Ambiente e modificazioni epigenetiche

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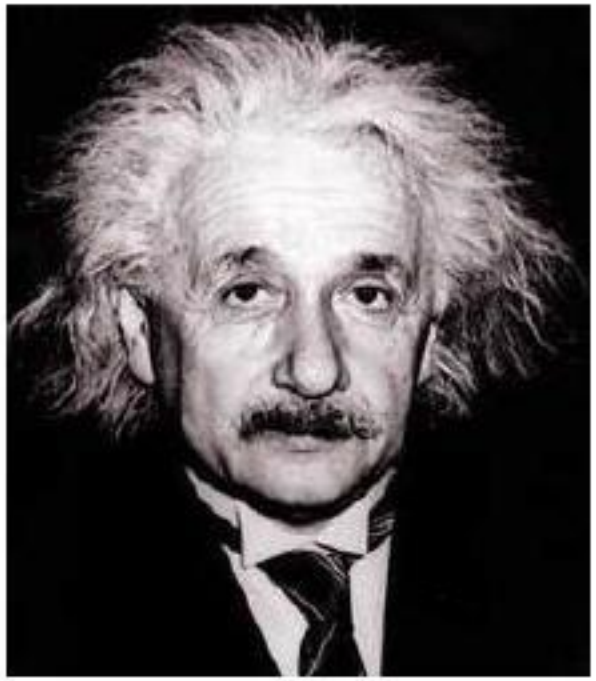


~21000 geni

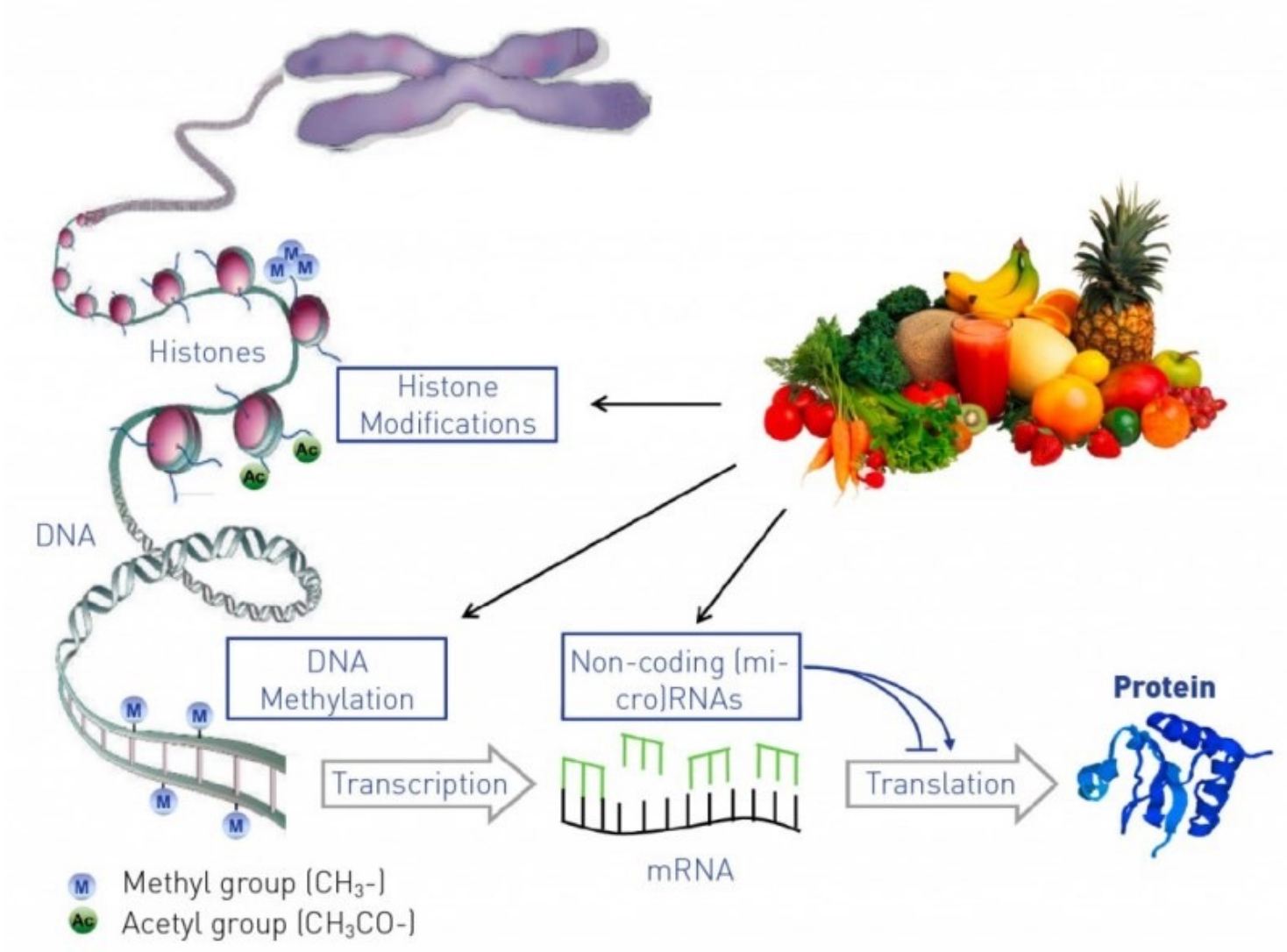
~25000 geni

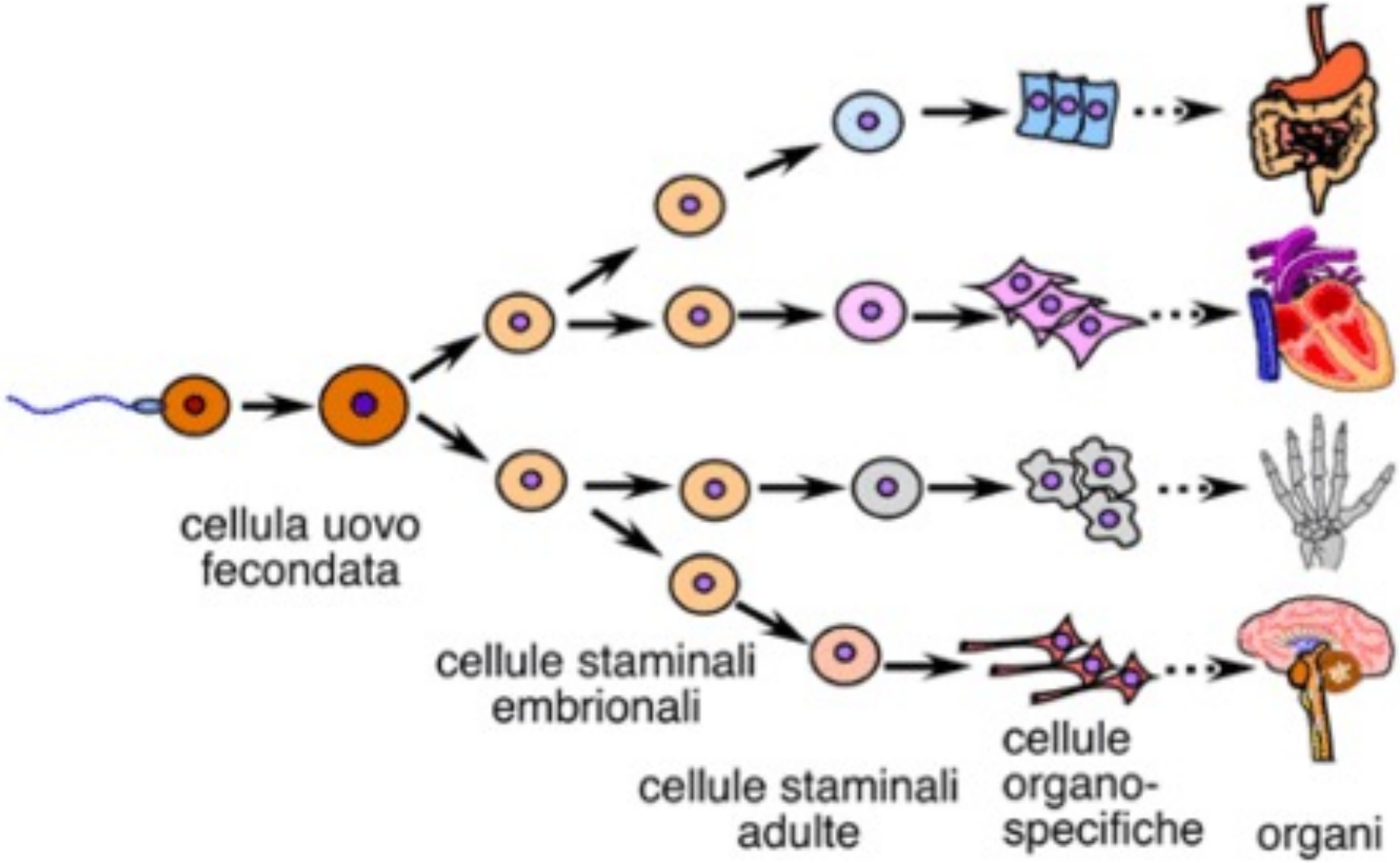
~60000 geni

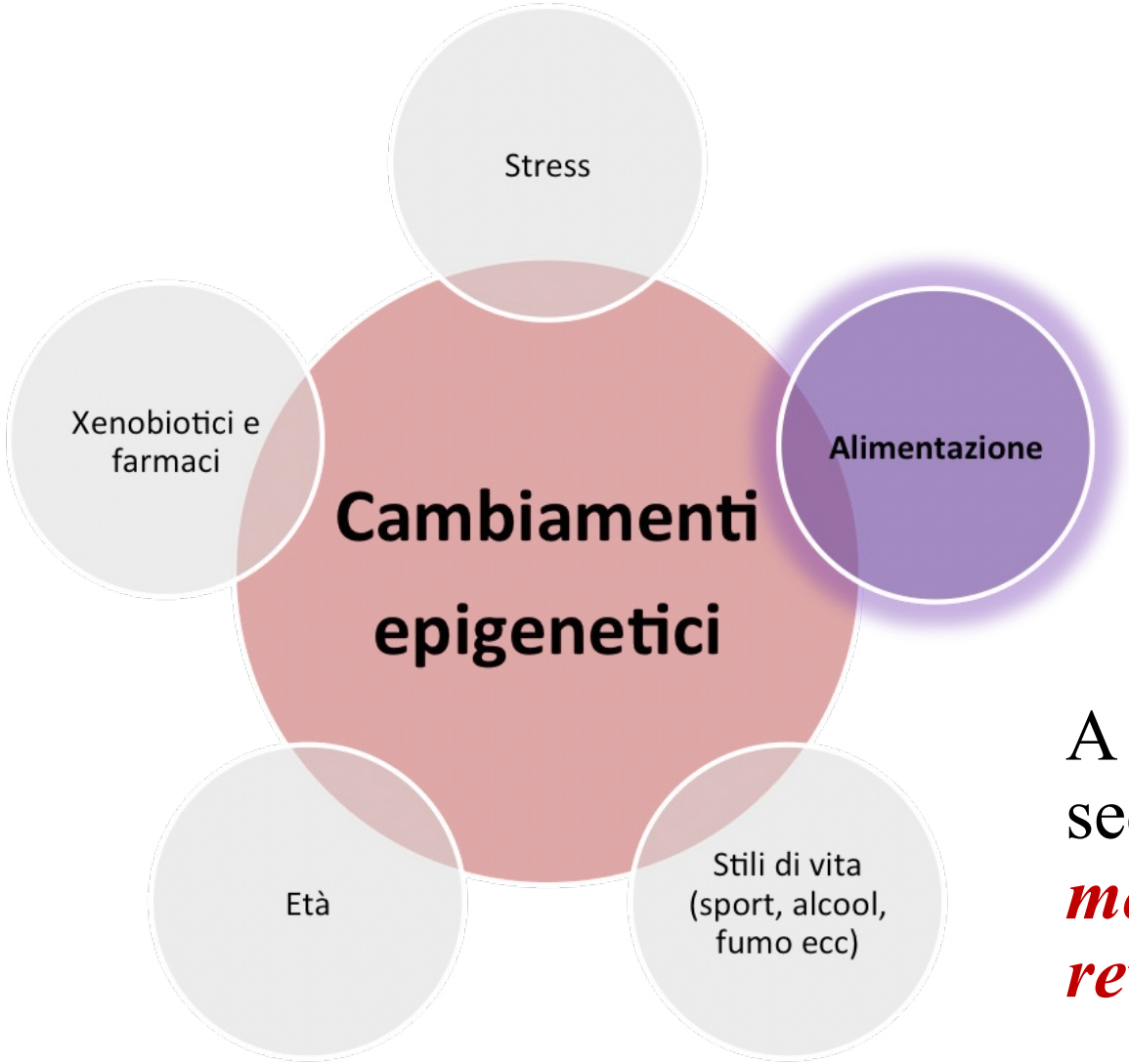
2003: conclusione progetto genoma.

La complessità dell'organismo non dipende dal numero dei geni

1942-Conrad Waddington




cellula uovo fecondata
cellule staminali embrionali
cellule staminali adulte
cellule organo-specifiche
organi



A differenza delle mutazioni nella sequenza del DNA le ***modificazioni epigenetiche sono reversibili***.

Le api operaie o regine hanno genotipo identico ma **fenotipo diverso**

Le larve delle future regine mangiano sempre **pappa reale**

La pappa reale "spegne" il gene della DNMT che metila il DNA

Le larve delle future operaie mangiano **pappa reale** soltanto nei **primi 2 giorni** di vita

Quando la larva è nutrita con pappa reale, la DNMT è silenziata e non può metilare alcuni **geni legati alla fertilità**, che quindi rimangono **attivi** per diventare la larva **regina**

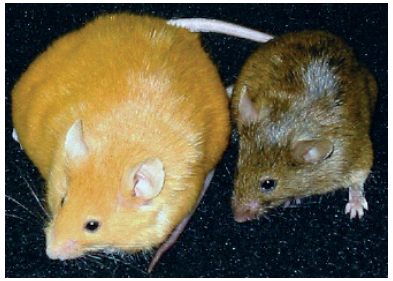
 → DNMT Gene attivo

Quando la larva non si nutre con pappa reale, la DNMT rimane attiva e metila i **geni** che caratterizzano la regina, **silenziandoli**, e la larva svilupperà come **ape operaia**

 → DNMT Gene inattivo

Nei roditori Agouti il colore del pelo può essere marrone o giallo

Madri nutrite normalmente



Madri nutrite con supplementi a base di **acido folico o vitamina B12**

L'acido folico e la vitamina B12 sono donatori di gruppi metile

Il **gene *agouti*** che definisce il colore del pelo e l'obesità del topo risulta **poco metilato.**

Progenie con pelo di colore giallo e obesa

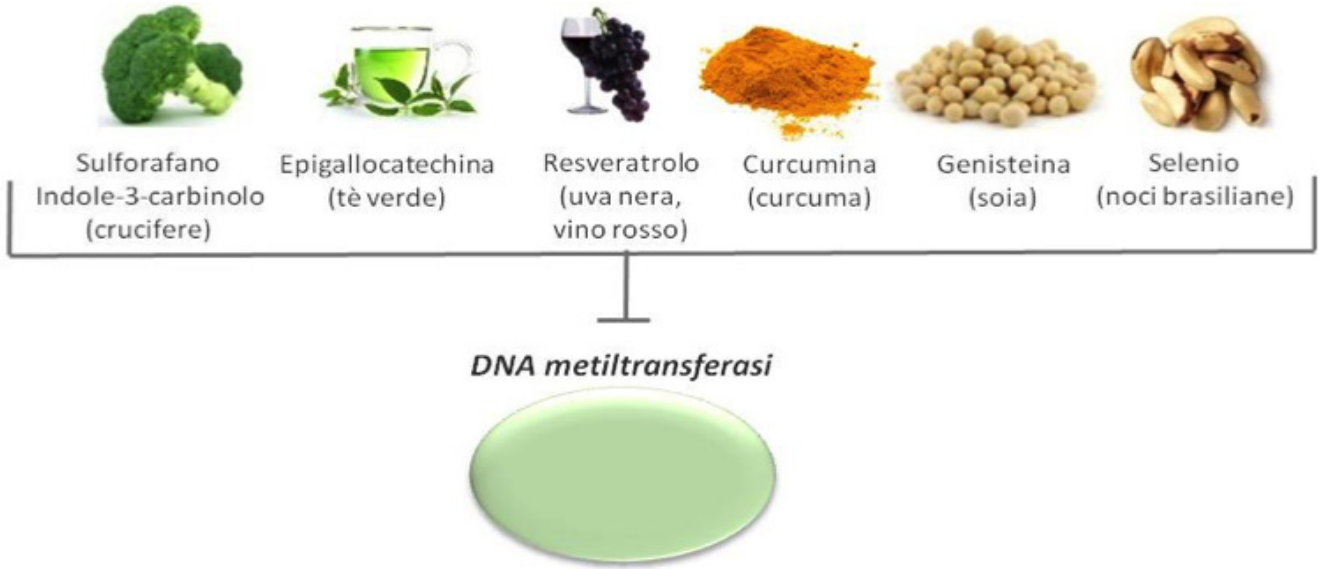
La supplementazione fa sì che il **gene *agouti*** sia **più metilato**.

Progenie con pelo di colore marrone e magra

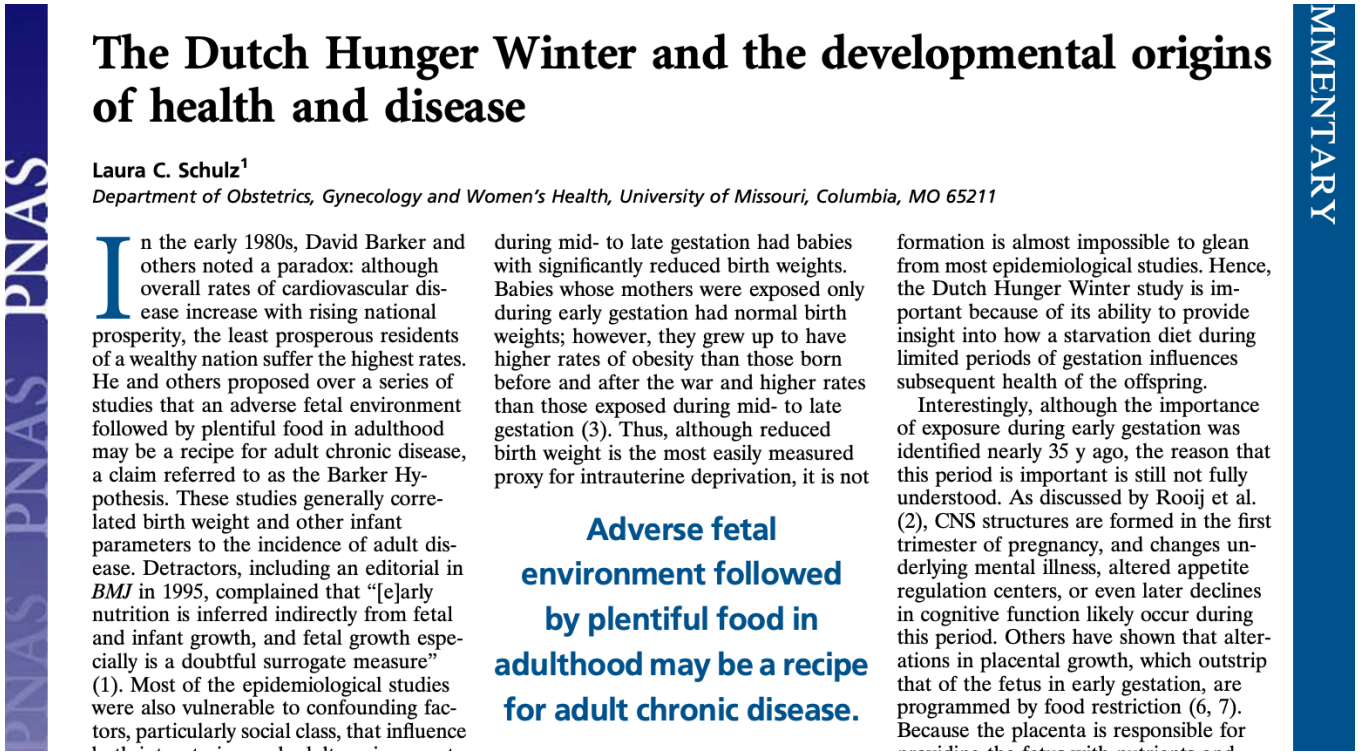
Agiscono INDIRETTAMENTE
attraverso l'alterazione della disponibilità di **substrati**

	NUTRIENTI	AZIONE
Vitamine del gruppo B	Acido folico (B9)	Accettore e donatore di metili nel metabolismo 1-C
	Cobalammina (B12)	Cofattore per MS
	Piridossina (B6)	Cofattore per SHMT, CBS
	Riboflvina (B2)	Cofattore per MTHFR
Molecole donatrici di metili	Metionina	Precursore di SAM
	Colina	Rimetilazione dell'omocisteine da parte di BHMT
	Betaina	Rimetilazione dell'omocisteine da parte di BHMT
	Serina	Donatore di metili al tetraidrofolato da parte di SHMT
Micronutrienti	Zinco	Cofattore per BHMT

Agiscono DIRETTAMENTE
sull'enzima DNA-metiltransferasi



Olanda, II guerra mondiale: I figli dell' "*inverno di fame*"



PNAS PNAS

The Dutch Hunger Winter and the developmental origins of health and disease

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In the early 1980s, David Barker and others noted a paradox: although overall rates of cardiovascular disease increase with rising national prosperity, the least prosperous residents of a wealthy nation suffer the highest rates. He and others proposed over a series of studies that an adverse fetal environment followed by plentiful food in adulthood may be a recipe for adult chronic disease, a claim referred to as the Barker Hypothesis. These studies generally correlated birth weight and other infant parameters to the incidence of adult disease. Detractors, including an editorial in *BMJ* in 1995, complained that "[e]arly nutrition is inferred indirectly from fetal and infant growth, and fetal growth especially is a doubtful surrogate measure" (1). Most of the epidemiological studies were also vulnerable to confounding factors, particularly social class, that influence

during mid- to late gestation had babies with significantly reduced birth weights. Babies whose mothers were exposed only during early gestation had normal birth weights; however, they grew up to have higher rates of obesity than those born before and after the war and higher rates than those exposed during mid- to late gestation (3). Thus, although reduced birth weight is the most easily measured proxy for intrauterine deprivation, it is not

Adverse fetal environment followed by plentiful food in adulthood may be a recipe for adult chronic disease.

formation is almost impossible to glean from most epidemiological studies. Hence, the Dutch Hunger Winter study is important because of its ability to provide insight into how a starvation diet during limited periods of gestation influences subsequent health of the offspring.

Interestingly, although the importance of exposure during early gestation was identified nearly 35 y ago, the reason that this period is important is still not fully understood. As discussed by Rooij et al. (2), CNS structures are formed in the first trimester of pregnancy, and changes underlying mental illness, altered appetite regulation centers, or even later declines in cognitive function likely occur during this period. Others have shown that alterations in placental growth, which outstrip that of the fetus in early gestation, are programmed by food restriction (6, 7). Because the placenta is responsible for

MMENTARY

I figli, nati sottopeso, da adulti presentavano disturbi psichiatrici, diabete, obesità e problemi cardiovascolari. Presenza di minore metilazione del gene che comanda la sintesi di IGF2.

La presenza di inquinamento ambientale aumenta il rischio di sviluppare allergia anche mediante alterazioni epigenetiche.

«Polycyclic aromatic hydrocarbons exposure has been shown to be associated with higher DNA methylation at several CpG sites within the *FOXP3* locus of peripheral blood mononuclear cells derived Treg cells, with the effect being more pronounced in asthmatic than in non-asthmatic children»
(Hew KM, Walker AI, Kohli A et al. Clin. Exp. Allergy 45(1), 238–248 (2015)

«Increased DNA methylation in response to traffic-related air pollution exposure was observed»
(Somineni HK, Zhang X, Biagini Myers JM et al. J. Allergy Clin. Immunol. 137(3), 797–805, e795 (2016).