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Obesity and diabetes: from genetics to epigenetics

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Abstract Obesity is becoming an epidemic health problem. During the last years not only genetic but also, and primarily, environmental factors have been supposed to contribute to the susceptibility to weight gain or to develop complications such as type 2 diabetes. In spite of the intense efforts to identify genetic predisposing variants, progress has been slow and success limited, and the common obesity susceptibility variants identified only explains a small part of the individual variation in risk. Moreover, there is evidence that the current epidemic of obesity and diabetes is environment-driven. Recent studies indicate that normal metabolic regulation during adulthood besides requiring a good balance between energy intake and energy expenditure, can be also affected by pre- and post-natal environments. In fact, maternal nutritional constraint during pregnancy can alter the metabolic phenotype of the offspring by means of epigenetic regulation of specific genes, and this can be passed to the next generations. Studies focused on epigenetic marks in obesity found altered methylation and/or histone acetylation levels in genes involved in specific but also in more general metabolic processes. Recent researches point out the continuous increase of "obesogens", in the environment and food chains, above all endocrine disruptors, chemicals that interfere with many homeostatic mechanisms. Taken into account the already existing data on the effects of obesogens, and the multiple potential targets with which they might interfere daily, it seems likely that the exposure to obesogens can have an important role in the obesity and diabesity pandemic.

Keywords Obesity · Diabetes · Genetics · Epigenetics · Obesogens

Introduction

It has been estimated that 2.8 million people die each year worldwide, as a consequence of being overweight (including obesity); an estimated 205 million men and 297 million women over 20 years were obese in 2008 [1]. Above all, the worldwide prevalence of obesity almost doubled between 1980 and 2008 [1].

If the current worldwide trends continue, the number of overweight individuals is expected to increase from 1.3 billion in 2005 to about 2.0 billion by 2030 [2]. Alarmingly, similar trends are also evident in children, and predictive models suggest that the number of obese children will continue to increase in the future. If the current situation persists, without any specific measure is taken, the number of overweight children in the European Union is expected to enhance by 1.3 million per year, and >300,000 of them would become obese each year [3].

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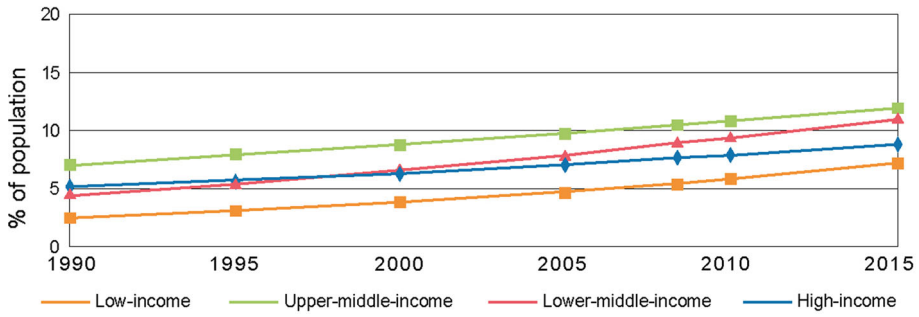

Fig. 1 Infant and young child overweight trends from 1990 to 2015, by World Bank income group (Adapted from WHO, 2010)

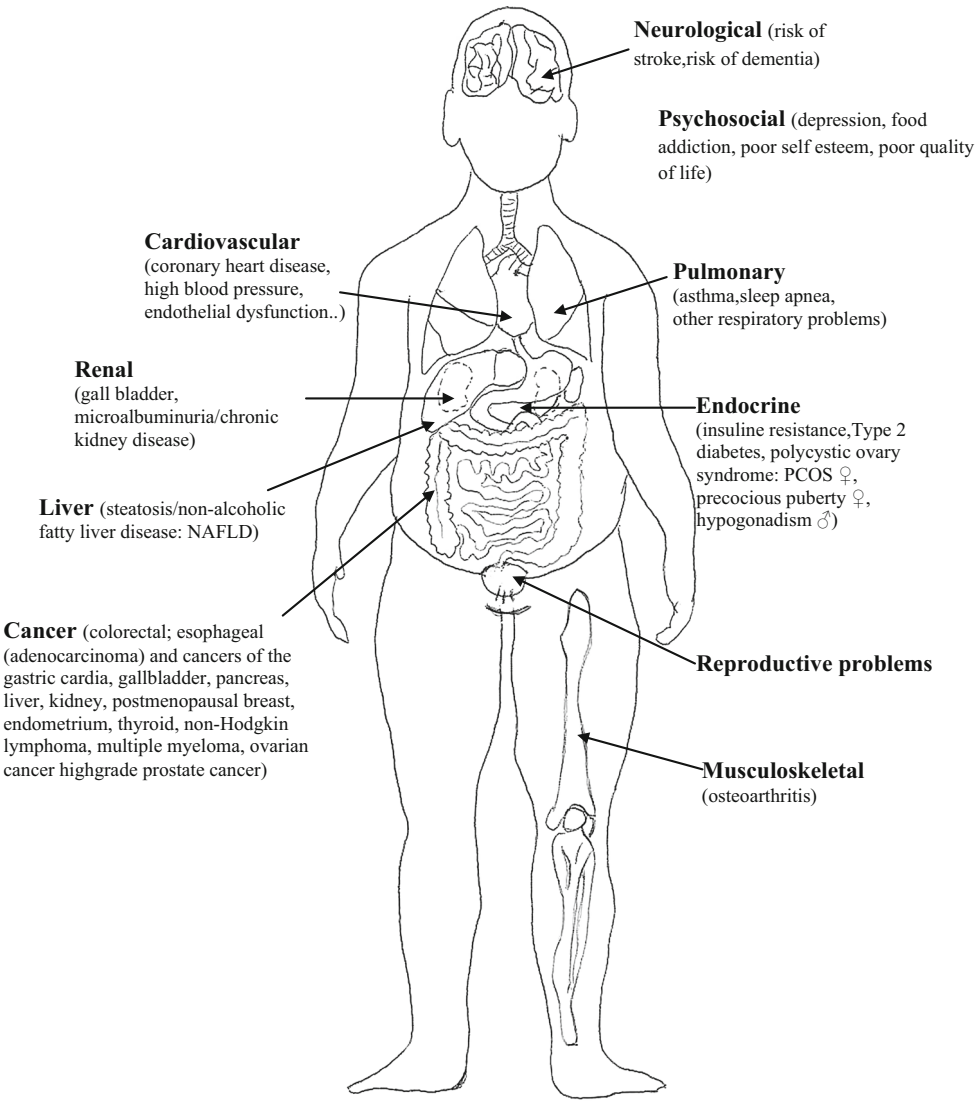

Fig. 2 Possible consequences of obesity

The problem has also begun to affect the populations of the developing countries. For example, in China the prevalence of overweight individuals doubled in women and nearly tripled in men in the period from 1989 to 1997 [4], with an increase of obesity prevalence in a relatively short period: from 1 % in 1,000 it has gone to 4 % in 2,000 with a dramatic increase in diabetes prevalence within a rather short time: in 1980 less than 1 % Chinese adults were obese, whilst in 2008 the proportion rose to 10 % [5].

Within different Countries obesity prevalence varies among socioeconomic groups.

The fastest rise in overweight among infants and young children in the last decades is in lower-middle-income countries, as shown in Fig. 1.

The actual problem, that we should try to better understand, is: what are the causes of such a huge epidemiological change, recently defined in terms of *quasi infectious* pandemic? Indeed some authors acknowledged that the current epidemic of obesity should be more properly considered as a *communicable* rather than *non-communicable* process: a "*socially contagious feature of globalization*" [6]. Others have pointed out that, in terms of evolutionary change, this is the first time that an entire species faces a dramatic change of its phenotype [7].

Obese adults are also at risk for a number of chronic diseases, including type 2 diabetes (T2D), insulin resistance, coronary heart disease, stroke, high blood pressure, asthma, liver and pulmonary problems, gall bladder and kidney disease, osteoarthritis, reproductive problems and also cancer of breast, kidney, colorectum, endometrium, oesophagus and pancreas [8, 9] and the list continues to grow [10] (see Fig. 2).

Metabolic syndrome, defined by a combination of disturbed glucose and insulin metabolism, central obesity, dyslipidemia and hypertension, is considered to be a risk factor for T2D and cardiovascular disease. Indeed T2D, previously considered a disease with adult onset, has risen sharply in children and young people simultaneously with the increase in obesity.

In the past decades obesity has been considered as the consequence of lack of balance between energy intake and expenditure, addressed by modified life styles including an increased consumption of high-caloric food and reduced energy consumption. From an evolutionary perspective the current pandemic should be essentially ascribed to the current adoption of a sedentary lifestyle, coupled with the easier access to high-caloric food [11]. These features accompanied the past decades with unprecedented transitions in our lifestyle: for the first time in human history, the number of obese and overweight people surpassed the number of those who are underweight [12].

Even if this basic concept retains its validity, it is increasingly evident that obesity cannot be simply explained as the result of an excessive intake of high caloric food and lack of exercise, but a systemic, immuno-neuro-endocrine and inflammatory disease resulting from a sustained disturbance in the energy metabolism regulation that favours triglyceride storage and hypertrophy of adipocytes [13, 14]. It is well known that food consumption, energy expenditure and body fat mass are homeostatically regulated. Key brain regions, including the hypothalamus and brainstem are continuously kept informed on the current state of energy balance by central and peripheral signals, which include neural and hormonal messages from the gut. Hunger and satiety are in turn coordinated responses to these signals [15]. In this context research has offered, in recent years, the most significant results, demonstrating that the accumulation and the mobilization of fat from adipose depots depends on complex hormonal circuits, glucose levels, basal metabolic rate, metabolic set points as well as on the abundance, size and metabolic activity of adipocytes [16].

This altered metabolic regulation ultimately leads to an increase in food intake, adipose tissue hyperplasia (increase in the number of cells) and/or hypertrophy (increase in cell size) [17], increased triglyceride storage. A whole series of "obesogens"—i.e. of molecules (especially *endocrine disruptors, EDC*) scattered in food chains—could interfere with this very complex and fine tuned circuits, altering the regulation of energy balance and favouring weight gain and obesity [18].

Genetic factors in obesity and diabetes

The genetic contribution to obesity and diabetes has been demonstrated by means of linkage analysis, twin, and adoption studies [19]. Twin studies allowed to show that genetic factors explain 40–80 % of the variance in body mass index (BMI) and in risk of obesity [20], while lower heritability values have been reported for family (20–50 %) [21] and adoption (20–60 %) [22, 23] studies. The greater concordance found in monozygotic twins for T2D (50–70 %) in comparison with dizygotic twins (20–37 %) supports a genetic contribution to this condition [24]. Studies on family history of T2D provide some evidence of a genetic component: while the lifetime risk of developing T2D is 7 % in the general population, in individuals who had one parent with T2D the risk increases of four- to six fold and tenfold if both parents had diabetes [25]. Anyway it has been recently pointed out that in T2D, our knowledge about the environmental factors (obesity, sedentary lifestyle) is much greater than the understanding of the underlying genetic factors, while our knowledge about the genes is clearly better for T1D, given the strong contribution of mutations found in the HLA region in this last case [26].

During the 90s obesity has been recognised as a complex, chronic disorder with a multifactorial etiology, stemming from a web of genetic, epigenetic, social, cultural, behavioural, physiologic, metabolic and environmental factors. As mentioned earlier the conventional theory holds that obesity is the result of a positive energy balance, due to increased high caloric food intake combined with a sedentary lifestyle superimposed on a background of genetic predisposition for the disease.

Nevertheless, albeit much attention has been paid on these factors, including the advices to take care of our diet by consuming healthy foods and to introduce more exercise into our lifestyle, these factors cannot alone explain the dramatic expansion of obesity [27].

Up to 1990s, adipocytes were considered as a sort of storage depots for the metabolic fuel in excess. But following the discovery of "leptin", an hormone derived from adipocytes [28] that informs about energy reserve other organs of the body including the central nervous system, these "fat storage cells" actually are believed to function as a major endocrine organ [29], producing hormones such as leptin, resistin, estrogens, and the cytokine TNFα [30].

The identification of the hypothalamic leptin-melanocortin signalling pathway as a critical regulator in energy homeostasis and food intake [31] has been essential for genetic research. Novel loci or DNA sequences from this pathway potentially involved in the onset of obesity have been recently discovered by mutation analysis, candidate gene and genome-wide association studies (GWAS), as well as copy number analysis. Their role in monogenic and complex forms of obesity is becoming more and more clear. In few years, 52 genetic loci were identified to be associated with obesity related traits [32].

Monogenic forms of obesity are due to mutations in single genes. To date, eight well-established monogenic obesity genes have been identified: leptin (*LEP*), leptin receptor (*LEPR*), brain-derived neurotrophic factor (*BDNF*), proopiomelanocortin (*POMC),* single-minded homologue 1 (*SIM1*), and neurotrophic tyrosine kinase receptor type 2 (*NTRK2*). Mutations in these eight genes are causative of early onset forms of obesity and hyperphagia and likely account for about 10 % of severely obese children [33]. The first single nucleotide polymorphism (SNP) identified in 2007 as significatively associated with increased BMI was found in a gene with at the time unknown function [34]. Subsequently the gene has been named *FTO;* it was found to be associated to fat mass and obesity and to affect obesity by regulating appetite; its involvement has been repeatedly confirmed in several ethnicities [35].

A recent study has shown the expression of fourteen probably causative genes for obesity (*FTO*, *MC4R*, *BDNF*, *NRXN3*, *ETV5*, *MTCH2*, *SEC16B*, *TFAP2B*, *TMEM18*, *KCTD15*, *NEGR1*, *GNPDA2*, *FAIM2*, and *LYPLAL1*) in the hypothalamus of obese and lean rats, this supports for a potential central effect of these genes on energy homeostasis [36]. Moreover the role of the genes involved in the central regulation of food intake in obesity predisposition has been reinforced by the finding that three obesity susceptibility loci are located near genes (*MC4R*, *SH2B1*, and *BDNF*) that have already been demonstrated to carry mutations disrupting hypothalamic functions and leading to monogenic forms of early-onset obesity with hyperphagia.

In a GWAS study on copy number variations (CNV), a type of mutation which has often been overlooked in previous surveys of mutations that cause genetic diseases [37], individuals with extreme phenotypes were found to carry a number of large and rare CNVs (in particular deletions on chromosome 16p11.2): besides developmental delay, this was also associated to obesity [38]. The search for CNVs in the context of obesity has proved interesting since in the last years other CNVs have been identified, in particular in relation to ethnicity [39].

Increasing evidence supports a role for haploinsufficiency of the gene *SH2B1* in the obesity of patients carrying the 220 kb deletion: this gene encodes an adaptor protein involved in the leptin and insulin signalling [33]. To date, about 150 genetic loci identified in GWASs are linked with obesity and T2D, each accounting for only a small portion of the predicted heritability [40, 41]. This suggests that heritability is not completely attributable to genetic variants [41].

Many GWAS publications on obesity and metabolic syndrome, including a few meta-analyses, have been recently published [32, 35, 42]. A huge number of SNPs derived from studies focused on BMI, extreme and early onset obesity, metabolic syndrome, waist circumference and waist/hip ratio, fat mass, metabolic syndrome is now available. Most of the reported SNPs are located in regions with many genes, sometimes including a specific gene related to obesity (e.g. *MC4R* and *POMC*). Several of the likely causal genes in the predisposition to obesity are highly expressed or known to act inside the central nervous system (CNS) and thus are thought to be involved in obesity susceptibility via CNS mediated effects [43]. Many low penetrance genes which confer susceptibility for human obesity likely act primarily on the central regulation of food intake. The genes nearest the lead SNPs in a recent GWAS on BMI showed high expression in the hypothalamus, which is central to appetite regulation [44]. Other Authors found SNPs in pathways related to many neuronal processes, and also to regulation of cellular metabolism and growth [45]. However in the majority of the QTL associated with obesity, genes have not been completely identified, and the activity of the most involved genes are not well defined [35].

Although GWAS represent an invaluable tool for the identification of genetic loci affecting complex phenotypes, having already identified many regions in the genome that are associated with obesity, in general we can say that hundreds of loci are involved in both common and rare variants, which contribute to a specific phenotypic trait for a small amount [35].

Beyond genetics

Although the approaches through family, twins and adoption studies, described in the previous paragraph, led to the

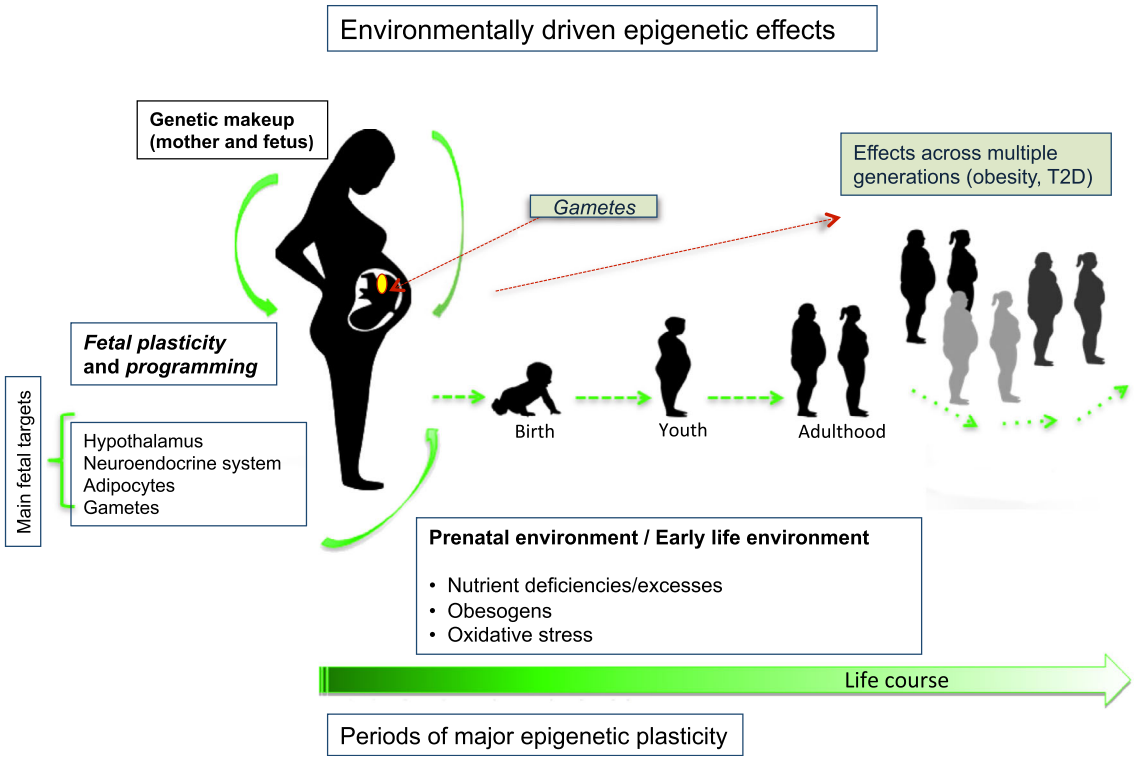

Fig. 3 Importance of environmentally driven epigenetic effects during life course and consequences across generations

identification of some causal genes in monogenic disorders, the GWAS approach was less fruitful in identifying the fundamental genes in complex diseases and in particular in common forms of obesity. As a general rule, genetic studies have been able to explain a definite portion of heritability. GWAS studies have identified a high number of genetic polymorphisms associated with complex human diseases and traits, and have provided valuable information into their genetic structure. Yet the majority of variants identified confer relatively small increments in risk, or even in protection and explain only a small portion of familial clustering, leaving the question of "missing heritability" still unexplained [26, 46].

On the other hand claiming that the origins of the pandemic of *obesity* and *diabesity* [47] are mainly due to genetic causes seems to be implausible: the human genome cannot be changed by mutations in so few years. According to the new perspectives, obesity and its related complications are associated with other factors such as environmental pollutants (obesogens), gut microbiota and specific nutrients, which can increase susceptibility to weight-gain and to other metabolic consequences through epigenetic changes.

Epigenetic studies have offered in recent years precious and perhaps decisive tools for the understanding of the worldwide spread of the pandemic of obesity and diabesity. We are just beginning to understand the way by which the "information" coming from the environment-signals coming from the uterine microenvironment, chemicals stored in maternal tissues-early (mal) nutrition and maternal prenatal stress may induce changes in the embryo-fetal epigenome, for better programming organs and tissues to meet the challenges of post-natal life (see Fig. 3). Thanks to epigenetics many pathogenic pathways described in the second half of the last century are starting to be elucidated throughout molecular mechanisms [48].

The first who tried to explain in terms of evolutionary adaptation the increase in obesity recorded in the second half of the last century, was the American geneticist J. Neel, who proposed the "*thrifty genotype*" hypothesis. According to this hypothesis during the course of human evolution certain genes, who enabled individuals to efficiently collect and process food and deposit fat during periods of food abundance, would have acquired an important role for survival in adverse nutritional conditions. Predictably such *'thrifty genes'* (whose identity was never possible to define) would be "rendered detrimental by progress" [49].

In other words, and to better clarify their possible role in the rapid spread of obesity and T2D, in conditions of relative lack of food, such as those of our ancestors, a *thrifty genotype* would have been selected that would allow to extract the calories required for survival and to reduce the utilization of glucose by peripheral tissues, establishing in

them a temporary condition of insulin resistance, to protect the vital organs (heart and brain). During periods of relative abundance, the production of specific molecules (adipokines) would facilitate the formation of fatty deposits, to be used in times of famine. Today, at least in more "developed" societies in which the diet tends to be high-caloric, high fat, such a genetic constitution would prove counterproductive, favoring the onset of obesity, stable insulin resistance, T2D.

Neel's theory was clearly simplistic and was widely criticized. The assumption that famines were common and severe enough to select for thrifty gene during the 2.5 million years of human paleolithic era was criticized by some anthropological evidence. In fact many of the populations that later developed high levels of obesity and diabetes seemed to have no clear history of famine or starvation; the modern hunter-gatherers do not deposit large fat stores in the periods between famines [50, 51].

Above all, once again, it is obvious that the genetic constitution of an entire species, cannot change in a few years. According to Neel the favorable genotypes in ancestral times were positively selected over millions of years (starting from primates), and the transformations of culture and especially of diet went too quickly to let human biology and especially its genetic constitution to adapt. Yet, even if the specific mechanisms proposed by Neel have been refuted, his basic assumption remains meaningful. And in subsequent years a partially new theory—the "thrifty phenotype hypothesis"—derived from challenges posed to the thrifty gene hypothesis [52]. Instead of hypothetical "thrifty genes", a "thriphty penotype" could emerge, through epigenetic mechanisms, as an adaptive and predictive reaction to the environment perceived by the fetus during development. In this new model, the development of insulin resistance is hypothesized to be directly related to the "wrong prediction" of a life of starvation by the developing fetus [53].

But to better understand this interesting change of perspective, it is essential to recall some of the conceptual passages that preceded and prepared it.

In the early 90s, Lucas enunciated the hypothesis, which would prove to be very fertile, of the *foetal programming*: namely a genomic, adaptive and predictive adjustment during the embryo-foetal period [54]. In the same years, Barker and the group of Southampton came to the hypothesis of the "thrifty phenotype" and of the foetal origin of adult diseases, according to which critical embryo-fetal and consequent low birth weight would be the main determinants of the onset of many chronic and degenerative diseases [55, 56]. In short, both hypotheses (based on some epidemiological and experimental evidences) claimed that conditions of poor nutrition, maternal-fetal distress and/or exposure to toxic substances, capable of interfering with cell differentiation and therefore with the programming of organs and tissues, could play a fundamental pathogenetic role. However such ideas, formulated in an era in which epigenetic mechanisms were not yet known, raised much debate and disputes.

In the following years it became evident that the entire embryo-fetal and perinatal period of development plays a key role in the programming of organs and tissues. And not only of adipose tissue or of the hypothalamic-pituitary–gonadal axis, but also of the mammary tissue [57], the renal parenchyma [58, 59], the cardio-circulatory system [60, 61], the respiratory and immunocompetent systems [62, 63] and the CNS [64, 65]: basically of all human tissues and organs.

In fact the two hypotheses of Neel (thrifty genotype) and Barker (thrifty phenotype) are complementary rather than alternative. There is no doubt that the genome cannot radically change in a few decades and it is likely that over the millennia the genomic structures more adaptable to ever changing nutritional intake have been positively selected. It is as well clear that what has happened in the world, in the last years, and the particularly dramatic consequences in subjects whose lifestyle has undergone a rapid transformation (high-caloric intake, physical inactivity) can not be explained by the neodarwinian *selection* of more genetically suitable subjects, but from a neo-lamarckian and epigenetic perspective: namely a *thrifty programming* in utero (*thrifty epigenotype*) induced by various types of stress, would reduce, later in life, the ability of the subject to adapt to a richer environment.

In conclusion the Neel's hypothesis (thrifty genotype) seems to be valid in the long term and adequate to explain the increasing prevalence of obesity and type 2 diabetes in the years following the Second World War; the Hales and Barker's hypothesis (thrifty phenotype) is applicable in the short term to better explain the rapidly progressive epidemics of obesity and T2D.

More recently some renowned pediatricians, epidemiologists and evolutionary biologists decided to put together the information originating from epidemiological and experimental studies and demonstrating the links between the distress suffered during fetal development and the increased risk of chronic diseases during the lifetime; the pathogenic models proposed to better elucidate this association, such as the *thrifty phenotype*, the *fetal programming* and *predictive adaptive response* theories and the concept of *match* or *mismatch*; the molecular mechanisms involved in these processes as effects of the environmental signals on epigenetic programming to build up a new, general pathogenic paradigm, the *Developmental Origins of Health and Disease (DOHaD)* theory, that could transform in a general frame to better explain the current epidemiological transition (consisting of the world wide increase of chronic, degenerative and inflammatory diseases such as obesity, diabetes, cardiovascular, neurodegenerative disease and cancer) [66, 67].

From genetics to epigenetics: fetal programming alterations

The final confirmation of the correctness of the assumptions made by Lucas and Barker on the foetal programming in utero and on the so called hypothesis of the *programmatic mismatch* (see below) came, in a very unexpected way, from two large epidemiological studies.

The studies were performed on two large cohorts of subjects exposed in utero to serious nutritional deficits during the Second World War, who later lived in totally opposite conditions: return to normal nutrition in the case of the Dutch cohort exposed to the so-called Dutch Famine in 1944, and, conversely, perduring conditions of poor nutrition in the case of children who survived the dramatic siege of Leningrad. The results of these studies greatly contributed to the understanding of the molecular mechanisms underlying the epigenetic programmatic mismatch, concerning the organs involved in metabolic organization (hypothalamus, adipose tissue, muscles) in subjects exposed in utero and post-natal life to quite different environmental and nutritional conditions.

Thanks to the scrupulous collection of data made by some researchers it was possible to study, decades later, the effects that the reduced intake of nutrients during the embryo-foetal development had determined in the survivors. It was clear, therefore, that the effects of such a nutritional stress were often apparent after decades and often without a definite relation to birth weight [68] and they were different depending on the period in which the foetus was exposed to such extreme reduction in calories [69]: if caloric restriction concerned the second part of pregnancy, the result, later in life, was an altered glucose tolerance and T2D, if the exposure concerned an earlier period of fetal development, the result was obesity and more complex symptoms tied to the "metabolic syndrome" with alterations in the lipid profile [70], hypertension [71], early atherosclerosis and cardiovascular diseases [72, 73] and even disorders concerning the affective behaviour and schizophrenia [74].

There is now sufficient agreement on the fact that many chronic diseases could be a late result of the fetal programming, namely of the epigenetic adaptation of cells and tissues to an early psychological and nutritional stress (thesis later corroborated by the report about the transgenerational effects) [75].

As sometimes it happens in scientific research, it was a study that seemed to contradict this hypothesis and that offered Barker and other researchers the opportunity to make another step forward. Indeed, analyzing the cohort of survivors of the starvation during the sieges of Leningrad and Stalingrad, it was noted that the incidence of chronic diseases was much lower than in the Netherlands [76, 77]. In an attempt to find a solution to the riddle, the scientists realized that while the survivors of the Dutch famine were apparently more fortunate and were able to quickly recover the lost weight, the survivors of the siege of Leningrad had endured a difficult childhood and had continued later on to have a very low caloric intake: yet, paradoxically, this had preserved them from developing obesity and insulin resistance. The solution was now at hand: Russian children, "programmed" for a life characterized by stress and nutritional deficiencies had been able to better face their difficult lives; whereas the Dutch children, programmed in the same way, had enjoyed a much better postnatal life and a diet much richer than expected and, although at the beginning recovered a good weight, then they were sick because of the *mismatch* between their (deficient, frugal) programming and the relatively rich diet they had in their adult life.

The two so much disputed assumptions made in the 90s—fetal programming and thrifty phenotype-proved complementary and concrete. The emerging concept was that of an epigenetic *mismatch* not so much between the ancestral and the current DNA of our species (as in Neel's theory), rather between the genome programmed in utero, on the basis of the "predicted " environment, and the "actual" one [78]. It is noteworthy that the *mismatch* between fetal programming and "actual life" is even greater among migrant populations, that is to say people living in low income countries and the most disadvantaged inhabitants of the rich countries, characterized by low weight at birth and severe nutritional deficiencies in early childhood, but also by consumption of junk food, rich in simple sugars and fat, and by a more and more sedentary way of life. Obviously such a *mismatch* could represent the main cause of the huge increase in childhood and adolescent obesity, almost tripled in the U.S. in the last 30 years.

Taking into account the increase of metabolic diseases either in Westernized and in developing countries, it is becoming clear that there is an environmental disconnection with the extrauterine environment, which can alter the projected growth pattern of various organs and systems of the body, conferring to the offspring an increased risk of metabolic disease [79]. The biological mechanisms mediating these connections are not completely known but are likely related to programming of insulin, glucocorticoid and leptin resistance in utero [80].

Molecular mechanisms

Epigenetic mechanisms such as DNA methylation and histone modifications, both involved in chromatin remodelling, largely concur to fetal metabolic programming. Throughout systems biology approaches it was realized that fetal adaptation to an impaired nutritional environment implies profound changes in gene expression that involve regulation of tissue-specific patterns of methylated cytosines, modulation of the histone tails acetylation/deacetylation, cell differentiation,

and stem cell pluripotency [81]. Maternal nutrition is the most influential environmental factor during fetal development. In the last decade many studies have been performed providing evidence that mothers' diet during pregnancy can exert major short- and long-term effects on the health of the offspring including the metabolic syndrome. The most sensitive time windows for the developmental programming of adiposity seem the gestation and lactation periods. During these stages, plasma levels of circulating factors as well as adipose tissue hormone sensitivity show perturbations in the offspring of females suffering from malnutrition, resulting in enduring adipose tissue programming (i.e., increased fat mass) [82].

In pregnancy and lactation, there may be restrictions or imbalances in energy or nutrient excesses that may lead to metabolic disorders mediated by epigenetic mechanisms. These epigenetic modifications induced by dietary or environmental factors may be transiently or transgenerationally transmitted to the offspring, and could be involved in obesity inflammation and susceptibility [83].

Godfrey and coworkers performed a study on two prospective cohorts by using DNA extracted from umbilical cord tissue obtained at birth in children who were assessed for adiposity 9 years later to measure methylation status level in the promoters of candidate genes [84]. Methylation of two genes (retinoid X receptor-α, *RXR-A*, and endothelial nitric oxide synthase, *eNOS*) was found to correlate with higher adiposity in later childhood. These findings, even if do not prove definitively causality between DNA methylation at birth and adiposity in childhood, confirm that modification of epigenetic marks may be crucial in fetal programming of later obesity.

Maternal obesity and diabetes are also able to induce latent metabolic defects and epigenetic variations in isogenic mice [85]. New explanations have recently emerged concerning the question of whether overnutrition in utero could have the same effect on fetal metabolic programming as undernutrition, suggesting that the mechanisms behind these two fetal nutritional imbalances are different. Intrauterine restriction seems to be associated with the induction of persistent changes in tissue structure and functionality. On the contrary metabolic reprogramming of glucose and lipid metabolism, as well as future risk of metabolic syndrome, fatty liver, and insulin resistance is associated with maternal overnutrition [81].

Epigenetic biomarkers

Studies are beginning to appear on the assessment of changes in the pattern of methylation of specific genes related with obesity. DNA methylation represents one of the most important epigenetic mechanisms for the regulation of gene expression, and so far the most widely studied. An association between methylation status of CpG islands located in clock genes (*CLOCK, BMAL1* and *PER2*) and obesity, metabolic syndrome and weight loss was found. The circadian clock system gives instructions about 24-h rhythmicity on gene expression in quite all cells, including adipocytes [86].

In overweight or obese adolescents a multidisciplinary weight loss intervention (10 weeks) was able to modulate methylation levels of five regions located in or near *AQP9*, *DUSP22*, *HIPK3*, *TNNT1*, and *TNNI3* genes, in function of high and low responders [87]. Recently a study was performed on obesity in parents before conception in relation to DNA methylation patterns at multiple human imprinted genes critical for normal growth and development. Paternal obesity was significantly associated with lower methylation levels at the mesoderm-specific transcript gene (*MEST*), paternally expressed gene 3 (*PEG3*) and neuronatin gene (*NNAT*). Changes in methylation levels related to maternal obesity were instead detected at pleiomorphic adenoma gene-like 1 (*PLAGL1*) and at the maternally expressed gene 3 (*MEG3*) [88].

Some studies support the idea of a preconceptional influence of parental life-style or diet on the re-programming of epigenetic marks during gametogenesis and early development. In particular the association between paternal obesity and the methylation status in the offspring suggests the susceptibility of the developing sperm for environmental triggers. It has been linked to the possibility that this epigenetic instability may be transferred to the next generation with an increased risk for chronic diseases in adulthood [88]. Obesity has adverse effects also on female gametes: it can interfere with oocyte quality and embryo development, also affecting the health status of the offspring. DNA methylation levels of many metabolism-related genes such as *Leptin* and *PPAR-alpha* are not only changed in oocytes of a high-fat-diet-induced mouse model, but also in oocytes and liver of their offspring [89].

A remarkable association was found between maternal antibiotic use during pregnancy, birth weight and aberrant methylation at growth regulatory imprinted genes among offspring. Methylation at five genes *IGF2, H19, PLAGL1, MEG3* and *PEG3* was associated with antibiotic exposure during pregnancy; moreover methylation at *PLAG* also correlated with birth weight [90].

Two appetite-regulatory genes associated with the weight regain process were also studied. Weith-regainers showed higher methylation patterns than non-regainers in proopiomelanocortin (*POMC*) and lower levels on neuropeptide Y (*NPY*) CpG sites. Moreover total baseline *NPY* methylation was associated with weight-loss regain, baseline plasma ghrelin levels and leptin/ghrelin ratio; lower methylation levels of *POMC* were associated with weight-loss maintenance, while lower total methylation levels in

NPY promoter were associated with higher risk of weight regain [91]. Leptin (*LEP*) promoter methylation was found associated in a tissue-specific manner with maternal (pre-pregnancy obesity, pregnancy smoking and gestational weight gain) and infant factors (small for gestational age, *LEP* genotype and gender) in non-pathological pregnancies. In particular methylation of *LEP* was lower in infants born to pre-pregnancy obese mothers [92].

Global DNA methylation was studied in human adipose tissue from 23 healthy men, with a previous low level of physical activity, before and after a six months exercise intervention. Also the differences of DNA methylation in adipose tissue of 31 individuals with or without a family history of T2D were investigated. In 1/3 of gene regions with altered DNA methylation differential mRNA expression was found. Furthermore, 18 obesity and 21 T2D candidate genes had methylation variations in adipose tissue in response to exercise [93].

The importance of epigenetic regulation in obesity is also shown by the study by Wang and co-workers in an in vitro model (a murine cell line with MeCP2 specifically deleted in POMC neurons which regulate energy homeostasis, in response to leptin signaling). The researchers demonstrated that MeCP2 positively regulates POMC expression in the hypothalamus. Absence of MeCP2 in POMC neurons leads to increased DNA methylation of the POMC promoter, which induces POMC expression downregulation and lead to obese mice showing an accentuating degree of leptin resistance [94].

An attempt to summarize recent findings dealing with epigenetic biomarkers (mainly differentially methylated specific genes) in obesity and T2D is shown in Table 1.

The obesogen hypothesis

According to recent findings among the most relevant environmental risk factors contributing to the onset of obesity and diabesity pandemics there are diet factors, stress, fetal environment and pharmaceutical or chemical. Among them a critical role is played by endocrine disrupting chemicals that interfere with the body's adipose tissue biology, endocrine hormone systems or central hypothalamic–pituitary–adrenal axis and are suspected to interfere with the major homeostatic mechanisms involved in weight control [18].

In 2002 Paula Baillie Hamilton noticed the coincidence in time between the beginning of the obesity epidemic and the worldwide spread of a large number of new industrial chemicals over the past forty years, and suggested that a number of endocrine disrupting chemicals (organophosphate pesticides, biphenyls and polybrominated biphenyls, phthalates, bisphenol A (BPA), heavy metals and solvents) could have damaged many of the body's natural weight-control mechanisms [95].

In 2006 Grün and Blumberg formulated the *obesogen hypothesis*, according to which the obesity epidemic would be, at least in part, a consequence of the spread in the environment (and especially within food chains), of xenobiotics able to act as endocrine disruptors, mainly during the fetal programming [96]: promoting hyperplasia of the adipocyte pool (a key factor because it seems that the size of adipocyte pool programmed in utero remains so throughout life); facilitating adipogenic pathways that activate the aforementioned hyperplasia during periods of increased physiological development; perturbing the lipid homeostasis (shifting the energy balance towards the accumulation of fat), interfering with feedback mechanisms of appetite and satiety pathways [97].

According to Grün and Blumberg, "obesogens" can be defined from a functional point of view as chemicals that, improperly interfering with lipid homeostasis, promote adipogenesis [98] by perturbing various endocrine axes, generally targeting nuclear receptors, including sex steroid receptors, retinoic acid receptors, gamma peroxisome proliferator receptor (PPARγ) or glucocorticoid receptors, affecting directly or indirectly adipocyte physiology and more generally the regulation of energy homeostasis [99]. Among obesogens we can find many heavy metals, solvents, pesticides, PCBs, organic phosphates, phthalates, organotins, diethylstilbestrol (DES) (for a review see 100). Eventually they include either mimetic substances of lipophilic hormones, such as bisphenol, tributyltin or inhibitors of endogenous hormone metabolism (e.g., tributyltin is an agonists of both retinoid X receptor and peroxisome proliferator-activated receptor gamma) [100]. Consequently, their sites of action are diverse and the interactions very complex, especially for compounds like organotins (chemical compounds based on tin with hydrocarbon substituents) having multiple molecular targets. The fact that in many cases dose–response curves are not monotonic (as in case of phytoestrogens and DES) is of great concern, since it is becoming increasingly clear that when it occurs, the effects of low doses can not be predicted on the basis of the effects exerted at high doses: in fact many EDCs act as metabolic toxicants at high doses, while at lower levels, what happens for environmental exposures, the effects may be fairly different and even paradoxical [101].

Other factors that can add complexity are timing of exposure, gender and genetic susceptibility. Exposure during fetal development represents a short window of heightened sensitivity where long-term effects can be established, only in a small fraction of the population. This delayed response and the objective difficulty in establishing experimentally cause and effect relation may give a partial explanation to the underappreciated role that chemical obesogens might play.

Table 1 Examples of epigenetic biomarkers in obesity and T2D

Genes	Functions/Epigenetic evidence	References
CLOCK, *BMAL1*, *PER2*	Circadian clock system's genes associated with obesity, metabolic syndromes and weight loss	[86]
AQP9, *DUSP22*, *HIPK3*, *TNNT1*, *TNNI3*	Their hypermethylation is associated to responsiveness of a diet intervention	[87]
MEST, *PEG3*, *NNAT*, *PLAGL1*, *MEG3*	Genes involved in normal growth and development, which methylation is influenced by parents obesity; first three are influenced by paternal obesity and the last two by maternal one	[88]
IGF2	Growth factor active in embryogenesis and fetal growth; its hypomethylation is associated with paternal obesity	[166]
IGF2, *H19*, *PLAGL*1, *MEG3*, *PEG3*	Genes involved in growth regulation	[90]
FFAR3	Gene influenced by microbiota; lower methylation levels associated to different composition of gut microbiota in obese and T2D	[155]
POMC, *NPY*	Appetite-regulatory genes associated with the weight regain process; regainers show higher methylation levels in *POMC* and lower in *NPY*	[91]
LEP	Lower methylation in infants born to pre-pregnancy obese mothers	[92]
TH, DAT	Genes involved in dopamine synthesis, hypomethylated in the hypothalamus upon high-fat feeding	[167]
FABP3	Its methylation in peripheral white blood cells is associated with plasma total cholesterol, insulin sensitivity and blood pressure	[168]
CPEB4, *MAP2K4*, *PRKD1*	Genes differentially methylated after exercise in obese people	[93]
DUSP8, *KCNQ1*, *TCFL2*	Risk genes for T2D; differential DNA methylation after exercise	[93]
PDX1, PPARGC1A	Increased methylation involved in the development of T2D (observed in pancreatic islets)	[169, 170]
PDK4	Increased methylation in skeletal muscle from T2D patients	[171]
INS	Increased DNA methylation of the insulin promoter in T2D	[172]
GLP1R	Its methylation in human pancreatic islets disrupts the production of insulin	[173]
HNF4A	Hypermethylated in adipose tissue of T2D patients	[174]
PGC-1	Epigenetic alterations were associated with reduced mitochondrial density and increased plasma free fatty acid concentration	[175]
GLUT 4	Its promoter is highly demethylated upon adipocyte differentiation and methylation at specific CpG sites can inhibit nuclear factor binding to the promoter	[176]
PPARG2	Progressively demethylated upon adipocyte differentiation	[177]
MC4	Hypomethylation has a direct impact on appetite and intake, and thus influences risk of obesity.	[178]
miR-138, miR-15b, miR-376a	Their percentage correlate with obese and T2D status	[179]
miRNA-130b	Inhibits adipogenesis and lipogenesis and reduces fat deposition in recipient adipocytes by targeting PPAR-γ	[180]
miR-200a, miR-200b, miR-429	Up-regulated in the hypothalamus of genetically obese and leptin deficient mice	[181]
miR-143 and miR-103	Induce adipogenesis in vitro and increase or accelerate expression of several key adipogenesis-regulated genes	[182]
miR-125a, miR-29, miR-143, miR-519d and miR-27	miRNAs in adipose tissue associated with obesity	[183]

Finally a confirmation that long-term deregulation of metabolic homeostasis is relevant at a population level is offered by the increased obesity risk due to maternal smoking during pregnancy [102].

We are still far from a complete knowledge of epigenetic changes induced by obesogens, however in these last years their potential long lasting, trans-generational effects are becoming clear [16]. As for the possible epigenetic and transgenerational effects of EDCs, the most studied molecule is bisphenol A, a synthetic chemical with weak estrogen agonist properties that has been found in food and beverage containers, baby bottles, and dental materials. For what concerns bisphenol A, the most famous experiment was made, a decade ago, on the Agouti mouse: BPA induced hypomethylation and consequently increased expression of the Agouti gene in prenatally exposed mice (early developmental stages generally representing the period of greatest sensitivity to these chemicals) led to the

birth of mice characterized by yellow rather than brown coating, as well as by tendency to develop obesity, diabetes and tumors [103]. Moreover, agouti mice females were more likely to have offspring with the same phenotype in the following generation. This experiment, that represents a milestone in epigenetic studies, constitutes a proof of the fact that prenatal exposure to synthetic estrogen agonists such as BPA can interfere with epigenetic marks, thereby leading to endocrinological consequences [104].

Recent observations demonstrated that widely diffuse environmental compounds such a mixture of plastic derived compounds, BPA and phthalates, and a hydrocarbon mixture involving jet fuel (JP-8) can promote epigenetic transgenerational inheritance of adult onset diseases, including obesity. Female rats were exposed during the fetal gonadal development period to a hydrocarbon mixture involving jet fuel (JP-8). The F1 generation showed an increased incidence of kidney abnormalities in both females and males, prostate and pubertal abnormalities in males, and primordial follicle loss and polycystic ovarian disease in females. The jet fuel lineage had an increased incidence of primordial follicle loss and polycystic ovarian disease in females as well as obesity in both males and females also in the first transgenerational generation (the F3 generation). Moreover analysis of the F3 generation sperm epigenome identified 33 differentially methylated DNA regions [105].

Similarly F0 generation female rats were exposed during pregnancy to a plastic mixture in a period ranging from days 8 to 14 of gonadal sex determination in the embryos and in F1 and F3 generation rats the incidence of adult onset disease was detected. Significant increases in the incidence of total disease/abnormalities both male and female rats s of F1 and F3 generations were found. In particular, in the F3 generation, pubertal abnormalities, obesity, testis disease, and ovarian disease were increased [106].

In Table 2 a number of environmental compounds shown with obesogenic (and diabetogenic) properties are listed. Much remains to be discovered about the possible molecular mechanisms characterizing environmental obesogens and their overall significance for the epidemic of obesity and T2D. However, taken into account the already existing data on the effects of obesogens, and the multiple potential targets with which they might interfere daily, it seems likely that the exposure to obesogens can have an important role in the obesity and diabesity pandemic.

Another possible indirect obesogenic mechanism induced by EDCs is interference with thyroid function, fundamental to maintenance of basal metabolism. In fact a large number of EDCs, including phthalates and BPA are thyroid disruptors, having the net effect of reducing circulating thyroid levels [107] and a large cross-sectional study in Denmark found that, after excluding people with thyroid dysfunction, small decreases in thyroid hormone were associated with significant increases in BMI [108].

Moreover, we have to take into account that of the more than 100,000 documented synthetic chemicals present in our environment, until now, few have been evaluated to assess their effects on the endocrine system and metabolism [109]. On the other hand some scientists have stressed that in addition to its endocrine function, adipose tissue can act as a reservoir for lipophilic chemicals and pollutants, that could enter and be lastingly stored in adipocytes, and subsequently they may be released in the blood during lipolysis and/or following apoptosis [110], targeting other tissues and contributing to tumor initiation and promotion, principally in obese people [111].

Diabetogens and diabetes epidemic

As for insulin resistance, metabolic syndrome and diabetes, despite the potential weight of EDCs in the pathogenesis of metabolic diseases, the role of such chemicals in the genesis of the diabetes epidemic remains largely hypothetical [112], even if some collaborative studies demonstrated that POPs-persistent organic pollutants [113], heavy metals [114], organochlorines [115], brominated flame retardants [116] and other compounds impairing β-cell function and or inducing insulin resistance [117] may be diabetogens; some environmental disasters—such as the dispersal of agent orange during the Vietnam War [118], the chemical plant explosion in Seveso, Italy [119], and rice oil contamination in Yucheng [120]—suggested an association between dioxin, PCBs, furans exposure and diabetes development; some studies on exposure in the workplace have revealed links between diabetes and organochlorine pesticides [121] and dioxins [122] and NHANES-based studies have shown links between phthalates [117], bisphenol-A [123] and various POPs [124] with levels of urinary metabolites often associated with insulin resistance and diabetes.

Moreover many pollutants as BPA [125], some phthalates [126], dioxins [127] and flame retardants [128] have been proven diabetogenic in experimental models.

As for mechanisms potentially concerned and in line with the DOHaD hypothesis, many experimental data demonstrate the epigenetic regulation of various genes influencing metabolic diseases, including diabetes [129] and, as already mentioned, some interesting links between EDCs exposure and epigenetic alterations of these genes are emerging [130] that could be heritable into at least the fourth generation [131, 132].

With regard to the link between the two major epidemics that we are considering here, that of obesity and

Table 2 "Obesogens" and "diabetogens" compounds

	Compounds	Experimental evidence	Reference
EDC		Induce functional changes in murine adipocyte differentiation in vitro accompanied by decreased global DNA methylation	[184]
	Bisphenol A	Increases prevalence rates of metabolic disorders such as obesity and T2D.	[185, 186]
		Induces hypomethylation and increased expression of agouti gene in prenatally exposed mice at risk to develop obesity and diabetes	[103]
	TBT	Prenatal exposure during gestation results in premature accumulation of fat in adipose tissues at birth, increases fat depot size, and alteres the fate of multipotent stromal stem cells	[187]
	DEHP, BPA, DBP, and DDT	Induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations	[108, 188]
	Hydrocarbons (jet fuel JP-8)	Promote epigenetic transgenerational inheritance of disease and sperm epimutations	[107]
	Polycyclic aromatic hydrocarbons (PAHs)	Total urinary PAH metabolites and naphthalene metabolites were associated with higher BMI, waist circumference, and obesity in children.	[189]
	Organochlorine pestidices (DDE, HCB)	Increasing serum concentrations of individual POPs considerably increase prevalence of prediabetes and diabetes in a dose-dependent manner in humans	[115]
		Increase incidence of obesity and diabetes after somministration to neonatal rats	[190]
	Brominated flame retardants (PBDEs, HBCD)	Lipophilic xenobiotics, including brominated POPs stored in adipose tissue, may be involved in the pathogenesis of diabetes and metabolic syndrome	[116]
Other industrial chemicals	Perfluoroalkyl compounds (PFCs)	PFNA might influence glucose metabolism in humans at the level of exposure seen in the general elderly population	[191]
	Dioxin-like compounds	Increased prevalence of metabolic syndrome associated with TCDD among women who were the youngest at the time of the exposition	[192]
	Phthalates	Low molecular weight phthalate metabolites are significantly associated with higher risk for obesity in male children and adolescents. High molecular weight phthalate and DEHP metabolites are significantly associated with higher risk for obesity in all adults; DEHP metabolites are significantly associated with obesity in all female adults.	[193]
Pharmaceuticals	Diethylstilbestrol STZ and ALX	Induces adipocyte differentiation and promotes obesity and obesity-related disorders in mice	[194]
		Potential diabetogens; in vitro STZ reduced the GLUT2 protein expression and ALX reduced the mRNA expression of GLUT2 and GK	[195]
Heavy metals	Fe, Zn, As	Iron overload is associated with an increased risk of T2D through the metabolism of adiponectin	[196]
		Zn deficiency may be a potential risk factor for insulin resistance and T2D in the later stages of life	[197]
		Chronic arsenic exposure may induce diabetes mellitus in humans	[114]
Phytochemicals	Genistein	Exposure during the early postnatal period favours the development of obesity in female	[198]
Life-style	Nicotine	Increasing prevalence of obesity and hypertension in children exposed to cigarette smoke in utero	[102, 199]

EDC endocrine-disrupting compounds, *TBT* organotin tributyltin, *DEHP* bis(2-ethylhexyl)phthalate, *BPA* bisphenol A, *DBP* dibutyl phthalate, *DDT* 1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene, *HCB* hexachlorobenzene, *PBDEs* polybrominated diphenylethers, *HBCD* hexabromocyclododecane, *PFNA* perfluorononanoic acid, *STZ* treptozotocin, *ALX* alloxan, *GLUT2* glucose transporter 2, *GK* glucokinase, *POP* persistent organic pollutant

T2D diabetes, it is the condition of *insulin resistance*, obesity, heart disease, metabolic syndrome, polycystic ovary syndrome, asthma, some cancers, Alzheimer's disease and above all T2D—that plays a key role. Understanding the causes of insulin resistance is one of the most critical endeavours in modern medicine [133]. Two main mechanisms, partly competing, partly complementary with each other have been proposed: the lipid overload hypothesis (according to which cells essentially are poisoned by fat) [134] and the inflammatory theory (whereby as fat cells accumulate fat and increase in size, they release a distorted array of adipokines and other inflammatory

cytokines) [135]. The discovery that obesity implies an inflammatory state in metabolic tissues opened a vast research field on the inflammatory mechanisms in obesity [136]. Obesity is currently seen as a low-grade inflammatory condition with increased macrophage infiltration of adipose tissue: "classically activated" macrophages are likely the primary source of many of the circulating inflammatory molecules that are detected in obesity and are hypothesized to play a role both in the onset of insulin resistance and progression to T2D, and in ectopic storage of lipid and impaired secretion of adipokines [137]. Finally it is important to mention what appears to be another important piece in this complex puzzle: the intestinal microbiota, whose disturbances in obese individuals have been linked with local and systemic inflammation, leading to the hypothesis that the obesity-related microbiota composition could have a proinflammatory effect [138].

Is there a role for gut microbiota?

There is increasing evidence that, as exposure to environmental chemicals, also the gut microbiota composition could affect obesity and diabetes. In such a context, gut microbiota is being increasingly recognized as an important factor connecting genes, environment, and immune system.

In the last 10 years genetic and environmental factors dealing with mutual host-microbiota interactions have been intensely investigated by means of metagenomic and metabolomic approaches [139]. The human gut is a luxuriant microbial ecosystem containing about 100 trillion microorganisms and up to 500–1,000 different species, whose collective genome, the "metagenome", contains 100-fold more genes than the whole human genome [140]. The symbiosis of our extended genome has certainly a role in host homeostasis and energy intake from the diet: Gordon and colleagues proposed that the microbiota from obese subjects specifically increases the energy harvested from the diet, providing an extra energy to the host [141].

While the human genome is inherited, the human microbiome is acquired from the environment anew every generation. Infants obtain initial microbes from the mother during vaginal birth [142] and the microbiome establishes during the first year of life, bacterial abundances increasing $\sim$ 6 orders of magnitude within the first weeks of life, becoming more adult-like within the first year [143]. Composition of microbiota is specific to each body site (each body site—e.g. oral, nasal, gut, skin, urogenital-includes a unique community), with few differences (over time and by gender), but over a lifetime can be continuously modified, especially from mid-age to elderly [144]. By means of metagenomic studies certain mixes of gut microbiota were shown to be protective or predisposing to obesity [145]. Some studies described an altered microbic colonization in the gut of obese individuals, for instance obese subjects were found to have an increase in Firmicutes and Actinobacteria and a decrease in Bacteroidetes in the gut in comparison with non obese controls [145, 146]. The consequences of gut microbiota alterations could regard intestinal permeability and the absorption of lipopolysaccharide (LPS), leading to increased activation of inflammatory pathways. Following these activations, an impairment of the insulin signaling is observed, with decreased phosphorylation of the insulin receptor, insulin receptor substrate and Akt, together with increased inhibitory serine phosphorylation of IRS-1 [147]. *Campylobacter rectus* and *Neisseria mucosa* have been found in sixfold higher amounts among obese adolescent subjects [148]. Also modified proportions of bacterial phyla have been shown to interfere with host's biochemical pathways In fact the gut microbiota is able to contribute to host metabolism by many mechanisms including increased energy harvest from the diet, fat storage in adipose tissue, modulation of lipid metabolism, altered endocrine function, and increased inflammatory tone. Also the interactions among different microorganisms seem to play an important role in host energy homeostasis, with hydrogen-oxidizing methanogens enhancing the metabolism of fermentative bacteria [149]. Ingested diet components can undergo differences in caloric extraction likely in function of the composition of the gut microbiota, suggesting that the metabolic activities of the gut microbiota besides facilitating the extraction of calories from ingested food substances may help to store these calories in the host adipose tissue for later use. Interestingly, germ-free mice do not become obese following the administration of a diet rich in high-fat/high-sugar 'Western' diet [150]. The gut microbiota could thus be considered to be an environmental factor of susceptibility to obesity and other metabolic diseases [151]. In fact mammalian gut microbiota has been already identified as epigenetic factor, in the pathogenesis of metabolic syndrome and associated diseases [152].

On the other hand variations in gut microbiota are likely to be involved also in human toxicodynamics and potentiate personal exposure to obesogenic and diabetogenic chemicals [153]: in fact many papers in the toxicology and pharmacology fields suggest that interindividual variations in gut microbiota may influence chemical metabolism by direct activation, depletion of endogenous metabolites needed for biotransformation, alteration of host biotransformation enzyme activities, changes in enterohepatic circulation, altered

bioavailability of environmental chemicals and/or antioxidants from food, or alterations in gut motility and barrier function [154]. Finally the microbiota was shown to interfere with epigenetic regulation in obese and T2D patients. The methylation analysis of the promoter region of *FFAR3* (free fatty acid receptor, used as target gene) showed a significant decrease in methylation in obese and T2D in function of a different composition of gut microbiota [155].

Concluding remarks

A truly alarming possibility is that of the transgenerational effects of endocrine disruptors, a risk that began to emerge after the experimental studies on pregnant mice exposed to the antifungal vinclozolin. Those studies documented a possible transmission of epigenetic marks at gametic level with consequent transgenerational negative effects: infertility, obesity and behavioral changes for at least three generations in the male offspring [130, 131]. Both the frequency and the experimental reproducibility of these induced pathological phenotypes suggest the mechanism at work to be epigenetic, rather than due to stochastic mutations in the DNA sequence [156].

On the other hand the possible transgenerational transmission of the obesogenic and diabetogenic effects was at first suspected and later confirmed also in humans. In fact groundbreaking epidemiological studies have demonstrated that high-caloric diet during puberty could have significant effects on the health of descendants of the same sex, leading to a significant increase in risk for diabetes and cardiovascular disease. From these studies it appears that the time prior to the pubertal growth spurt is a critical period in which the excess of nutrients could induce specific epigenetic modifications in the gametes (in genes essential for the programming of key metabolic tissues). These epigenetic marks could be transmitted transgenerationally and determine a significant increase of obesity, T2D and cardiovascular diseases in the descendants of the same sex [157, 158].

The bibliography of the last five years has been increasingly in search of epigenetic alterations of fetal programming: not only changes in the programming of adipose tissue, but also of the whole neural circuitry of appetitive regulation [159, 160]. In this context obesity is increasingly considered as a result of systemic, psycho-neuro-immune-endocrine dysregulation, rather than a disease essentially concerning the adipose tissue.

Everything seems to reconnect and recompose as part of a large framework, according to which the dramatic transformation of the environment operated by humans in a few decades (above all the spread through food chains of man-made molecules that interfere with the epigenetic programming of embryonic and fetal organs) is leading to a true "epidemiological transition" characterized by the increase all over the world of many chronic, inflammatory and degenerative diseases. This could be, in particular, the main cause of the rapid increase and the continuous anticipation of the time of onset of obesity (we should never forget that until a few decades ago the exceptional cases of pediatric obesity were associated with rare genetic diseases) and T2D (which was considered, in the last century, a disease of the elderly, whereas today it affects more and more often the adolescents) [161].

There is also compelling and growing evidence about a promising employment of "epigenetic drugs" (compounds able to interfere with epigenetic mechanisms, e.g., histone deacetylases (HDAC) inhibitors), in the treatment of obesity and diabesity, as several epigenetic mechanisms have been reported to control adipogenic differentiation and influence energy metabolism [162].

Moreover, there is evidence that several diet factors could modulate DNA methylation or histone tail modifications and some of them could be useful in obesity therapy thanks to their epigenetic mechanisms. Some good results have already been achieved through the use of the methyl donors (folate, choline, methionine, and vitamin B12), especially by maternal diet supplementation. In fact methyl donors are of fundamental importance during fetal ontogenesis, since they can influence DNA methylation and consequently neural precursor cell proliferation and brain development. Even in the adult population there are interindividual differences in the disease risk also in function of low methyl donor levels (fatty liver, insulin resistance) due to predisposing genetic polymorphisms [163].

Inhibitors of two classes of epigenetic enzymes, the DNA methylation inhibitors and the histone deacethylase inhibitors, have already been shown useful to combat specific cancers, and have been approved as drugs for these pathologies [164]. Thus a promising research field deals with the applications of drugs targeting epigenetic enzymes as a novel therapy for obesity and related pathologies. An indirect confirmation comes from the use of tranylcypromine, a histone demethylase inhibitor. Psychotropic agents are known to increase fat mass in psychiatric patients. It has been hypothesized that some of these compounds utilize a common epigenetic effector pathway, leading to an increased adipogenesis or to a reduced energy metabolism. On this basis some authors have recently claimed for the potential therapeutic effects of the clinically approved antidepressant tranylcypromine (a histone demethylase inhibitor), which exerts important therapeutic effects on obesity metabolism [165].

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