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Epigenetics and neurodegeneration: role of early-life nutrition

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Abstract

Neurodegeneration represents a global problem due to the progressive increase in the aging population all over the world. The quality of life in aging and the cost for the health care system requires actions to promote healthy aging. In this regard, several risk factors associated with the development of neurodegeneration can be identified and programs to educate people on the key role of prevention could significantly ameliorate the future picture of the aging population. Here we

describe the key role of the pre- and post-natal period of life during the first 1000 days of life, focusing on the importance of nutrition and a healthy life style of mother and offspring for the prevention of neurodegeneration later in life. Environmental risk factors (i.e. nutrition, stress, xenobiotics, alcohol, drugs, smoking, etc.) mediate the genetic and epigenetic signature of offspring which may have long-term effects on the onset of neurodegeneration.

Key words: epigenetics; early-life nutrition; nutrigenomics; neurodevelopment; neurodegeneration.

1. Introduction

It is now well-recognized that the environmental effects experienced during the first 1000 days of life, represented by the nine months of pregnancy plus the first two years of life and as early as pre-conception, are transmissible to offspring and to subsequent generations. Animal studies using rats and mice appear to indicate that the predisposition to cardiovascular (CV), metabolic and neurological diseases may originate *in utero* and is associated with inheritance of epigenetic alterations to gene expression. This in turn is partly linked to the early life experiences of the mother and to the offspring's nutrition, especially during its first two years of life in the case of humans [1,2]. Some of the environmental risk factors which shape the genetic and epigenetic signature of offspring range from nutrition, stress, xenobiotics to alcohol, drugs and smoking. While plenty of studies have focused on the association between nutrition in early-life (pre-natal and post-natal period) and the risk of CV and metabolic diseases later in life, the link with neurodegenerative diseases is however still not clear. Since diet influences every organ and body system, which can in turn affect brain health, the question arises as to whether nutrition in the early stages of life may affect neurodevelopment and predispose for the onset of neurodegeneration in the long term. This is of interest considering that the field of epigenetics is emerging as an important and novel mechanism in neurodegenerative diseases. This review summarizes the major breakthroughs and discoveries that have been mainly made over the last five years, and discusses the evidence for the possible connections and mechanisms involved between early-life nutrition during the 1000 days of window of plasticity and predisposition for neurodegeneration later in life. In other words, our brain's health and mental wellbeing throughout our life span is not just influenced by 'what we eat' but probably also by 'what our mothers ate during our early-life' and 'what our mothers fed us in the first two years of life'.

2. C1 metabolism, DNA methylation and early-life programming of adult health

Early life represents a key period for the programming of adult health. During the first 1000 days of life, the differentiation process leading to specialized cells from the pluripotent ones is mediated by epigenetic remodelling required for switching off genes that do not have to be expressed in a particular tissue while maintaining active those that do [3,4]. In this context, DNA methylation and post-translational modifications work to differentiate cells properly. DNA methylation depends on the activity of DNA methyltransferases (DNMTs) which catalyse the methylation of CpG islands at the gene's promoter leading to a progressive switching off of the gene. The obstruction of the interaction between the transcription factors and the promoter region due to methyl groups, limits binding with RNA-polymerases required for gene expression to begin (Figure 1A). At the same time, methylation of regulatory regions contributes to an additional control of gene expression (Figure 1B), likewise for histone methylation which is however more complex (Figure 1C). The methylation process is strongly dependent on the availability of methyl group donors during pregnancy and through life via the one-carbon metabolism (folate) pathway (Figure 1D) [4]. The availability of methyl groups is associated with a folate-rich diet (i.e. green leaves, asparagus, beans, lentils, peas, liver, etc.) and to supplementation of folic acid during pregnancy, together with the availability of B6 and B12 vitamins. Methylenetetrahydrofolate reductase (MTHFR) catalyses the transfer of a methyl group to folate leading to 5-methyl tetrahydrofolate and finally to homocysteine which is then converted into methionine by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR). For this step, the presence of B12 is necessary and because it is present only in animal food (i.e. meat, fish, eggs), in vegans, a synthetic one can be taken orally through sublingual treatment to avoid its hydrolysis by the liver. Methionine adenosyltransferase (MAT) catalyses the synthesis of *S*-adenosylmethionine (SAM), which is the key factor for methylation, because DNMTs employ its methyl groups to methylate DNA. Alcohol intake for example, can interfere with SAM synthesis and for this reason should be avoided during pregnancy and breast-feeding, likewise deficits of folic acid and folate from food (Figure 1D).

The epigenetic mechanisms associated with a healthy/unhealthy phenotype include not only DNA methylation that plays a key role during the first 1000 days of life, but also post-translational modifications, like histone modifications. In this context histone methylation, acetylation, phosphorylation, ubiquitination, sumoylation and glycoylation can work with opposing effects leading to chromatin remodelling associated with activation or inhibition of gene expression (Figure 1C). Every time that a gene is expressed, chromatin remodelling represents the first step required to permit the start of gene expression. In the modulation of this process, nutrition plays a key role because supply precursors are required for histone-methyltransferases (HMTs), which need the methyl group donor SAM to methylate histones (Figure 1C); moreover, the methylation process

depends also on the FAD/FADH₂ ratio which is always related to the quantity and the quality of nutrient intake. Acetylation of lysine's positive charge in histones is a fundamental event promoting histone-DNA remodelling necessary to support gene transcription; to this aim, acetyl groups deriving from the oxidative glucose pathway or beta-oxidation of fatty acids are used by histone acetyltransferases (HATs) which need coenzyme A as cofactor. The flexible process is reversed when chromatin is stabilized by deacetylation catalysed by histone deacetylases (HDACs) that require NAD⁺ as cofactor [5]. Phosphorylation instead depends mainly on the activity of histone kinases, which transfer a phosphate group to the hydroxyl group of threonine and serine in histone H3. Overall, ATP-dependent remodelling complexes require the energy of ATP hydrolysis to achieve nucleosome structure required for transcription [6].

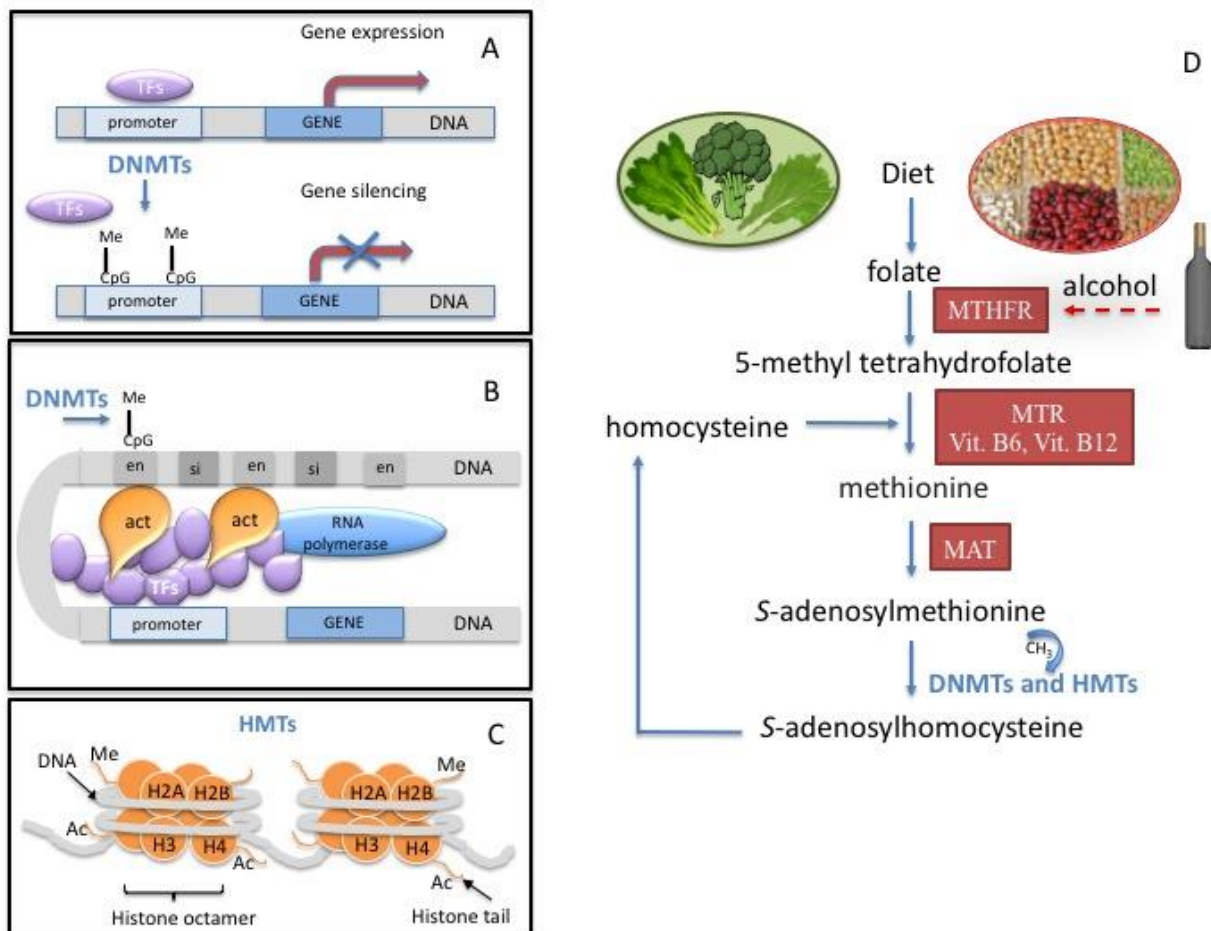


Figure 1. Simplified folate pathway and connection with DNA/histone methylation.

Panel A: Cytosine methylation hampers gene expression by limiting binding of TFs and RNA polymerases. Panel B: Gene expression controlled by methylation of regulatory regions. TFs are depicted in violet. Panel C: Methyl groups from the folate pathway are used by histone

methyltransferases (HMTs) for modifying chromatin structure and finally regulating gene expression. Panel D: Simplified folate pathway leading to methyl groups useful for DNA and histone methylation. TFs: transcription factors; MTHFR: methylenetetrahydrofolate reductase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase; MAT: methionine adenosyltransferase; en: enhancer; act: activator; si: silencer.

Reduced folate intake during early life has been associated with incorrect DNA methylation that leads to long term effects, as observed during the Dutch famine where low nutrients intake by mothers during pregnancy has been associated with a decrease in promoter methylation of the insulin growth factor 2 (IGF2) of the maternal allele in the offspring. The long term consequences of this imbalance in the maternal IGF2 promoter methylation associated with deficits in nutrient intake, have been correlated with the development of overweight in men at 20 years old and glucose intolerance when they reached 50 years old, and to an increase in BMI in females at the same age [7]. Despite these outcomes, Lumey et al. did not find any significant correlation between pre-natal famine and global DNA methylation on 350 births with pre-natal exposure to the Dutch famine [8]. Recently, Tserga et al. [9] studied the correlation between folate supplementation and IGF2 methylation in cord blood of 90 mothers-child which resulted in a complex picture depending on the MTHFR genotype. Tobi et al. in a recent work on 60 individuals with periconceptional famine exposure and genetic variation within the IGF/H19 region, suggested that both famine and genetic factors can alone or together be responsible for DNA methylation at the same regulatory site [10]. Overall, there are various aspects that can modify the DNA methylation of the imprinted IGF2 gene and the absence of an epigenome-wide association study of DNA methylation in humans contributes to delineate a heterogeneous picture. Furthermore, Tobi et al. found differences in offspring in DNA methylation of genes involved in growth, development and metabolism only when famine exposure was during the first 10 weeks of gestation of their mothers [11]. In agreement with this is Stein et als. work on 923 individuals affected by depressive symptoms in adulthood that were born from mothers exposed to famine prior to conception [12]. Similarly, 360 offspring from prenatally undernourished fathers, but not mothers, were heavier and more obese than offspring from parents receiving a normocaloric diet before conception [13].

The association between birth weight and obesity, coronary heart disease (CHD) and glucose intolerance later in life was first discussed by Barker [14] who observed a correlation between low birth weight and CHD death rates. Furthermore, low birth weight has also been associated with impairment of neurocognitive development later in life, and maternal smoking during pregnancy seems to promote this phenotype [15,16]. Additionally, studies on monozygotic and dizygotic twins

revealed a non-genetic negative association between birth weight and insulin resistance and glucose intolerance and it was estimated that the genetics associated with birth weight was 38% [17]. The mechanisms linked to the long term effects of prenatal and postnatal dietary nutrients on obese phenotype seems to be mediated by the early life programming of appetite regulatory hormones [18]. Studies on animal models showed that a protein restricted diet or a high fat diet during pregnancy is associated with decreased beta-cells in the pancreas, early or reduced leptin source, increased orexigenic peptide, resistance to glucose, hypertrophic adipocytes and finally development of the obese phenotype [19].

3. Risk factors associated with neurodevelopment and neurodegeneration

Exposure to unhealthy environmental factors in early life and during the life span have been associated with neurodevelopmental disorders and neurodegeneration later in life [20]. An unbalanced diet negatively modulates gene expression leading to reversible epigenetic signatures that are responsible for various features later in life. Other environmental factors that contribute to epigenome remodelling associated with early and long-term neurobehavioral deficits are smoking, alcohol, stress and exposure to pesticides during pregnancy. In this review we focus on food, alcohol, and food pesticides.

A general consensus based on several evidences on human and animal models supports the hypothesis that the development of idiopathic neurodegenerative diseases is strongly associated with the quality of life style starting from prenatal age. Alcohol and food intake modulate the epigenome but another important environmental risk factor is the presence of pesticides and metal residues in food, because these xenobiotics are associated with promoting neurodegeneration in the long term.

Pesticides are required to respond to the increasing demand of food by the population and to guarantee the absence of microorganism contamination in fresh and long term stored food (i.e. mycotoxins). However, the main concern regarding with risks linked to food pesticides should take into account not only the presence of single chemicals over the authorised limits, but also the presence of mixtures of pesticides that are within the maximum residue levels permitted by the legislation. Pesticides can modulate gene expression later in life by early remodelling of the epigenome. Exposure to these hazard factors is associated with genetic and epigenetic modifications leading to oxidative stress, mitochondrial damage, change in calcium homeostasis, reduction of overall brain volume, loss of dopaminergic neurons in substantia nigra, shortened fetal telomere length, microbiota-imbalance promoting proinflammatory cytokine release and finally altered brain development which has long term effects on the onset of the more common neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD) [21–24].

Worthy of note are the studies on animal models where the long-term effects of early life exposure to pesticides, herbicides and metals, identified as residues in food, can be demonstrated. Neonatal exposure to permethrin pesticide during brain development, promotes a progressive neurodegeneration characterized by the typical features of PD with behavioural and dopamine deficit, and a worrisome intergenerational effect [25,26]. Permethrin is able to induce a progressive PD-like neurodegeneration if administered in early life, because it can cross the blood-brain barrier (BBB) and remains long after the exposure [26-30]. In particular, permethrin binding to sodium channels, induces neuron depolarization that seems to modulate DNMTs activities responsible for DNA methylation [31]. Accordingly, changes in DNMTs have been demonstrated in the striatum of animals exposed to permethrin during brain development [32]. Furthermore, permethrin is able to decrease global DNA methylation in mothers exposed to the food pesticide during early life as well as in their untreated offspring, underlining the intergenerational effect of the pesticide [26]. This effect seems to be mediated by reactive oxygen species production induced by the pesticide that leads to up-regulation of DNMTs [33].

Of particular concern are the recent data obtained by the CHAMACOS cohort in the US on the association between increased biomarkers of organophosphate exposure in urine of farmworker mothers and abnormal mental development in their children [34]. Other studies support the capacity of organophosphates to act as endocrine disruptors underlining their possible involvement in promoting neurodevelopmental toxicity in early life [35,36]. Dialkyl phosphates (DAPs) and 3-phenoxybenzoic acid (3-PBA), the urine metabolites of organophosphate and pyrethroids respectively, result increased in children's urine affected by Attention-Deficit/Hyperactivity Disorder (ADHD). The risk of developing ADHD increases by 55% when the level of urine's DAPs is increased ten-fold compared with controls, while the risk of developing ADHD may be twice when children have detectable concentrations of 3-PBA with respect to the undetectable metabolite [37]. The PELAGIE cohort in France has associated urine 3-PBA levels with a decline in verbal and memory functions in children of six years old [38]. The mechanisms associated with these effects might be mediated by both genetic and epigenetic modulation. Recently PON1, a detoxifying enzyme for organophosphate and pyrethroid pesticides, has been shown to modulate DNA methylation [39].

Low levels of heavy metals in early life and higher levels later in life identified in the food chain (i.e. fish and molluscs), also represent risk factors associated with the promotion of neurodegenerative diseases [40]. High levels of cadmium in food have been linked to global DNA methylation [41] and aluminium, a metal present in water can cross the BBB promoting chromatin remodelling associated with oxidative stress, inflammation, mitochondrial dysfunction, impairment of glutamate transport and finally neuronal death [42].

Iron deficit in early life has been connected with permanent deficits in recognition memory and procedural memory in adult age; at the same time an excess of maternal iron or during adult age might lead to poor developmental consequences and long term effects mediated by epigenetic and neuroinflammatory processes, respectively [43,44]. Studies on animal models have demonstrated that deficit of iron during neonatal age is associated with neurodevelopmental dysfunction that is a consequence of altered hippocampal DNA methylation and to changes in expression of genes involved in the regulation of the BBB permeability, hypoxia and angiogenesis [45]. Furthermore, iron deficiency has been related to changes in histone deacetylase 3 which modifies hepcidin expression involved in the regulation of systemic iron homeostasis [46]. Deficiencies in two other metals, copper and zinc during pregnancy and in early life have been associated with decreased fetal neurogenesis due to impairment of DNA methylation [47], and both can promote amyloid- β peptide production typically present in the plaques of patients with AD [48].

Concerning alcohol as a risk factor for neurodegeneration later in life, several studies on human and animal models have indicated that maternal alcohol consumption during pregnancy and lactation is associated with a decrease in DNA methylation, [49]. Alcohol interferes with the methyl donor transfer to methylenetetrahydrofolate (Figure 1D) and the co-administration of the methyl donor betaine, was effective in contrasting DNA hypomethylation due to ethanol intake [50] Furthermore, chronic alcohol intake perturbs folate homeostasis due to decrease in folate absorption in the small intestine, abnormal uptake and low folate storage in the liver [51]. Overall, mother alcohol consumption inhibits the 1-carbon metabolism pathway affecting the DNA methylome. This in turn influences several genes associated with brain development, oxidative stress and pro-inflammatory cytokine production [52,53]. Physical and cognitive abnormalities known as fetal alcohol spectrum disorder (FASD) have in fact been observed in children following mother alcohol intake [54].

These risk factors exert their impact differently on people according to their own genetic profile: the individual responses to the exposome, which includes all external and internal factors interacting with humans, leads to a healthy or unhealthy phenotype according to the genetic polymorphism differences ultimately mediating the onset of PD and AD neurodegeneration. Of particular interest is the hypothesis that the incidence of neurodegeneration is mainly increased when a secondary exposure to toxicants occurs in adult age. This hypothesis known as the “two hits” model, is in agreement with studies on PD where occupational and non-occupational exposure to toxicants has been associated with the increased incidence of neurodegeneration [55–58]. Table 1 summarizes some of the epigenetic modulators treated in this section, with the possible outcomes, while the others will be discussed in the subsequent sections.

Table 1: Time frame for epigenetic remodelling by diet/environmental factors and outcomes during the first 1000 days of life (early life) and overall life span.

Epigenetic modulators	Period of exposure	Outcomes	References
Exposure to food and food pesticides/metals	Pregnancy Early life Adult age	Inflammation Neurodevelopmental /neurological disorders	[20] [22] [25] [27] [29] [34] [35] [38] [40] [41]
Alcohol	Pregnancy Early life	Reduction in folate absorption	[49-54]
Low folate intake	Pregnancy	Decrease in methyl groups	[51] [103] [105] [106]
Low B12 intake	Pregnancy	Decrease in methyl groups	[4] [10]
High fats intake	Pregnancy	Inflammation	[63-68] [73] [75]
High meat intake	Adult age	TMA-N-oxide mediates inflammation	[90]
High vegetables intake	Pregnancy Adult age	Inhibition of inflammation	[80] [106] [164] [175]
Intake of whole cereals	Pregnancy Adult age	Inhibition of inflammation (SCFA)	[116]
Intake of phytochemicals	Pregnancy Adult age	Inhibition of inflammation and oxidative stress	[107] [163-179]

4. Strategies for prevention: Maternal diet during pregnancy

Maternal diet is a major determinant of offspring health. Most studies have focused on the metabolic consequences of perinatal nutrition but very few have addressed those concerning neurodegenerative diseases. There are now several indications in the literature demonstrating that neurodevelopmental health and cognitive deficits of offspring are also associated with maternal obesity and an association between increased BMI in healthy mothers and decreased cerebellar growth in offspring has been observed [59-62]. The link between obesity and neurodegeneration appears to be in part associated with inflammation. Systemic inflammation is a common consequence of obesity and high fat diet (HFD) consumption, hence it is logical to question whether a maternal inflammatory diet may have adverse outcomes in off-spring both in early life and later life that could

predispose to neurodegenerative diseases and whether correction of a high fat maternal diet might prevent this.

The source of the low-grade systemic inflammation characteristic of obesity is believed to derive from lipopolysaccharide (LPS), a potent trigger of the innate immune system. LPS is an endotoxin naturally present in the intestinal lumen as a component of the cell wall of Gram-negative bacteria and it enters the circulation along with other nutrients following a meal, initiating a transient postprandial endotoxaemia. Under normal conditions the immune system responds normally to this acute endotoxin stimulus and once the toxin is neutralized and removed, the state of inflammation returns to baseline levels. However, frequent consumption of high fat meals chronically elevates LPS in circulation contributing to the low-grade inflammatory state observed in the obese phenotype [63,64]. This is exemplified by a recent study in which pregnant and lactating mice regardless of whether they were fed on a HFD or continuous infusion of LPS, had similar outcomes in their offspring: obese phenotype and greater inflammatory response in adulthood even if they consume normal diets throughout adulthood [65]. This prenatal inflammation has not only been associated with an obese phenotype, but also with long-term impaired adult neurogenesis and hypothalamic inflammation [66,67].

Neuroinflammation is mediated by microglia which are resident macrophages and are the first line of active immune defence in the central nervous system (CNS) and systemic inflammation has been shown to induce long-lasting neuroinflammation via $\text{TNF}\alpha$ and inflammatory cytokines that cross the BBB. In fact, microglia abundantly express TLR-4, a signal-transducing receptor that responds to saturated fats through the $\text{IKK}\beta/\text{NF}\kappa\text{B}$ pathway releasing proinflammatory cytokines (such as IL-6 and $\text{TNF-}\alpha$) [68]. Obesity has been demonstrated to induce the expression of cytokines and the proinflammatory transcription factor $\text{NF}\kappa\text{B}$ in the hypothalamus [69], and since $\text{TNF}\alpha$ and inflammatory cytokines can cross the placenta and BBB as they have been measured in the uterus, fetal circulation and the fetal brain, it is expected that maternal diet-induced inflammation may directly influence the developing fetus's CNS and brain with far reaching consequences [70-72]. Maternal dietary fatty acids have in fact been found to induce hypothalamic inflammation via $\text{TLR4}/\text{NF}\kappa\text{Bp65}$ signaling in adult offspring, but also normolipidic diets with unbalanced quantities of different fatty acids (trans-fats, palm oil and interesterified fats) have led to inflammatory responses on the hypothalamus (increased TLR-4 expression) in the offspring of dams [73-75].

Inflammation caused indirectly via LPS administration, and not through diet during gestation, has also been shown to increase $\text{TNF}\alpha$ and IL-1 β mRNA in the fetal brain and alter the glial cell population thus impairing neuronal differentiation and neurogenesis [76]. Interestingly, Graciarena et al. found that prenatal and adult LPS treatments in Wistar rats reduced adult neurogenesis and

provoked specific microglial activation in the dentate gyrus (DG), but more importantly, that *only* prenatal inflammation-mediated effects were long-lasting (>60 days). In fact, only prenatal LPS treatment reduced the local levels of TGF- β 1 mRNA in the DG of offspring and that it exerted its pro-neurogenic effects via the Smad 2/3 pathway in a neural stem cell culture [66]. These data highlight the importance of the consequences that prenatal immune programming has on CNS physiology compared to the limited response observed in the adult brain. Others have also led to similar conclusions using mouse models and LPS that accurately mimic intrauterine inflammation in humans: exposure to intrauterine inflammation during pregnancy results in postnatal brain injury, with chronic inflammation, presence of macrophages in the adult cortex, activation of microglia and long-term EEG biomarkers of neurodegeneration, setting the stage for development of neurodegenerative diseases in adulthood [77-79].

The already well-established link between diet and inflammatory biomarkers in the non-pregnant population also persists in pregnant mothers, particularly in those that are obese [80,81]. This is particularly worrisome considering that the sharp rise in obesity over the last 25 years is reflected in the increasing trend of obesity during pregnancy [82]. Increased adiposity associated with a HFD also increases the number of resident macrophages in white adipose tissue, the major type of immune cells in this tissue involved in the development of chronic inflammation [83]. These secrete inflammatory cytokines and chemokines and inhibit the production of anti-inflammatory adiponectin, further exacerbating an inflamed state. A maternal HFD is not the only contributor to chronic inflammation. Intra-uterine growth restriction (IUGR) in which maternal under/poor-nutrition is one of the principal causes, also leads to an inflammatory response in pregnant mothers and fetuses which is reflected by elevated serum concentrations of inflammatory markers, including TNF α , IL-6 and C-reactive protein (CRP) [84]. Prenatal protein restriction in maternal diet has also been associated with a pro-inflammatory state in offspring since increased expression of the pro-inflammatory genes, IL-6 and IL1 β in white adipose tissue macrophages of Sprague Dawley rat offspring was observed [85].

In a recent cohort study, an inflammatory diet was associated with small-for-gestational age infants among mothers with pre-pregnancy obesity and with high levels of the inflammatory marker, CRP [86]. Evidence from cell models suggest that cytokines such as IL-6 released by an inflammatory state may influence the epigenome by altering DNMT1 expression patterns which could result in disruption of epigenetic programming. [87]. This is in accord with accumulating evidence showing the association between maternal obesity (an inflammatory condition) and offspring methylation. Nomura et al. showed that maternal obesity was associated with placental global hypermethylation, which was also linked to infant length and head size. Although their findings did not reach significant levels, maternal obesity could potentially affect fetal programming of development, including

neurodevelopment. This study was conducted on a small sample size therefore the results would need to be reconfirmed on a greater sample size [88]. In another epigenetic study, maternal pre-pregnancy BMI (body mass index) was associated with offspring DNA methylation of the CpG sites in genes involved in a broad array of chronic diseases, including inflammation-mediated disorders and lipid metabolism, suggesting that maternal BMI-induced alteration in DNA methylation may be one of the mechanisms underlying fetal origins of adult diseases, comprising neurodegeneration [89]. However, because of some pitfalls in this study regarding sample size, possible inadequate techniques that had low coverage of CpG sites for each gene as well as a lower coverage of genes in the genome (~15k genes, <50% known human genes), small DNA methylation differences across BMI categories for the top hits found and possible misclassification of maternal pre-pregnancy BMI, future studies in a larger sample and using denser chips would be required to strengthen these findings.

Recently, in a non-human primate model, maternal over-nutrition via *in utero* exposure to a HFD lead to developmental programming of obesity and to pro-inflammatory gene signatures along with alterations in DNA methylation in key developmental genes in the offspring. Significant changes in gut microbiota were also observed [90]. In HFD-fed rats, Reynolds et al. were able to demonstrate that the dietary anti-inflammatory nutrient, conjugated linoleic acid (CLA), a lipid commonly found in beef and dairy produce, was effective in reversing the increased expression of the immunomodulatory cytokines TNF α and IL-1 β in the gut of offspring. In the same offspring, they also observed that CLA was able to partially reverse the altered expression of the gut taste receptors Tas1R1 and Tas1R3 which are linked to metabolic diseases [91].

The hypothesis that a pro-inflammatory diet leads to elevated concentrations of cytokines and other inflammatory molecules that alter the regulation of key genes in the developing fetus, mediated by epigenetic mechanisms, was recently investigated by McCulloch et al. They found consistent inverse associations between maternal inflammatory cytokine concentrations (IL-12, IL-17, IL-4, IL-6, and TNF α) and lower methylation at the MEG3 regulatory sequence in offspring but their results failed to support the link between a maternal inflammatory diet and circulating cytokines. However, they did observe that women with pro-inflammatory diets had elevated rates of preterm birth among female offspring but not male ones and higher rates of caesarean delivery among obese women. Based on their findings, they concluded that other factors may be more important contributors to inflammation than diet in the pregnant population. There are many sources of inflammatory molecules in pregnant women which could make it more difficult to observe than the contribution of diet alone [92].

In rodents, several relationships have also been established between inflammation, iron homeostasis and neurobehavioural changes induced by a maternal HFD [93]. Hepsidin is a critical

hormone in iron homeostasis and is primarily stored in oligodendrocytes. It is increased following inflammation causing subsequent decreases in ferroportin expression and the available iron needed for myelination [94]. Therefore disruptions in these interconnected processes may have deleterious effects on neurodevelopment by reducing myelination. Evidence is the decrease in myelination in the medial cortex recently observed in male pups (but not in females) born to maternal HFD-fed dams at PN21 with resulting changes in behaviour at 4 months [95].

Vitamin D is an anti-inflammatory nutrient, and its role in maternal diet and consequent systemic inflammation in offspring has recently been investigated. Low maternal vitamin D status is associated with systemic low grade inflammation, assessed via serum LPS in mouse offspring at adulthood [96]. However, when mothers were fed a diet enriched with vitamin D before pregnancy and during lactation, this was shown to be reversed in male offspring only. Long-lasting benefits to the metabolic, gut and bone health of C57BL/6J adult male mouse offspring exposed to an obesogenic diet were observed along with lower intestinal permeability and lower circulating levels of LPS [97,98]. At present, an understanding of the specific mechanisms responsible for the sex-specific alterations in offspring born to obese dams is not known, and whether the same occurs in humans. However, if it were to be confirmed, it would be an area of investigation worth pursuing for developing preventive and treatment strategies.

In summary, maternal dietary-induced inflammation appears to directly affect the developing fetus and offspring that includes neurodevelopment, and this may have a long-term impact on the onset of neurodegenerative disease later in life. Since most studies have focused on intervention in early life as a possible effective strategy for preventing developmental programming of metabolic dysfunction, this could also be valuable for preventing neurodegenerative diseases later in life, since they share a common denominator: inflammation. Controlling and preventing maternal obesity which is linked to inflammation, would not only be beneficial to expectant mothers but also to their offspring in the long run. Epigenetic modifications that control genes involved in inflammation, together with oxidative stress, may provide a mechanistic link between obesity and the promotion of neurodegeneration [99], therefore epigenetic markers may in the future be used for assessing the effects of intervention.

5. Strategies for prevention: Folate intake and microbiota during pregnancy

In the previous sections we have mentioned how epigenetic marks are determined by nutrition and this cannot be better exemplified than in the Agouti mouse model. Female mice fed on a high methyl supplemented diet (folic acid, vitamin B12, choline, betaine) deliver offspring that are brown in colour and healthy as opposed to controls which are yellow in colour and obese. This is associated with increased DNA methylation and silencing of the Agouti viable yellow (A^{vy}) gene [100].

There are specific micronutrients that act as cofactors and methyl donors which are responsible for mediating epigenetic processes in response to the maternal diet. Both prenatal iron and zinc deficiencies [101,102] have been reported to affect histone modifications and DNA methylation, likewise maternal folate and choline [103]. Offspring of rats fed on a maternal diet poor in the methyl donors folate, choline and methionine, showed increased anxiety behaviour and altered methylation of *neurontin*, an essential gene in neonatal brain development [104]. Severe maternal folate deficiency also results in neural tube defects (NTDs) where brain and spinal cord fail to develop normally, and in other congenital defects [105]. Early pregnancy is a critical period with rapid cell division, growth and proliferation, as well as high responsiveness to external influences, therefore optimal maternal folate concentrations are vital. However, the ideal concentrations are frequently not achieved through regular dietary folate intake (leafy green vegetables, beans and pulses) and deficiencies can lead to compromised epigenetic programming associated with long-term health consequences [106]. Because of this risk, women are advised to increase folate intake during pregnancy and a red blood cell folate level of greater than approximately 900 nmol/L is considered sufficient to reduce the risk of NTDs [107]. A recent study has highlighted the importance of folic acid supplement during the vulnerable peri-conception period (14 weeks before and 10 weeks after conception) on embryonic growth. A negative association was found between inadequate maternal folic acid supplementation and embryonic growth as well as growth rate during the first trimester [108]. In rodents, folic acid supplementation to pregnant rats prevents epigenetic and phenotypic effects on offspring [109], while paternal folate dietary deficiency is associated with increased birth defects in the offspring. Genome-wide DNA methylation analysis and the subsequent functional analysis showed differential methylation in sperm of genes implicated in development and chronic diseases suggesting that epigenetic transmission may involve sperm histone H3 methylation or DNA methylation and that adequate paternal dietary folate is essential for offspring health [110]. However, in this study overlap between genes that were identified as being differentially methylated in sperm and differentially expressed in placenta was limited to only two genes which moreover, did not show methylation differences in the placenta. This suggests that mechanisms other than DNA methylation are involved such as histone methylation. Although the study demonstrated that paternal environment can influence offspring phenotype by transfer of epigenetic information through sperm, at present no definitive convincing mechanism has been established, neither in this study nor in other similar studies. Both diet and stress are common examples for rodent models of intergenerational transfer of information about paternal conditions that have key metabolic outcomes in future generations, and these have been recently reviewed in [111,112].

Folic acid is recommended prior to and during the first trimester of pregnancy. However, because of folic acid food fortification programmes in many parts of the world for ensuring sufficient intakes in women approaching pregnancy, and because many women continue to take folic acid supplements beyond the recommended first trimester, there has been an overall increase in folate intakes. This has raised concerns on the consequences of this for the developing fetus, recently reviewed by McStay et al.[113]. Based on several human studies, they bring into question the role of folic acid intake in late pregnancy in the development of allergic disease in children, after the critical period of time for protection against NTDs. In animal studies, folic acid has been found to modify gene expression linked to the development of allergic disease in offspring which strengthens their findings [114].

Since maternal dietary folates and other micronutrients are involved in epigenetic programming of offspring, and because they all pass through the gut in order to be metabolized and absorbed, the role of a healthy gut and microbiome is thus of vital importance. The gut microbiota with its variability and complexity, modulates gastrointestinal functions because it works actively on the degradation of products derived from food intake, releasing active metabolites able to exert local and systemic effects even on the brain, through the gut-brain axis (GBA) [117]. Food intake plays an essential part in the gut microbiota composition and metabolite's production: fibers can actively promote the production of short chain fatty acids (SCFA) like butyric acid, propionic acid and acetic acid which have systemic effects. In particular, butyric acid can promote anti-inflammatory and anti-apoptotic effects in the colo-rectal region by promoting inhibition of TNF- α and IL6 production and encouraging IL10 release [116]. At the same time, SCFA work actively to promote glucose production and ATP synthesis in the colonocyte, with systemic effects on the hypothalamic hunger-satiety centre, insulin production and lipid synthesis [117]. Of particular relevance are recent elegant studies on human and animal models that underline the key role of microbiota composition in the mediation of gut inflammatory cytokines promoting neuroinflammation in PD and AD diseases [118-124]. The control of inflammation represents a key factor in the prevention of neurodegeneration: intrauterine infection has been suggested to inhibit microglial-derived growth factors which are associated with deficit in brain development and promotion of neurodegeneration in adulthood [125,126]. A well-designed recent study on 43 neonates born before 28 weeks of gestation, showed the association between placental indicators of inflammation and mRNA expression of 445 genes in umbilical cord tissue, six of which were correlated with cognitive deficit later in life [127]

In the previous section we discussed how an obese phenotype contributes to inflammation and how this is believed to arise in the gut following a HFD that induces increased circulatory LPS. It follows therefore, that changes in the maternal gut microbiome and intestinal permeability consequent to inflammation, may alter folate levels thus affecting epigenome programming in the offspring with

long-term consequences. Indeed, a significant role of gut microbiota as an epigenetic factor that influences DNA methylation and other epigenetic signatures has been speculated. Microbes within the human gut are important in the regulation of various elements of the GBA via immunological, endocrine and direct neural mechanisms [128,129]. Therefore it is plausible that neurodegenerative disorders may partly derive from dysregulation of this axis associated with gastrointestinal manifestations. This for example, has been postulated for PD where dysregulation of the gut-brain-microbiota axis may significantly contribute to the pathogenesis of the disease, reviewed in [130]. Indeed, a mechanistic hypothesis has been advanced indicating the gut as the gateway in neurodegenerative disease [131]. A wide gut microbial diversity represents a fundamental aspect associated with a healthy phenotype required to guarantee the maintenance of gut permeability in order to avoid any absorption of toxic compounds (i.e. lead, pesticides and other xenobiotics), and the release of pro-inflammatory cytokines that could reach the brain via the GBA and promote neuroinflammation associated with neurodegeneration (Figure 2) [132].

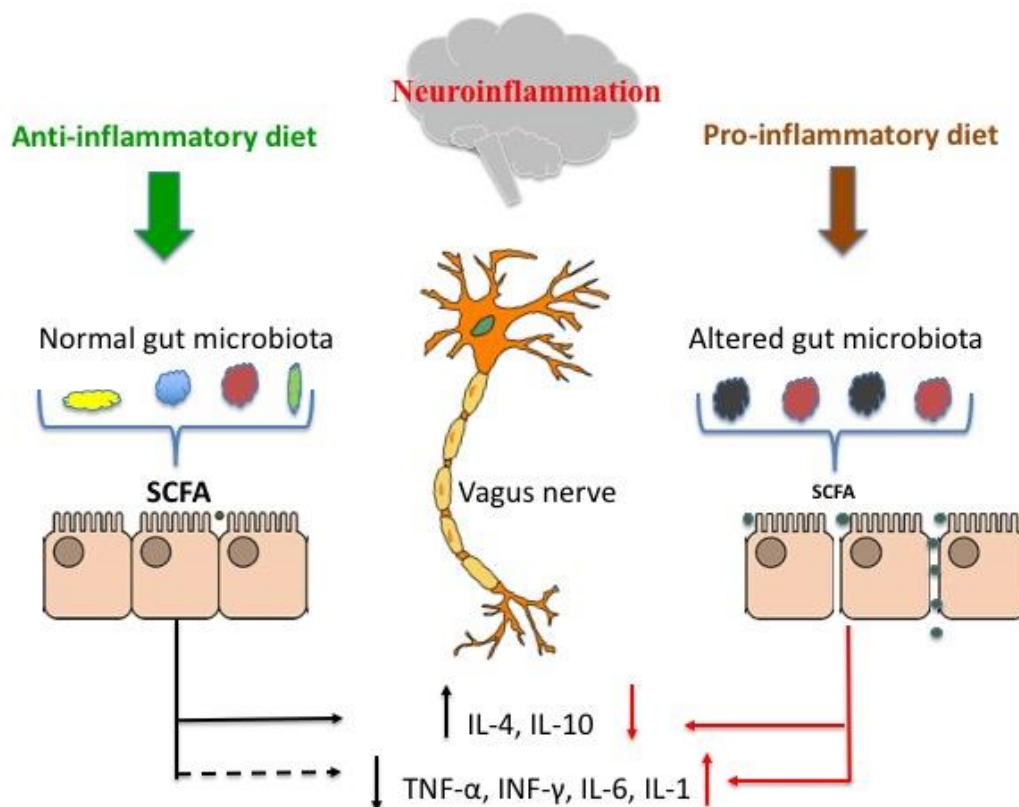


Figure 2. Simplified scheme on how diet modifies cytokine production by gut microbiota and its connection with neuroinflammation. SCFA: Short chain fatty acids

Hence, the microbiota of a pregnant mother may shape neurodevelopment of her off-spring and predispose her child to neurodegeneration later in life. Maternal microbiota, obesity and dietary intake are known to influence the composition of the infant gut microbiota. This is particularly relevant since the mother plays a direct role in initial colonization of the infant microbiota depending on whether infants are born vaginally or by caesarean section [133]. Furthermore, microbiota of pregnant obese women are different from normal pregnant women: the former have significantly higher *Staphylococcus*, *Enterobacteriaceae* and *E. coli* and fewer *Bifidobacterium*, *Bacteroides* and *Akkermanisa muciniphila* [134]. These differences could influence microbial colonization of the infant with important metabolic consequences in adulthood, recently reviewed in [135,136]. Could similar associations between obese mothers and their offspring predispose towards increased risk of developing neurodegenerative diseases later in life? A recent review by Contu and Hawkes who investigated the impact of maternal obesity on the cognitive function and mental health of offspring, points in this direction [137]. In fact, a few animal studies have reported disrupted DNA methylation patterns and altered clearance of the β -amyloid peptide, marker of AD, in the brains of adult offspring exposed to a HFD during the prenatal period. However, no work has been done yet to determine epigenetic changes in the brains of human offspring born to obese mothers for obvious ethical reasons, although alterations in the extent of DNA methylation in cord blood and microRNA in amniotic fluid have been reported in human studies of maternal obesity, supporting the above hypothesis [138,139].

6. Strategies for prevention: Postnatal nutrition on differences between breast-fed and formula-fed

The importance of early-life feeding patterns is vital since it shapes the early pioneering bacteria in the new-born, setting the stage for gut function and immune system development. This in turn may influence susceptibility to intestinal inflammatory disorders and other health and disease risks, and in the context of this review, possibly neurodegenerative disorders too later in life. The immune system of neonates is immature and requires the exposure of gut bacteria to develop properly and this is particularly important within the early days of life [140,141]. Other functions such as vitamin biosynthesis, energy retention and intestinal permeability essential for human health, also develop in parallel with gut microbe expansion. Initially, the infant gut is colonized by facultative anaerobes such as *Enterobacteriaceae* and *Lactobacillus*, followed by *Bifidobacterium*, *Bacteroides* and *Clostridium* [142]. Subsequently, milk-feeding practices play an essential role in microbiota composition. Compared to formula-fed milk, breast milk in healthy women contains a wider variety of viable and more beneficial bacteria, including *Staphylococcus*, *Streptococcus*, *Lactobacillus* and

Bifidobacterium, the two latter known to stimulate the developing immune system and improve intestinal barrier function [143-145]. The source of this diverse population of bacteria in breast milk is unclear, but it appears to derive from bacteria residing in the mother's gut. Human milk also contains secretory IgA, antimicrobial peptides, cytokines, and immune cells and over 200 non-digestible oligosaccharides (HMOs) which provide nutrients to the microbes colonizing the infant gut that produce specific SCFAs [146]. The HMOs and sIgA present in human milk are involved in preventing the colonization of pathogenic *Proteobacteria* during establishment of the early gut flora. *Proteobacteria* are believed to be important contributors to inflammation associated with metabolic disease in adults, and their role in infant immunity is critical for early priming of the innate and adaptive immune system [147-149]. Recently, differences in HMOs composition in mother's milk have also been associated with infant growth and body composition [150].

The gut microbiome of formula-fed infants is instead dominated by members of the *Enterobacteriaceae*, *Streptococcus*, *Bacteroides*, *Clostridium*, and *Bifidobacterium* families [151]. The SCFA profiles of formula-fed infants is also different to those that are breast-fed, the latter being characterized by high proportions of acetate and lactate and a lower proportion of propionate [152]. Since SCFAs play essential roles in host-immune regulation and have anti-inflammatory effects, considered important to protect against obesity and metabolic syndrome, it follows that the differences found between SCFAs consequent to the two types of milk-feeding, will lead to different outcomes in terms of health risks later in life. For instance, the different gut microbial community of formula-fed infants which have significantly higher levels of *Bacteroides* than breast-fed infants, has been linked to the possible risk of celiac disease [153].

Overall, breast-feeding compared to formula feeding which is more calorie-dense, is widely recognized to provide significant health benefits to infants, particularly in reducing the risk of pediatric obesity [154,155], and this risk is inversely related to the duration [156]. Since obesity is linked to inflammation and this in turn to neuroinflammation, then the risk of developing neurodegenerative diseases later in life may also be reduced by breast-feeding. Worthy of note is that breast milk from obese mothers has been shown to harbour a different and less diverse and beneficial bacterial community than that of normal-weight subjects, such as higher levels of *Staphylococcus* and *A. muciniphila* and lower levels of *Bifidobacterium* [157], along with a different composition of hormones, cytokines, and oligosaccharides [158]. In fact, infants born to obese mothers are exposed to higher levels of the hormones leptin and insulin present in mother's milk and these appear to be correlated with changes in the composition and characteristics of the neonatal microbiome [159]. Whether the early effects of human milk from obese mothers on changes in the microbiome contribute to future disease risks in their infants remains to be explored.

7. Strategies for prevention: what can be done in adult age?

Strategies for prevention could be defined mainly in three phases: the first includes nutrigenomic dietary interventions for the mother during pregnancy, the second is defined during the postnatal age in a different way by breast- or formula -feeding, both described above, while the last one includes both nutrigenomics and supplements useful to counterbalance the progression of neurodegeneration. It is important to mention that all these approaches exhibit common mechanisms of action: the first and the second might be useful for avoiding or delaying the development of neurodegeneration, while the third in adult age may be useful to also counterbalance/inhibit the alterations that have already initiated.

An anti-inflammatory diet might represent a key strategy to prevent the risk factors associated with the development of neurodegeneration later in life. To this aim, the daily diet should include food able to promote an active modulation on genes involved in the control of inflammation and in the maintenance of a balanced redox state starting from toddlers which should be educated on their importance and use throughout their whole life. Food containing phosphatidylcholine (i.e. red meat, fish, egg and other animal products) should be controlled in adult age because they can promote microbiota-mediated trimethylamine (TMA) which is converted into trimethylamine-oxide (TMA-N-oxide) after hepatic metabolism, and that can be accumulated inside the vascular wall leading to atherosclerosis and promoting macrophages pro-inflammatory responses [90]. A high fat diet also should be avoided because it modifies the inflammatory responses via NF κ B stimulation and pro-inflammatory cytokines that may change intestinal permeability. The latter can also be regulated by the level of *Akkermansia muciniphila*, a mucin-degrading bacterium, that has been reported to be positively associated with a reduction in adipose tissue inflammation, insulin resistance and restoration of the gut barrier [160-162].

Foods such as green/white/red/orange vegetables, red fruits, broccoli, curcuma, tea represent an important source of bioactive compounds able to protect against neurodegeneration [163]. Broccoli, kale, and radish of the *Brassicaceae* family contain sulforaphane, an isothiocyanate which becomes active only after myrosinase-mediated degradation of glucosinolate precursors such as glucoraphanin. However, the myrosinase contained in the *Brassicaceae* is inactivated by high temperatures (> 60 °C). Recently, it has been observed that gut microbiota can exert a myrosinase-like activity giving the possibility to produce sulforaphane even after cooking of vegetables [164]. The protective effect of sulforaphane is linked to its modulation of anti-inflammatory and antioxidant pathways. Several reports have demonstrated that sulforaphane is able to inhibit COX-2, while promoting the Nrf2/ARE pathway, an indicator and modulator of oxidative stress in neurodegeneration [165,166]. Moreover,

sulforaphane has been reported to improve behavioural cognitive impairments and attenuated brain A β burden in an Alzheimer's disease animal model [167]. Studies on mitochondria from human neuroblastoma SH-SY5Y cells treated with hydrogen peroxide, show that sulforaphane is able to protect mitochondrial membrane against lipid and protein oxidation; moreover it can also protect against loss of ATP [168]. For these reasons, its use against particular signs and symptoms of AD has been suggested [169].

Green tea for its high content in the flavonoid epigallocatechin gallate (EGCG) exerts a significant antioxidant and anti-inflammatory activity. In a mouse model of dopaminergic oxidative damage induced by the prodrug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), EGCG was shown to regulate the iron-export protein ferroportin, reducing oxidative stress in the brain [170]. In neonatal mice, EGCG inhibited the damage induced by exposure to sevoflurane, a toxicant used to induce neurodegeneration, and improved learning and memory by acting on the activation of the CREB/BDNF/TrkB-PI3K/Akt signalling pathway [171]. Quercetin, another flavonoid widely distributed in nature, has also been associated with a reduced risk of development of neurodegenerative disorders because it may mitigate oxidative stress and mitochondrial dysfunctions [172].

Resveratrol and curcumin, found in the skin of red and blue berries and in turmeric powder respectively, have anti-inflammatory properties due to their ability to decrease the expression of inflammatory genes (i.e. NF κ B, AP1, COX-2, and iNOS); it has been suggested that histone acetylation by activated NF κ B can be repressed by resveratrol [173]. The numerous reports on the positive effects of resveratrol and curcumin against the production of anti-inflammatory cytokines, underline their key protective role against neurodegeneration. A recent review that has summarized the data on curcumin in the last five years, highlights the neuroprotective role of curcumin which is able to cross the BBB, and exerts anti-inflammatory, antioxidant, and anti-protein-aggregating roles [174, 175].

Melatonin, produced by the pineal gland in animals, but also produced in plants, has been suggested as a strategic compound for its long-term effect on neuroprotection. Studies on LPS-treated animals show that melatonin can stimulate the SIRT1/Nrf2 pathway reducing reactive oxygen species production [176]. Similarly, a protective effect against the neurotoxin polychlorinated biphenyls (PCBs) on motor coordination and anxiety-like behaviour was observed when animals were co-treated with melatonin [177]. In a rat model of AD, melatonin improved the neurotoxicity and astrocyte activation due to β -amyloid1-42 (A β 1-42) exposure in the cerebral cortex. Furthermore, melatonin was able to inhibit the reduction of Reelin and Dab1 expression stimulated by A β 1-42 [178].

Lutein, a xanthophyll found in high quantities in green leafy vegetables, has been proposed to be useful in the protection of brain damage because of its beneficial properties during brain development. Lutein concentration has been correlated with lipid and energy metabolites, brain osmolytes and aminoacid neurotransmitters [179].

Lastly, since a high fat diet promotes hypothalamic inflammation and epigenetic programming, the composition and the content of fatty acids in the diet should be under control during all stages of life. At present, the main problem in early life nutritional strategies to prevent neurodegeneration is associated with the poor knowledge on ‘how much’ and ‘which’ foods should be included in the diet, that actually become bioavailable in order for their bioactive compounds to exert their protective effects. In dietary supplements, how much of the bioactive compounds should be present in order to achieve only long-lasting positive effects? These are all questions which are waiting to be addressed. Further research aimed to identify the association between “quantity/quality of food” and individual metabolic responses, should be promoted to finalize the data on the numerous bioactive compounds known, and those still awaiting to be discovered for contrasting the development of neurodegeneration (Figure 3).

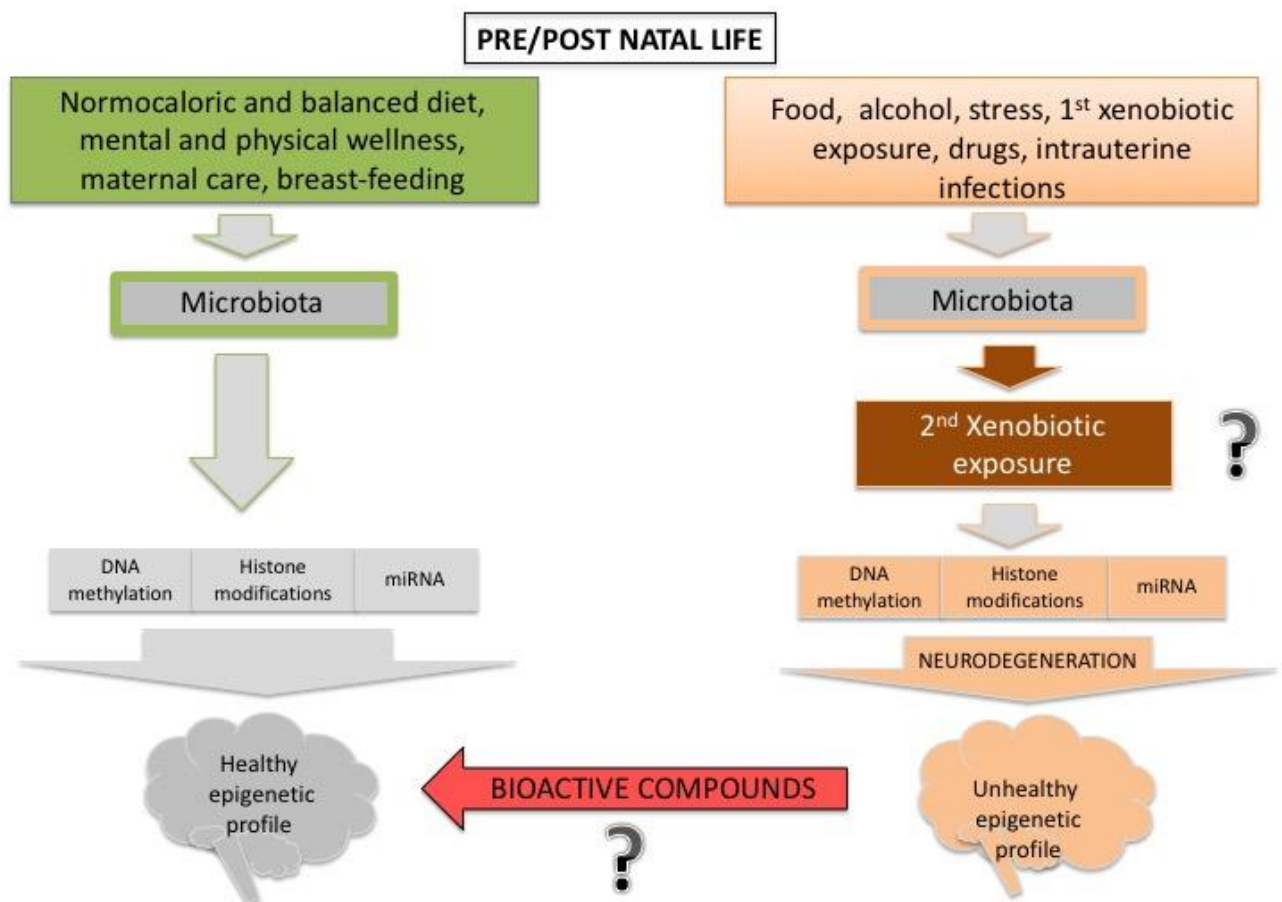


Figure 3: Risk factors for neurodegeneration and possible prevention strategies

8. Conclusion

Neurodegeneration is a complex aging process which starts as early as the intrauterine period of life. Early life actions are here suggested to prevent and counterbalance its development: 1) mother-to-be life style should be carefully monitored to guarantee the required balanced micro/macronutrients, avoidance of stress, drugs, xenobiotics or smoke exposure and finally any intrauterine infections; 2) early postnatal age of life should be under control for mother's food intake and environmental exposure if offspring is breast-fed; 3) vaginal delivery should be preferred, when possible, with respect to cesarian-section delivery particularly when the mother has a lean phenotype; 4) breast-feeding should be promoted longer because of its protective effect on offspring; 5) a diverse organic fruit and vegetable intake should be present in the diet of both young and adult people because of their key role in the maintenance of microbiota diversity which is importantly linked with SCFA production and with their anti-inflammatory activity associated with a healthy metabolic profile; 6) moderate physical activity, equilibrated emotional status and mental wellness contribute to the maintenance of an anti-inflammatory status; 7) intake through diet or supplements of bioactive compounds able to reduce oxidation and inflammation, thus preventing or counterbalancing progressive neurodegeneration, should be taken into account particularly in people exposed to environmental chemical and physical stressors.

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