2008; Baur and Sinclair, 2006a, 2006b; Hubbard and Sinclair, 2014
Extra virgin olive oil	Olives	Genes involved directly or indirectly in ageing	Influence of the methylation and acetylation of genes directly or indirectly involved in ageing and metabolic diseases.	Fernández del Río et al., 2016

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; DNMT: DNA methyltransferase; HDAC: histone deacetylase; HAT: histone acetyltransferase; miRNA: microRNA; SIRT-1; sirtuine-1; FOXO; Forkhead box O3; HSF-1; Heat shock factor 1; PGC-1 alpha; Peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

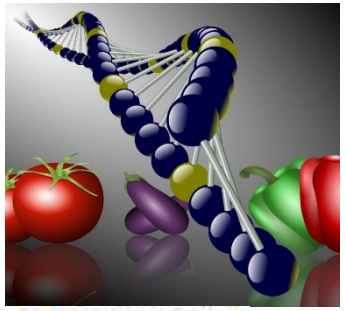
Epigenetica e nutrizione

I centenari come modello

Centenarians as a model to discover genetic and epigenetic signatures of healthy ageing

Annibale Alessandro Puca[a,b,*], Chiara Spinelli[a], Giulia Accardi[c], Francesco Villa[a], Calogero Caruso[c]

[a] Cardiovascular Research Unit, IRCCS MultiMedica, 20138 Milan, Italy
[b] Department of Medicine and Surgery, University of Salerno, 84084 Salerno, Italy
[c] Department of Pathobiology and Medical Biotechnologies, University of Palermo, 90134 Palermo, Italy



As previously stated, phytochemicals are naturally present in all plant foods. Red fruits and vegetables, such as grapes, red, purple and black berries and vegetables of the same colours, such as cabbage, aubergines, and red onion, for example, contain anthocyanins and resveratrol. The resveratrol is a polyphenolic compound. This category of bioactive molecules has antioxidant and anti-inflammatory effects but in a dose-dependent manner. In fact, their bioavailability is low in human but many in vivo and in vitro experiments confirm their role. Resveratrol has been identified as a potent SIRT1 activator, mimicking calorie restriction and extending lifespan from yeast to humans. These effects are mediated by the deacetylase activity of SIRT1 that leads to deacetylation of p53, NF-κB, heat shock factor 1, FOXO 1,3,4 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha, influencing replicative senescence, inflammation, apoptosis, metabolism and stress resistance (Barger et al., 2008; Baur and Sinclair, 2006a, 2006b; Hubbard and Sinclair, 2014; Park et al., 2017).

About anthocyanins, flavonoids with important free radical scavenger properties, it was demonstrated that 3 weeks administration of 300 mg/die decreases the plasma concentrations of several NF-κB-regulated pro-inflammatory mediators (Karlsen et al., 2007; Rea et al., 2016).

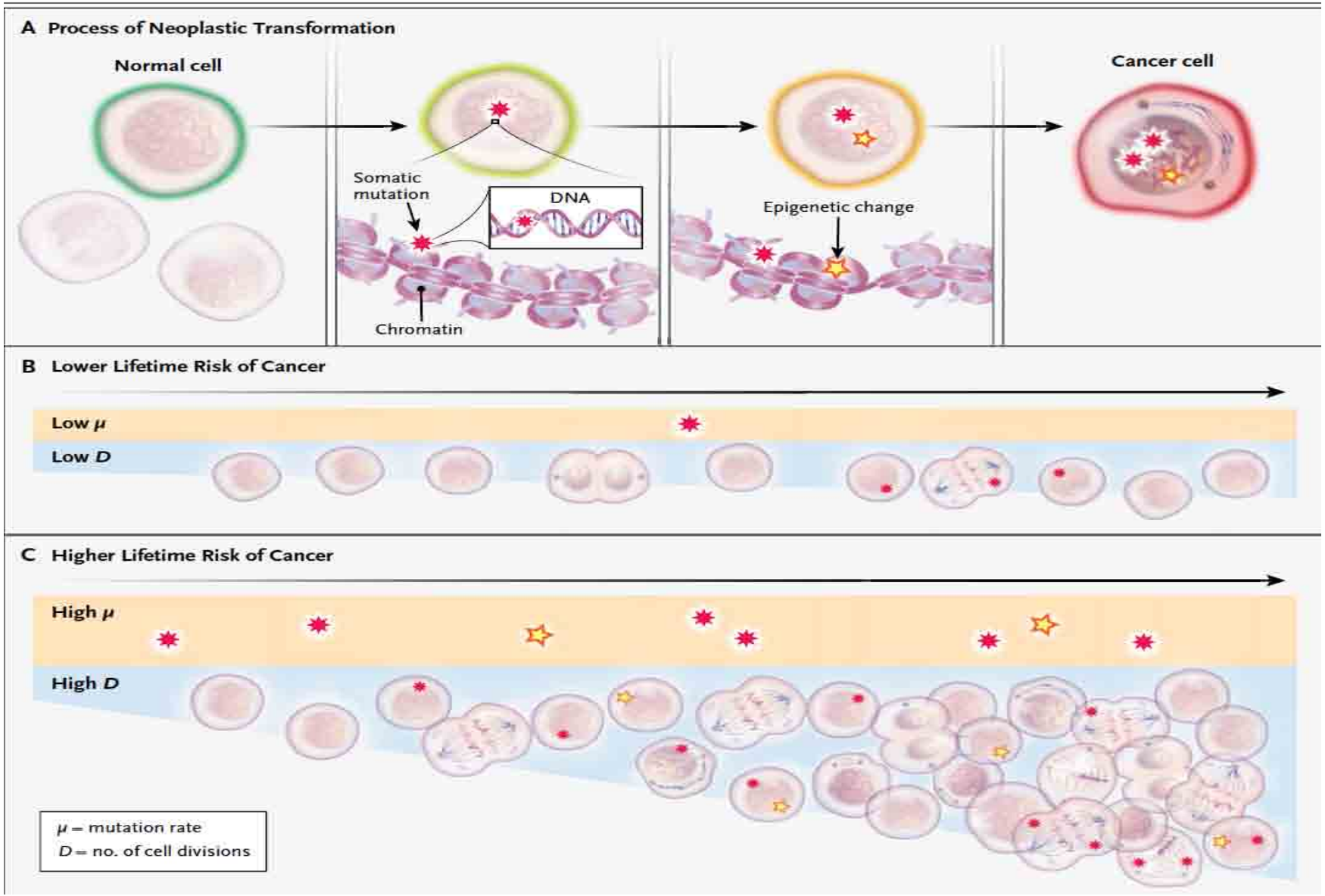
Extra virgin olive oil (EVOO) and curcumin are two other importan epigenetic modulators, although the first one is a cornerstone of dietar habits in Mediterranean basin and the second in Southeast Asia.

EVOO, obtained from olives, is able to modulate ageing process b its multitude of phytochemicals, differently expressed by cultivars o olive trees. It can influence the methylation and acetylation of genes directly or indirectly involved in ageing and metabolic disease (Fernández del Río et al., 2016).

Curcumin, especially the one from *Curcuma longa*, has been ex tensively studied for its properties against brain inflammation an oxidative stress (Davinelli et al., 2016), especially in Alzheimer's dis ease (Davinelli et al., 2014). Is has been proven it inhibits the expres sion of pro-inflammatory mediators by affecting histone acetylation o transcription factors and methylation pattern of gene promoters asso ciated with inflammatory response. DNA methyltransferase, histon deacetylase, histone acetyltransferase inhibitor and microRNA mod ulator are their targets, with a consequent delay of ageing proces (Boyanapalli and Tony Kong, 2015; Kang et al., 2006).

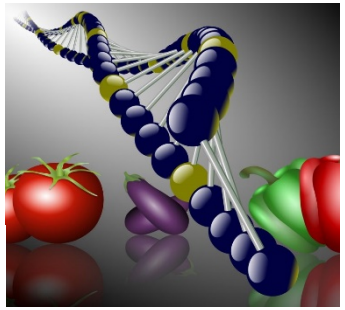
Nutrizione ed epigenetica

Cancro e longevità



Nutrizione ed epigenetica

Cancro e longevità



REVIEW

Epigenetic linkage of aging, cancer and nutrition

Michael Daniel[1] and Trygve O. Tollefsbol[1,2,3,4,5,*]

ABSTRACT

Epigenetic mechanisms play a pivotal role in the expression of genes and can be influenced by both the quality and quantity of diet. Dietary compounds such as sulforaphane (SFN) found in cruciferous vegetables and epigallocatechin-3-gallate (EGCG) in green tea exhibit the ability to affect various epigenetic mechanisms such as DNA methyltransferase (DNMT) inhibition, histone modifications via histone deacetylase (HDAC), histone acetyltransferase (HAT) inhibition, or noncoding RNA expression. Regulation of these epigenetic mechanisms has been shown to have notable influences on the formation and progression of various neoplasms. We have shown that an epigenetic diet can influence both cellular longevity and carcinogenesis through the modulation of certain key genes that encode telomerase and p16. Caloric restriction (CR) can also play a crucial role in aging and cancer. Reductions in caloric intake have been shown to increase both the life- and health-span in a variety of animal models. Moreover, restriction of glucose has been demonstrated to decrease the incidence of age-related diseases such as cancer and diabetes. A diet rich in compounds such as genistein, SFN and EGCG can positively modulate the epigenome and lead to many health benefits. Also, reducing the quantity of calories and glucose in the diet can confer an increased health-span, including reduced cancer incidence.

KEY WORDS: Epigenetics, Diet, Aging, Cancer, Nutrition

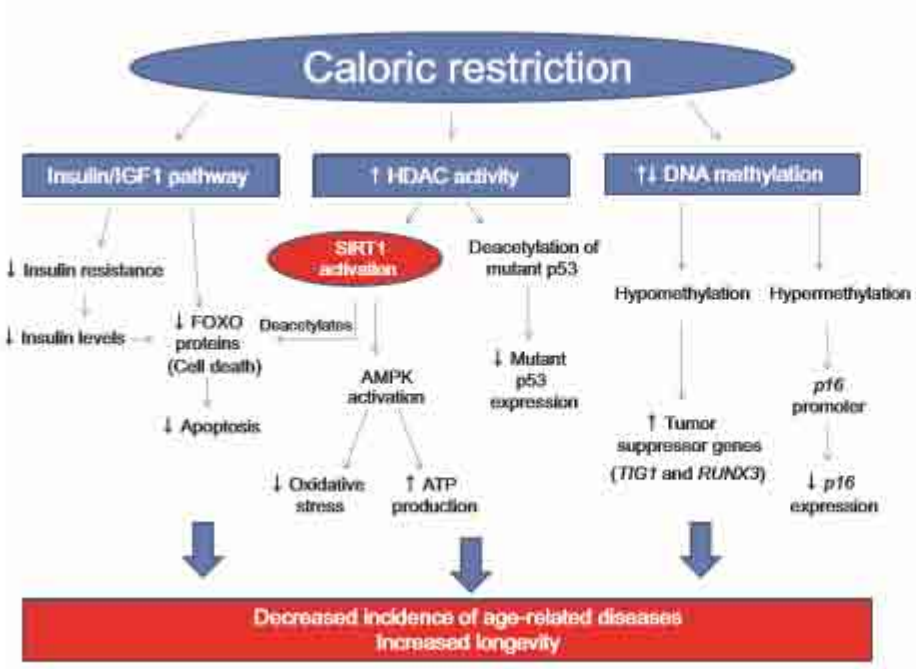


Fig. 1. Effects of caloric restriction on the reduction of age-related diseases and increased longevity. Caloric restriction (CR), at safe levels, has been shown to reduce the onset of various age-related diseases, as well as increase cellular longevity in both *in vivo* and *in vitro* models. CR can act as an activator of SIRT1, which inhibits FOXO proteins, leading to a reduction in apoptosis. Moreover, CR has been characterized as a modulator of aberrant DNA methylation patterns, which are often associated with the aging process. Studies have shown that hypermethylation of the *p16* promoter can be facilitated by CR, causing a notable decrease in *p16* expression and subsequent evasion of cellular senescence.

Nutrizione ed epigenetica

Cancro e longevità

REVIEW

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Epigenetic mechanisms play a pivotal role in the expression of genes and can be influenced by both the quality and quantity of diet. Dietary compounds such as sulforaphane (SFN) found in cruciferous vegetables and epigallocatechin-3-gallate (EGCG) in green tea exhibit the ability to affect various epigenetic mechanisms such as DNA methyltransferase (DNMT) inhibition, histone modifications via histone deacetylase (HDAC), histone acetyltransferase (HAT) inhibition, or noncoding RNA expression. Regulation of these epigenetic mechanisms has been shown to have notable influences on the formation and progression of various neoplasms. We have shown that an epigenetic diet can influence both cellular longevity and carcinogenesis through the modulation of certain key genes that encode telomerase and p16. Caloric restriction (CR) can also play a crucial role in aging and cancer. Reductions in caloric intake have been shown to increase both the life- and health-span in a variety of animal models. Moreover, restriction of glucose has been demonstrated to decrease the incidence of age-related diseases such as cancer and diabetes. A diet rich in compounds such as genistein, SFN and EGCG can positively modulate the epigenome and lead to many health benefits. Also, reducing the quantity of calories and glucose in the diet can confer an increased health-span, including reduced cancer incidence.

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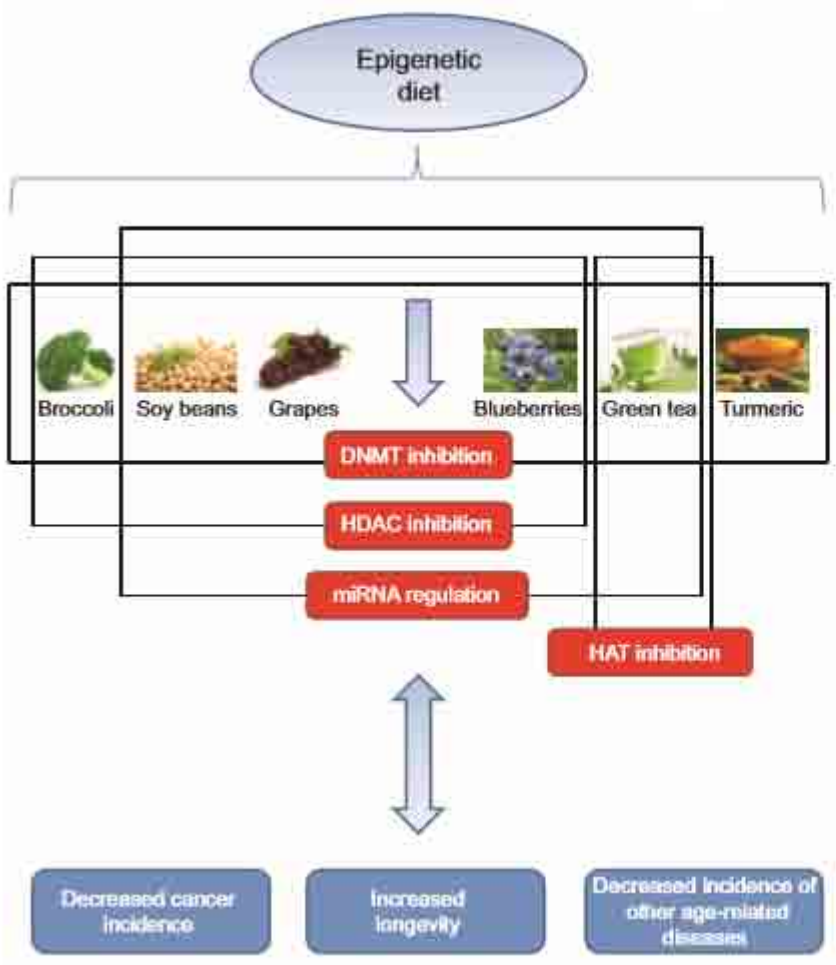

Fig. 3. Effects of an epigenetic diet. Consumption of foods that modulate epigenetic mechanisms has been shown to decrease the incidence of cancer and increase longevity, as well as prevent the onset of other age-related diseases. Cruciferous vegetables, such as broccoli, which are rich in sulforaphane, can act as HDAC inhibitors, regulating certain cancer-related genes. Genistein, which is found in soy beans, also exhibits chemopreventive properties and can result in both the partial reversal of aberrant DNA hypermethylation and the regulation of key miRNAs. Grapes contain resveratrol, a phenol that activates SIRT1 (a known HDAC inhibitor) and increases longevity, mimicking the effects of caloric restriction.

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Mediterranean Diet and Healthy Ageing: A Sicilian Perspective

Sonya Vasto[a, b] Silvio Buscemi[c] Annalisa Barera[d] Marta Di Carlo[a]
Giulia Accardi[d] Calogero Caruso[d]

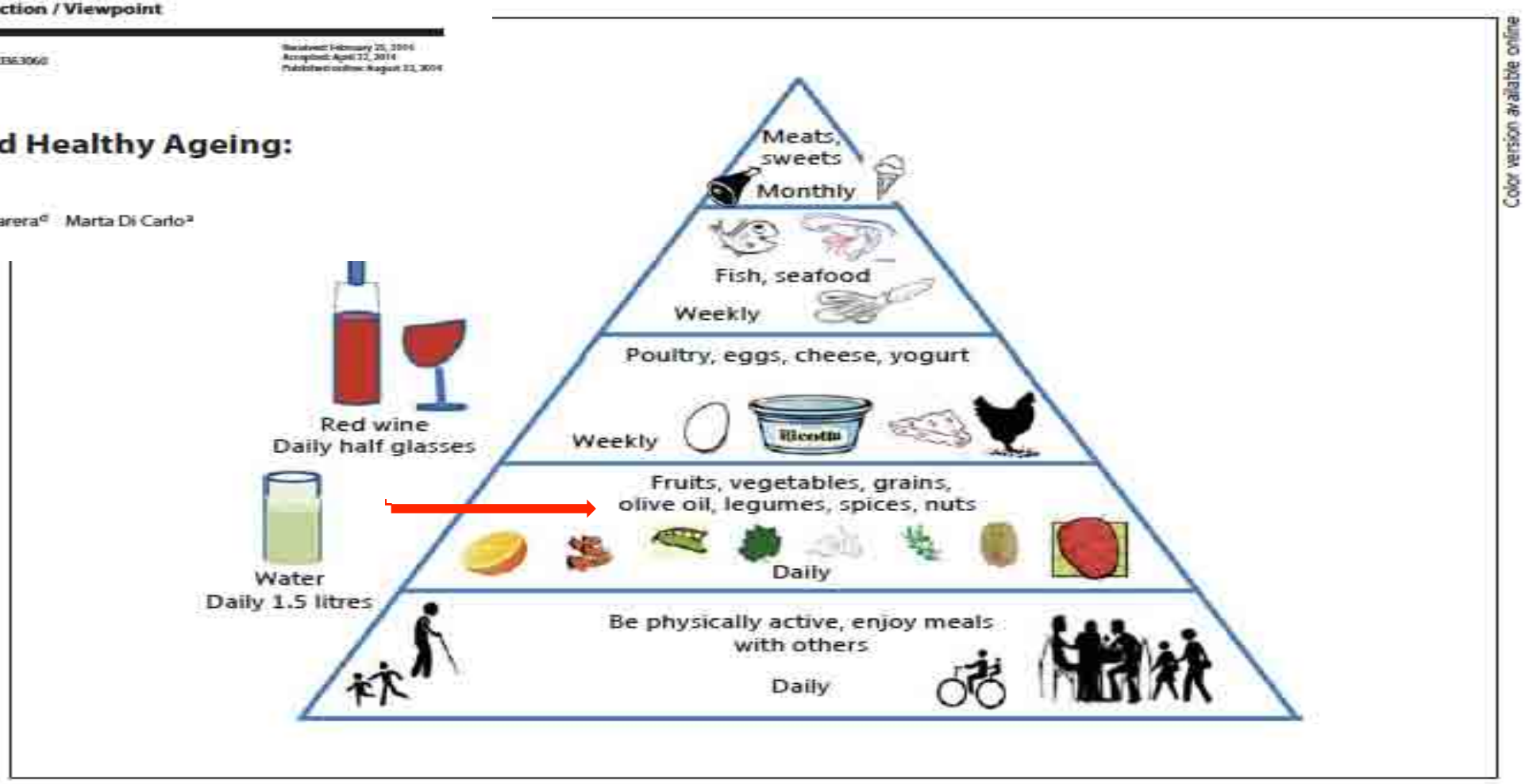

Fig. 1. Pyramid representation of the MedDiet. In this representation, everyday main meals should contain three basic elements: whole-grain cereals, vegetables and fruit. A daily intake of 1.5–2 litres of water should be guaranteed. Dairy products should be preferred in the form of low-fat yogurt, cheese and other fermented ones. In the middle of the pyramid, olive oil is located as the principal source of dietary lipids. A reasonable consumption of olives, nuts and seeds should be chosen for healthy snacks. Furthermore, herbs and spices can contribute either to the regional identities of Mediterranean dishes or to further nutrient supplementation such as 1 or 2 glasses per day of wine at the most,- depending on gender. Every week, a variety of plant and animal origin proteins should be consumed (fish, white meat, eggs, legumes, whereas red meat should be consumed in smaller quantity and frequency). The top of the pyramid is represented by sugar, candies, pastries and sweet beverages such as sweet fruit juices and soft drinks that should be consumed occasionally and in small amounts. However, all portion sizes should be based on frugality in order to adopt a healthy lifestyle. So, at the bottom we find foods that should sustain the diet, and at the upper levels foods to be eaten in moderate amounts (i.e. daily, weekly or less frequently), reported according to nutritional habits of the Sicilian countryside (references in the text).

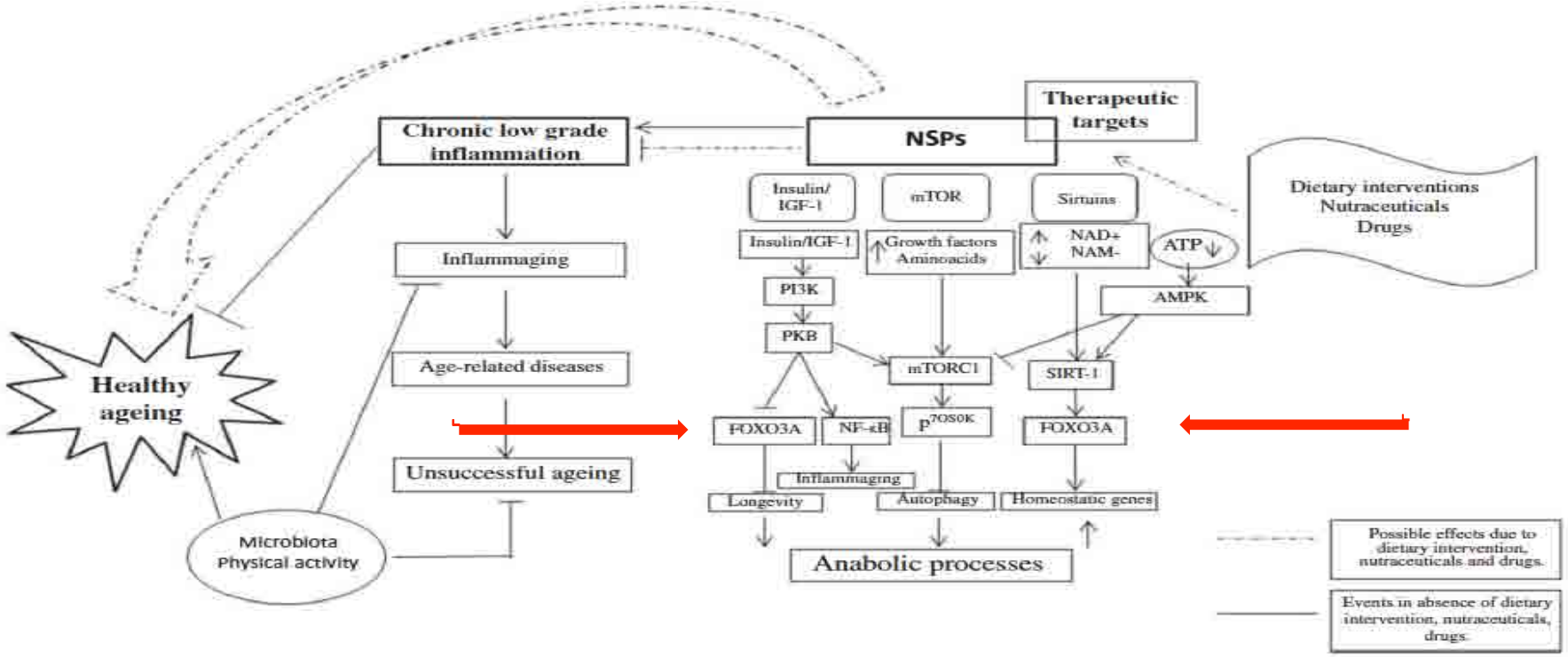

Figure 1. Overview on NSPs and their role in healthy ageing.
The figure shows molecular events involved in insulin/IGF-1, mTOR and sirtuin pathways, known as NSPs, and the possible effects due to their modulation by dietary interventions, nutraceuticals, and drugs. These act inhibiting insulin/IGF-1 and mTOR pathways and increasing that of sirtuins, favouring longevity, autophagy and the activation of the homeostatic genes, and reducing inflammation and anabolic processes. Microbiota and physical activity are external factors that influence successful ageing, through inflammation control. See the text for the acronyms.

Moreover, currently available evidence suggests that anabolic signalling accelerates ageing and age-related diseases, whereas decreased nutrient signalling extends survival and longevity. The process is, at least in part, linked to the modulation of downstream nutrient sensing pathways (NSPs), such as the activation of forkhead box O (FOXO) 3A or the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). The activation of the former counteracts the oxidative stress through the transcriptional activation of homeostatic genes. The inhibition of the latter one switches off the transcription of inflammatory genes, thus slowing down the inflammaging process.

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REVIEW

Nutrient sensing pathways as therapeutic targets for healthy ageing

Anna Aiello[a], Giulia Accardi[a], Giuseppina Candore[a], Caterina Maria Gambino[a], Mario Mirisola[b], Giusi Taormina[b], Claudia Virruso[b] and Calogero Caruso[a]

[a]Department of Pathobiology and Medical Biotechnologies, University of Palermo, Palermo, Italy; [b]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy

ABSTRACT

Introduction: In the present paper, the authors have discussed anti-aging strategies which aim to slow the aging process and to delay the onset of age-related diseases, focusing on nutrient sensing pathways (NSPs) as therapeutic targets. Indeed, several studies have already demonstrated that both in animal models and humans, dietary interventions might have a positive impact on the aging process through the modulation of these pathways.

Areas covered: Achieving healthy aging is the main challenge of the twenty-first century because lifespan is increasing, but not in tandem with good health. The authors have illustrated different approaches that can act on NSPs, modulating the rate of the aging process.

Expert opinion: Humanity's lasting dream is to reverse or, at least, postpone aging. In recent years, increasing attention has been devoted to anti-aging therapies. The subject is very popular among the general public, whose imagination runs wild with all the possible tools to delay aging and to gain immortality. Some approaches discussed in the present review should be able to substantially slow down the aging process, extending our productive, youthful lives, without frailty.

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The Blue Zones: areas of exceptional longevity around the world

*Michel Poulain, Anne Herm and Gianni Pes**

Gruppo di ricerca di Invecchiamento e Immunosenescenza

ITALIAN CHAPTER

+39 091 6555903

centenari@unipa.it

centenari.unipa

facebook.com/centenariedietamediterranea

- Prof. Calogero Caruso
- Prof.ssa Giuseppina Candore
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