



# Epigenetic signatures underlying inflammation: an interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition

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## Abstract

**Aim and objective** Emerging translational evidence suggests that epigenetic alterations (DNA methylation, miRNA expression, and histone modifications) occur after external stimuli and may contribute to exacerbated inflammation and the risk of suffering several diseases including diabetes, cardiovascular diseases, cancer, and neurological disorders. This review summarizes the current knowledge about the harmful effects of high-fat/high-sugar diets, micronutrient deficiencies (folate, manganese, and carotenoids), obesity and associated complications, bacterial/viral infections, smoking, excessive alcohol consumption, sleep deprivation, chronic stress, air pollution, and chemical exposure on inflammation through epigenetic mechanisms. Additionally, the epigenetic phenomena underlying the anti-inflammatory potential of caloric restriction, *n*-3 PUFA, Mediterranean diet, vitamin D, zinc, polyphenols (i.e., resveratrol, gallic acid, epicatechin, luteolin, curcumin), and the role of systematic exercise are discussed.

**Methods** Original and review articles encompassing epigenetics and inflammation were screened from major databases (including PubMed, Medline, Science Direct, Scopus, etc.) and analyzed for the writing of the review paper.

**Conclusion** Although caution should be exercised, research on epigenetic mechanisms is contributing to understand pathological processes involving inflammatory responses, the prediction of disease risk based on the epigenotype, as well as the putative design of therapeutic interventions targeting the epigenome.

**Keywords** Inflammation · Epigenetics · Nutrition · Environmental factors · Personalized nutrition

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## Introduction

Inflammation encompasses a myriad of pathophysiological and immune responses to diverse environmental “insults”, such as toxins or pathogens, in order to facilitate tissue recovery and to maintain homeostasis [1]. These mitigation and repair processes are mediated by the production and recruitment of cytokines, chemokines, adhesion molecules, and other autocrine/paracrine molecules focused on the local site of damage, thus inducing an acute inflammatory reaction [2]. However, when inflammation persists for a long time, it becomes a chronic condition, triggering a cascade of inflammatory events that eventually lead to durable cellular harms, permanent tissue injury, and organ dysfunction [3]. This state involves the induction of several pro-inflammatory mediators produced predominantly by activated macrophages, including Interleukin 1 beta (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin 6 (IL-6) to perpetuate the inflammatory phenotype [4]. The

inflammatory signaling is mediated by enzymes and adhesion molecules as well as the activation of nuclear factor kappa  $\beta$  (NF- $\kappa$ B) and other transcription factors as central regulators where the immune system and associated cells also play an orchestrated role [5]. The identification of factors involved in the onset and progression of inflammation is essential for the better understanding of inflammation-related disorders and the search for therapeutic targets.

Emerging evidence suggests that epigenetic processes affecting gene expression without changes in the nucleotide sequence may contribute to the pathophysiology of inflammatory processes [6]. In this context, it has been documented that epigenetic modifications (such as DNA methylation in CpG islands, chromatin remodeling by histone tail modifications, and non-coding RNA expression) occur after environmental stimuli and play a fundamental role in inflammatory gene transcription [7]. Indeed, integrative epigenome-wide association studies (EWAS) using large-scale bioinformatics analysis have reported different epigenetic marks related to several circulatory inflammation markers [8]. Therefore, epigenetic signature alterations may exacerbate inflammatory responses and influence the risk of chronic inflammatory disease, including diabetes, cardiovascular diseases, cancer, and neurological disorders [9]. However, elucidation of the specific epigenetic pathways involved in the modulation of the inflammasome and disease susceptibility remain largely unknown.

This review summarizes the current knowledge about the effects of obesity, infections (comprising bacterial and viral agents), smoking/excessive alcohol drinking, chronic stress, climate, pollution and other environmental factors including physical activity and the role of nutrients and dietary bioactive compounds on inflammation status through epigenetic mechanisms, and how these events may influence chronic disease development. This knowledge may allow the implementation of personalized nutrition based on inflammatory epigenetic signatures for the prevention and management of chronic inflammatory diseases.

## Nutrition/dietary bioactive compounds

Nutritional factors have been related with a pro-inflammatory potential [10]. Particularly, the consumption of Western-type diets evokes a state of chronic metabolic inflammation “metainflammation” that contribute to the development of many prevalent non-communicable diseases [11]. In this context, complex interactions among food components and the epigenome modifications shape the cellular phenotype by a dynamic regulation of gene expression from some time ago [12]. Thus, epigenetic phenomena may account for the observed relationships between diet, inflammation, and diet-related diseases [13].

Transgenerational animal studies have shown an increased inflammatory response after the consumption of high-fat/high calorie diets by altering miRNA expression and DNA methylation processes [14, 15]. In individuals at high-cardiovascular risk, the epigenetic signature associated with the consumption of fruit juice (rich in fructose) was enriched for pro-inflammatory pathways [16]. Consistently, compelling evidence supports the association of excessive fructose consumption with the presence of non-alcoholic fatty liver disease (NAFLD) involving alteration of transcriptomic and epigenetic mechanisms underlying lipid metabolism deregulation, increased liver fat accumulation, and inflammation [17]. Additionally, maternal low-dietary protein regulated miRNA expression targeting genes mapped to inflammatory-related pathways and metabolic health in offspring mice [18].

The role of dietary fatty acids in epigenetic and inflammatory processes has also been explored [19] and is summarized (Table 1). In this context, the *trans* fatty acid “elaidate” induced pro-inflammatory and adipogenic transcriptional profiles through methylation changes in cultured human monocytes [20]. Likewise, the saturated fatty acids “stearate” and “palmitate” were associated with DNA hypermethylation of the *PPAR $\gamma$ 1* gene promoter, which was identified as a critical determinant of pro-inflammatory activation and insulin resistance in macrophages [21]. Of note, DNA methylation levels of the *TNF* promoter were associated with adiposity measures and *n*-6 polyunsaturated fatty acid (PUFA) intake, suggesting a nutriepigenomic regulation of this recognized pro-inflammatory marker [22]. Remarkably, it has been reported that short-chain fatty acids (produced by the gut microbiota) can also target the epigenome to regulate host pathophysiological processes, including inflammation [23].

On the other hand, the anti-inflammatory potential of essential fatty acids mediated by epigenetic phenomena has also been analyzed (Table 1). For example, *n*-3 PUFA supplementation was associated with changes in DNA methylation profiles in blood leukocytes related to pathways involved in inflammatory and immune responses, among others [24]. In addition, *in vitro* analyses revealed that the anti-inflammatory effect of oleic acid, a monounsaturated fatty acid (MUFA), was related to DNA methylation signatures [25].

In relation to dietary fiber, an epigenome-wide association study in African American adolescents showed that DNA methylation levels at *LPCAT1* and *RASA3* genes (playing a role in colon cancer) were associated with fiber consumption, adiposity, and inflammation [26]. Concerning micronutrients, unbalanced intakes of folate [27], manganese [28], and carotenoids [29] have been associated with changes in the methylation status of candidate inflammatory genes in some populations.

**Table 1** Studies analyzing the epigenetic effects of different fatty acids concerning inflammatory conditions

Type fatty acid	Dose/concentration	Study model	Epigenetic signatures	Modification types	Inflammation	Reference
Trans fatty acid elaidate sup	50 $\mu$ M	THP-1 monocytes	Global DNA methylation	↑	↑	[20]
Saturated fatty acids stearate and palmitate	200 $\mu$ M palmitate and 200 $\mu$ M stearate	Bone marrow-derived macrophages	PPAR $\gamma$ 1 promoter DNA methylation	↑	↑	[21]
n-6 PUFA	Intake inversely associated	Peripheral white blood cells	TNF $\alpha$ gene promoter methylation	↓	↑	[22]
n3-PUFA supplementation	3 g	Blood leukocyte	Differentially methylated CpG sites related to inflammatory and immune response	ND	↓	[24]
Arachidonic acid	100 $\mu$ M	THP-1 cells	Global DNA methylation	↑	↑	[25]
n3-PUFA supplementation	EPA and DHA provided in the form of 0.5% Gromega <sup>TM</sup>	Five sows	On chromosome 4, a 27.7-kb differentially methylated region downstream of RUNX1T1 gene	↓	↓	[196]
n3-PUFA supplementation	EPA and DHA provided in the form of 0.5% Gromega <sup>TM</sup>	Five sows	Intergenic regions of chromosomes 4 and 12	↑	↓	[196]
Oleic acid supplementation	5 $\mu$ M	THP-1 cells	Global DNA methylation	↑	↓	[20]
Oleic acid supplementation	100 $\mu$ M	THP-1 cells	Global DNA methylation	↓	↓	[25]

ND non-determined

On the other hand, dietary bioactive compounds are known to negatively regulate several inflammatory pathways [30]. Thus, it has been reported that plant-derived polyphenols exert anti-inflammatory properties by interfering with immune cell regulation, synthesis of pro-inflammatory cytokines, and gene expression, which are associated with health benefits for different chronic diseases related to inflammation such as obesity, type 2 diabetes (T2D), neurodegeneration, cardiovascular disease (CVD), and some types of cancer [31]. Polyphenols are compounds with phenolic structural features naturally distributed in fruits, vegetables, whole grains as well as in tea, chocolate, and red wine [32]. These include phenolic acids, flavonoids (i.e. epicatechin, luteolin, and fisetin) and phenolic amides, and other non-flavonoid polyphenols found in foods such as resveratrol, gallic acid and its derivatives, and curcumin [32]. Interestingly, studies have revealed that the protective effects of polyphenols on inflammation are partially modulated via epigenetic modifications, thus contributing to the current understanding of the molecular mechanisms of action of these biologically active compounds (Table 2).

For instance, the daily intake of grape extract resveratrol for 1 year modified the expression of a group of miRNAs involved in the regulation of the inflammatory response in PBMCs from hypertensive male patients with T2DM,

including miR-21, miR-181b, miR-663, miR-30c2, miR-155, and miR-34a [33]. Moreover, mango (*Mangifera indica* L.) polyphenols, containing gallic acid and gallotannins, reduced inflammation in two in vitro and in vivo models of intestinal colitis by regulating the PI3K/AKT/mTOR pathway partially through up-regulation of miR-126 expression [34]. Additionally, the administration of (–)-epicatechin attenuated the high-glucose-induced inflammatory response in human monocytes by epigenetic modulation of H3K9 acetylation and H3K4 dimethylation [35], notably the combination of luteolin- and fisetin-induced anti-inflammatory effects in human monocytic cells under high-glucose concentrations involving histone acetyltransferase/histone deacetylase modifications [36]. In a similar high-glucose condition, curcumin decreased the production of pro-inflammatory cytokines by inhibiting histone acetylation in monocytes [37].

In addition to polyphenols, the anti-inflammatory role of other dietary factors and specific functional foods has also been assessed in different experimental models. In this regard, extra virgin olive oil (EVOO) and *Nigella sativa* oil displayed anti-inflammatory activities in lipopolysaccharide (LPS)-exposed human macrophages through epigenetic mechanisms [38]. In this study, the administration of both oils reverted the altered expressions of *DNMT3A* and *HDAC1* to normal levels under inflammatory conditions,

**Table 2** Studies analyzing the anti-inflammatory effects of dietary polyphenols via epigenetic regulation in several chronic inflammatory conditions

Type of polyphenol	Dose/concentration	Study model	Epigenetic signatures	Modification types	Reference
Grape extract resveratrol	8 mg	PBMCs from T2DM and hypertensive patients	miR-21, miR-181b, miR-663, and miR-30c2 expressions	↑	[33]
Resveratrol	10 μM	LPS-stimulated RAW 264.7 macrophages	miR-146a expression	↓	[197]
Resveratrol	1 g/kg	SAMP8 mice offspring	<i>Nrf2</i> and <i>Nfkb</i> methylation levels	↑	[198]
Resveratrol	10 μM	ARPE-19 cells exposed to GOx and LPS	DNMT and SIRT1 expressions	↑	[199]
Trans-resveratrol	50 mg/kg	Postnatal rats exposed to perinatal asphyxia	miR132 and miR15a expressions	↓	[200]
Mango ( <i>Mangifera indica L.</i> ) polyphenols	10 mg/L	Rats exposed to dextran sodium sulfate (DSS)	miR-126 expression	↑	[34]
Mango ( <i>Mangifera indica L.</i> ) polyphenols	10 mg/L	LPS-treated CCD-18Co cells	miR-126 expression	↑	[34]
Oleocanthal and oleacein	25 μM/L	Adipocytes	miR-155-5p, miR-34a-5p and let-7c-5p	↑	[201]
Hydroxytyrosol	10 μM/L	Adipocytes	miR-155-5p, miR-34a-5p	↓	[202]
Polyphenol-rich green tea	500 mg/body weight	White adipose tissue	miR-335	↓	[203]
Apigenin	10 mg/kg	C57BL/6 J mice	let-7f	↑	[204]
(-)-Epicatechin	5 μM	THP-1 cells exposed to high glucose	H3K9 acetylation and H3K4 dimethylation	↓	[35]
Polyphenol-rich lingonberries ( <i>Vaccinium vitis-idaea</i> )	20% w/w	High-fat fed C57BL/6 J mouse	<i>Ncor2</i> methylation	↑	[205]
Luteolin	10 μM	THP-1 cells exposed to high glucose	HAT activity	↓	[206]
Gallic acid	25 μM	THP-1 cells exposed to high glucose	HAT activity HDAC2 expression	↓	[207]
Fisetin	10 μM	THP-1 cells exposed to high glucose	HAT activity	↓	[208]
Red raspberry polyphenols	10 μg/ml <sup>-1</sup>	J774 macrophages	H3K27Ac expression	↓	[209]
Epigallocatechin gallate	20 μM	Regulatory T cells	HDAC activity	↑	[210]

with an additional role of EVOO in the reduction of global methylation. Also, a nutritional intervention with Mediterranean diet plus EVOO influenced the methylation status of genes involved in inflammatory pathways in PBMCs [39]. Similarly, higher adherence to Mediterranean diet was positively associated with the methylation of a set of genes related to inflammation and immunocompetence in high cardiovascular risk volunteers [40].

Meanwhile, increased DNA methylation of the tumor necrosis factor (*TNF*) gene was found after supplementation of grapefruits extracts in rats, which may contribute to reduce chronic low-grade systemic inflammation in obesity [41]. Also, ginger extracts ameliorated obesity and inflammation in white adipose tissue of rats fed a high-fat diet via regulation of miR-21/132 expression and AMPK activation [42].

A maternal diet rich in methionine pathway metabolites induced global hypermethylation on T cells from F1 C57Bl/6 mice, which was associated with lower expression of inflammatory T cell chemokine receptors (*CCR2*, *CCR5*, *CXCR3*) and cytokines (*TNF*, *IL2*, and *IL4*) [43]. Furthermore, selenium and coenzyme Q10 supplementation reduced pro-inflammatory markers in healthy elderly participants through changes in plasma miRNA expression [44]. Vitamin D has been reported to down regulate inflammation-linked miRNA expression in adipocytes both in vitro and in vivo [45]. Besides, maternal high-zinc diet attenuated intestinal inflammation in offspring chicks by epigenetic changes [46].

Further, increasing research has provided evidence about the long-lasting epigenetic effects of calorie restriction which mediates expression of genes related to immuno-metabolic processes that may enhance quality of life and extend

lifespan, with important applications for the prevention of chronic inflammatory diseases [47]. Interestingly, methylation profiles in inflammatory genes have been proposed to be used as epigenetic biomarkers concerning adiposity and metabolic outcomes in response to low-calorie diets (30% of energy restriction, 55% of energy as carbohydrates, 15% as proteins, and 30% as lipids) [48, 49]. Moreover, findings from the RESMENA and DIOGENES trials have evidenced a decline in inflammation [50, 51] and improvements of metabolic syndrome features [52, 53] after following an energy-restricted diet (−30% energy of the calculated requirements, 40% total energy value from carbohydrates, 30% from proteins and 30% from lipids), which was partially explained by epigenetic signatures.

## Physical activity

Studies have shown that some physical exercise may exert anti-inflammatory effects through epigenetic regulation depending on the type of activity, exercise duration, body composition, gender, and age [54]. However, excessive physical activity (i.e. in 10-km marathons, or treadmill runs for 120 min followed by a 5-km time trial in a fasted condition) can also induce inflammation [54]. Thus, in a population-based cohort study, substituting light-intensity physical activity (<3 METs; acceleration intensities 1–3) for sedentary time was associated with higher methylation of the *ASC* gene, a potential biomarker of systemic inflammation [55]. Also, aerobic capacity, as measured by peak oxygen uptake (17.31 ml/kg/min), was positively associated with increased *ASC* methylation as well as with decreased plasma IL-1 $\beta$  levels in stable outpatients with heart failure, suggesting that inflammatory processes may influence aerobic capacity [56]. Furthermore, interval walking training (IWT) increased *NFKB2* gene promoter methylation, indicating that this physical regime may epigenetically impact the susceptibility to inflammation [57]. IWT consisted of performing several continuous sets of 3-min low-intensity walking periods at 40% of the peak aerobic capacity, followed by 3-min high-intensity walking periods at >70% peak aerobic capacity for as many days as possible over a period of 6 months [57]. Of note, diet could interact with physical activity since the supplementation of dried tofu during IWT enhanced *NFKB2* gene methylation more than IWT alone, suggesting an immunomodulatory synergistic effect of diet and physical activity via epigenetic modulation [58]. Consistently, higher dose of dairy product intake (1 unit of cheese + 2 units of yogurt) plus IWT produced increases in *NFKB1* and *NFKB2* gene methylations in older women, suggesting a larger pro-inflammatory cytokine gene suppression effect [59].

In patients with obesity, physical activity (26 mixed aerobic and endurance training sessions of 90 min administered

twice a week during 3 months) modulated the overexpression of the inflamma-miR-146a-5p, which was postulated as a biomarker and personalized predictor of the clinical response to physical activity weight-reduction programs in obesity [60]. Surprisingly, acute aerobic exercise (30 min, 75%  $VO_{2max}$ ) elicited higher elevation of inflammatory miRNAs in obese patients compared to lean individuals [61]. In basketball players, changes in circulating miR-146a after acute exhaustive exercise (the average playing time of every athlete was 260 min for 3 months, peak  $VO_2 \approx 35$  ml/min/kg) showed linear correlations with levels of the inflammatory marker high-sensitivity C-reactive protein [62]. Moreover, distinct and specific circulating inflammatory miRNA (c-inflammamiRs) signatures were found in plasma samples from active middle-aged males following different doses of acute aerobic exercise (0 h, 24 h, 72 h) 10-km, half-marathon, and marathon races), suggesting an epigenetic mechanism controlling the exercise-induced inflammatory cascade [63]. The results of this study revealed a dose-dependent effect of aerobic exercise on systemic inflammation, with higher levels detected after 10-km race [63]. Compared to age-matched sedentary controls, master athletes (European Veterans Athletics Championships in 2010, Nyiregyhaza, Hungary) had decreasing ageing-related inflammation in skeletal muscle related to lower levels of miR-7, which has been suggested to be involved in chronic inflammation in the elderly [64]. Additionally, acute strenuous exercise (consisting of stepping up and down from a step until complete exhaustion) led to enhanced chronic low-grade inflammation in PBMCs from obese individuals via an imbalance on Histone H4 Acetylation/Histone Deacetylase 2 as compared to lean subjects [65]. Together, these findings suggest that the impact of physical activity in inflammation is dependent of type, intensity, and clinical settings of exercise interventions [54].

## Obesity and associated diseases

Obesity is a metabolic condition associated with adipose tissue dysfunction and low-grade systemic inflammation that causally contributes to the development of chronic disorders such as T2D and CVD, where epigenetic mechanisms may be involved [66]. Indeed, it has been reported that the alteration of the adipocyte physiology in obesity might be related to specific alterations in the expression pattern of miRNAs related to inflammatory processes [67]. Also, the adverse effects of the inflammatory state include insulin resistance in the adipose tissue and pancreatic  $\beta$ -cell dysfunction, which may induce epigenetic changes that perpetuate inflammation [68]. In consequence, the resulting hyperglycemia and hyperlipidemia conditions as well as persistent inflammation involving

epigenomic deregulation could cause damage to the vasculature with putative risk to develop CVD [69]. In the same time, excessive adiposity negatively impacts immune function and host defense in obese individuals, increasing the susceptibility to infection and related morbidity and mortality [70].

Epigenetic mechanisms involved in obesity-related inflammation are summarized (Table 3). For example, global DNA hypermethylation has been positively associated with increased expression of specific pro-inflammatory genes (including the *CCL2* gene) in adipocytes from obese individuals [71]. BMI-discordant twin pair analyses detected methylome deregulations of subcutaneous adipose tissue in obesity that trigger inflammation and may contribute to the development of unhealthy obesity outcomes [72]. Thus, methylation analyses in obese individuals showed significantly lower methylation of four CpGs in the first exon of the *TLR4* gene, suggesting epigenetic regulation of inflammatory processes in obesity [73]. Moreover, it was reported that aberrant methylation of the *IL6* gene promoter may play a role in the etiology and pathogenesis of excessive body weight in humans [74]. Findings from the Methyl Epigenome Network Association (MENA) project revealed associations between methylation sites in peripheral blood mononuclear cells (PBMCs) and waist circumference, which were located in genes related to inflammation and obesity [75]. Likewise, it was reported that DNA methylation in adipose-derived stem cells was significantly modified by an obese environment, affecting pathways involved in adipogenesis, inflammation, and immunosuppression [76]. Genome-wide DNA methylation analysis in visceral adipose tissue of severely obese men with and without metabolic syndrome detected differentially methylated regions mapped to genes related to inflammation and immunity [77].

Of note, the expression of the *NNMT* gene, a major methyltransferase enzyme, was positively correlated with markers of inflammation in adipose tissue samples from morbidly obese patients [78]. In addition, a higher expression of *DNMT3b* methyltransferase was found in adipose tissue macrophages isolated from obese mice, supporting a role for *DNMT3b* in regulation of macrophage polarization and inflammation in obesity [79]. In adipose tissue of obese mice, gene expression levels of the *Dnmt3a* methyltransferase were markedly increased, as were many inflammatory cytokines, suggesting that increased expression of *Dnmt3a* may contribute to obesity-related inflammation [80]. Remarkably, DNA methylation changes of the *Klf14* gene (a master regulator of gene expression) provided prediction for chronic inflammation in the adipose tissue of mice suffering obesity and diabetes conditions [81]. Furthermore, altered gene methylation profiles on immune cells were related to impaired metabolism and inflammatory response in a porcine model of obesity [82].

In mice, diet-induced obesity led to hypermethylation of the *Ankrd26* gene (previously associated with the development of obesity and T2DM), which in turn, contributed to enhanced secretion of pro-inflammatory mediators in white adipose tissue [83]. Consistently, epigenetic silencing of the *ANKRD26* gene by increased promoter methylation correlated with a pro-inflammatory profile and the presence of cardio-metabolic risk factors in peripheral leukocytes from obese individuals [84]. Transgenerational studies detected DNA methylation changes of key inflammatory genes in monocytes from neonates born of obese mothers, underlying an intrauterine epigenetic programming of immune function by maternal obesity [85]. Accordingly, maternal pregravid obesity has been associated with epigenetic modifications altering the inflammatory program of the offspring's monocytes at birth [86].

A bioinformatic approach identified a total of 23 active microRNAs (miRNAs) and transcription factor regulatory pathways significantly associated with obesity-related inflammation [87]. Also, a set of exosomal miRNAs differentially expressed in abdominal obesity was associated with inflammation [88]. Overweight and obesity led to deregulation of circulating inflammatory miRNAs, which may contribute to the heightened inflammatory state associated with these conditions [89]. In adipocytes and macrophages, inflammation boosted a specific miRNA pattern, with a negative impact on the physiopathology of obesity-induced inflammation [90].

Particularly, circulating miR-374a-5p was characterized as a potential modulator of the inflammatory response in obesity [91]. In vitro analyses unveiled a key role of miR-326 expression in mediating obesity-induced adipose tissue inflammation through regulating the differentiation toward Th17 cells [92]. Also, miR-30 was identified as an important regulator of macrophage polarization in mice, indicating that miR-30 could be a therapeutic target for obesity-induced metabolic inflammation [93]. Besides, adipocyte-secreted exosomal miR-34 was progressively increased with the development of dietary obesity, transmitting signals of nutrient overload to adipose-resident macrophages for exacerbation of obesity-induced systemic inflammation and associated metabolic complications [94]. In the same way, obesity induced an imbalance in macrophage polarization in adipose tissue through miR-155 up-regulation, thus causing chronic inflammation and insulin resistance [95]. Accordingly, obesity-associated inflammation induced miR-155 expression in adipocytes resulting in an increased inflammatory state in these cells [96]. Using an obese mice model, it was observed that the expression of miR-27a increased concomitantly with the activation of pro-inflammatory pathways [97]. Meanwhile, miR-130b contributed to obesity-associated adipose tissue inflammation and insulin resistance in diabetic rodents [98]. Endoplasmic reticulum stress and inflammatory

**Table 3** Some studies showing relevant epigenetic mechanisms underlying obesity-related inflammation

Study model	Epigenetic signatures	Modification types	Reference
<i>DNA methylation</i>			
Human adipocytes	Global DNA methylation	↑	[71]
Human subcutaneous adipose tissue	Methylation of 17 novel obesity-associated genes	DMRs	[72]
Human white blood cells	Methylation of four CpGs in the first exon of <i>TLR4</i> gene	↓	[73]
Human white blood cells	DNA methylation of <i>IL6</i> gene promoter	↑	[74]
Human peripheral white blood cells	DNA methylation of 375 CpGs	DMRs	[75]
Human adipose-derived stem cells	Global DNA methylation	↓	[76]
Human visceral adipose	8578 methylation probes (3258 annotated genes)	DMRs	[77]
Human visceral adipose	Global DNA methylation affecting DNMT expression	DMRs	[78]
Mice macrophages	DNMT3b expression	↑	[79]
Mice adipose tissue	Dnmt3a expression	↑	[80]
Mice adipose tissue	<i>KLF14</i> gene methylation	↑	[81]
Porcine leukocytes	Global DNA methylation	↑	[82]
Mice white adipose tissue	<i>Ankrd26</i> gene methylation	↑	[83]
Human peripheral white blood cells	<i>ANKRD26</i> methylation	↑	[84]
Human monocyte-derived macrophages	<i>IL1B</i> gene promoter methylation	↑	[85]
Human monocyte-derived macrophages	<i>IL10</i> gene promoter methylation	↓	[85]
Human cord blood monocytes	Global DNA methylation	↓	[86]
<i>miRNA profiles</i>			
Human subcutaneous adipose	Obesity-related miRNAs expression	DERs	[87]
Human adipose tissue	Exosomal miRNAs expression	DERs	[88]
Human plasma	miR-34a expression	↑	[89]
Human plasma	miR-126, miR-146a and miR-150 expression	↓	[89]
Human adipose tissue	miR-221, miR-222, and miR-155	↑	[90]
Human peripheral blood	MiR-374a-5p expression	↑	[91]
Human Th17 cells	miR-326 expression	↑	[92]
Mice adipose tissue macrophages	miR-30 expression	↓	[93]
Mice adipose tissue	miR-34a expression	↑	[94]
Mice adipose tissue macrophages	miR-155 expression	↑	[95]
Human adipose tissue	miR-155 expression	↑	[96]
Mice adipose tissue	miR-27a expression	↑	[97]
Mice peritoneal macrophages	miR-130b expression	↑	[98]
Human adipose tissue	miR-320 expression	↑	[99]
Mice adipose tissue	miR-221 expression	↑	[100]
Human macrophages	miR-223 expression	↑	[101]
Human adipose tissue	miR-193b and miR-126 expressions	↑	[102]
Mice adipose tissue	miR-1934 expression	↓	[103]
Mice adipose tissue	miR883b-5p expression	↓	[104]
Mice adipose tissue macrophages	miRNA-146a	↓	[105]
Mice adipose tissue	miR-706 expression	↓	[106]
Human PBMCs	miR-21 expression	↓	[107]
Mice adipose tissue	miR-301a expression	↓	[108]
Mouse chondrocytes	miR-26a expression	↓	[109]
<i>Histone modifications</i>			
Human adipose tissue	HDAC2 expression	↑	[110]
Human adipose tissue	HDAC4, 5, and 6	↓	[110]
Mice adipose tissue	KDM1A expression	↓	[111]
Human and mice adipose tissue	Sirt1 expression	↓	[112]
Mice adipose tissue	Lipin 1 expression and HDAC recruitment	↓	[113]

DMRs Differentially methylated regions, DERs differentially expressed regions

markers were up-regulated in obese patients, showing positive correlations with miR-320 expression in adipose tissue [99]. miR-221 triggered white adipose tissue inflammation and insulin resistance in obesity partially through suppressing SIRT1 [100]. Visceral adipose miR-223 up-regulation modulated macrophage-mediated inflammation in human and murine obesity models [101]. miR-126 and miR-193b were further identified as important regulators of adipose inflammation in human obesity through effects on CCL2 production [102].

In contrast, the anti-inflammatory miR-1934, miR532-5p, and miR-146a were down-regulated in obesity, which promoted inflammation in adipose tissues [103–105]. Moreover, down-regulation of miR-706 played a role in increasing adipose tissue inflammation in the offspring during maternal obesity in mice [106]. Likewise, decreased expression of miR-21 was associated with enhanced inflammatory cytokine production in PBMCs from obese individuals [107]. Decreased levels of miR-301a and miR-26a correlated with increased chronic inflammation in circulation in obese mouse models [108, 109].

Furthermore, transcriptional analyses showed associations between expressions of histone deacetylases (HDACs), adiposity indices, and obesity-induced inflammation in adipose tissues from obese women [110]. Interestingly, diet-induced and genetic mouse models of obesity displayed decreased expression of the histone demethylase (HDMs) KDM1A in adipose tissue, which promoted the expression of inflammatory genes, thus contributing to the development of obesity-associated inflammation [111]. Furthermore, it was evidenced that SirT1 expression, an essential nutrient-sensing HDAC, regulated adipose tissue inflammation during overnutrition in rodents and humans [112]. Also, it was demonstrated that lipin 1 (a bifunctional protein that regulates gene transcription and triacylglycerol synthesis) inhibited the secretion of inflammatory factors in adipocytes via repression of NFATc4 transcriptional activity and HDACs recruitment; however, this anti-inflammatory effect was attenuated during obesity [113].

Together, these insights support the role of epigenetic mechanisms underlying obesity-induced inflammation and accompanying chronic diseases, including T2D and CVD [66]. This knowledge opens new possibilities for a potential use of epigenetic signatures as biomarkers for diagnosis, prognosis, and personalization of obesity treatment as well as targets for disease management [67].

## Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are common environmental compounds (i.e. phthalates and bisphenol A) that may induce chronic disease through hormone dysfunction

and inflammatory processes [114]. In this regard, exposure to many EDCs can influence the onset or progression of CVD by epigenetic modifications affecting lipid homeostasis and atherosclerosis [115]. Indeed, the association of bisphenol A exposure with CVD and hypertension encompasses endocrine disturbance, induction of oxidative stress and inflammation, and epigenetic phenomena [116].

Concerning the role of epigenetic phenomena in mediating EDCs-induced inflammation, it was reported that mono-(2-ethylhexyl)phthalate led to an increased inflammatory response by impairing important epigenetic regulators and inflammasome activation in macrophages [117]. Also, maternal exposure to butyl benzyl phthalate increased the risk for allergic airway inflammation in the offspring through methylation modifications [118]. Meanwhile, perinatal bisphenol A exposure enhanced the mast cell-mediated production of pro-inflammatory mediators of adult mice, which was associated with pulmonary inflammation and global DNA methylation levels [119]. Similarly, gestational exposure to bisphenol A increased inflammation/oxidative stress markers in sheep through epigenetic alterations [120].

## Infections

Infectious diseases are caused by a broad range of pathogenic microorganisms including viruses, bacteria, parasites or fungi. In the past years, new infectious diseases have emerged, including the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2/COVID-19) in December 2019, with serious public health implications worldwide due to rapid spread and the absence of specific treatment schemes or vaccine [121].

After invading the host, complex signaling pathways between immune cells are activated in order to coordinately initiate an inflammatory response against infection, where epigenetic mechanisms shaping the course of inflammation are involved [122]. In some cases, the immunological response to infection may be excessive, producing an inflammatory cytokine storm that eventually lead to extensive tissue damage and organ dysfunction [123].

For instance, it has been reported that inflammation triggered by *Helicobacter pylori* infection was related to differential DNA methylation patterns in human gastric mucosa [124]. Also, *H. pylori*-induced chronic inflammation played a direct role in the induction of aberrant DNA methylation, which correlated with gastric cancer risk [125]. In humans, the levels of methylation in gastric mucosae were associated with *H. pylori* virulence and measures of chronic inflammation [126]. During chronic *H. pylori* infection, inflammation-induced epigenetic silencing of miR-210 was identified as a mechanism of proliferation of gastric epithelium, with implications in gastric cancer development [127].

Experimental periodontitis using systemic microbial challenge (*Porphyromonas gingivalis* gavage) led to distinct patterns of inflammatory and epigenetic features [128]. miR-181a-5p and miR-21a-5p influenced the expression of inflammatory mediators in macrophages infected with *Bruceella abortus*, thus contributing to bacterial control in host cells [129]. In addition, bacterial vaginosis predicted the length of gestation through miRNA-related epigenetic programming of the inflammatory response [130]. Furthermore, histone H3K14 hyperacetylation and differentially expressed miRNAs regulated the host inflammatory response during *Staphylococcus aureus* infection in mice mammary tissue [131]. Similarly, *Escherichia coli* infection in murine mammary tissue promoted histone hyperacetylation at genes related to the expression of inflammatory genes and drastic immune response [132].

Sepsis is defined as life-threatening organ dysfunction caused by a deregulated systemic immune response to infection. Interestingly, DNA methylation changes have been associated with sepsis in monocytes, which correlated with inflammatory signals [133]. Besides, chromatin modifications have been implicated in the regulation of the cellular immune/inflammatory responses in patients with sepsis [134].

Regarding viral infections, it was demonstrated that TLR3 activation increased HIV-1 transactivation in primary human macrophages via the inflammatory JNK and NF $\kappa$ B pathways and histone acetylation [135]. In vivo analyses revealed that respiratory syncytial virus infection induced the H3K4 demethylase KDM5B to promote an altered immune/inflammatory response that contributed to the development of chronic disease [136]. Human cytomegalovirus infection resulted in profound effects on the host cell DNA methylation machinery and was associated with inflammation in vivo [137]. Hypermethylation of PPAR gamma (*PPARG*) promoter was associated with liver inflammation and fibrosis in chronic hepatitis B virus infection [138]. An in vitro assay showed that loss of TIMP-3 by hypermethylation promoted chronic inflammation and tumor invasion during human papillomavirus infection [139]. miR-155, an indicator of inflammation-induced hepatocyte damage, was up-regulated both in monocytes and in the serum of patients with chronic hepatitis C infection [140]. Remarkably, DNA methyltransferase inhibition of regulatory T cells (Tregs) accelerated resolution of influenza-induced lung inflammation and related injury repair in mice [141].

Indeed, the development of immunomodulatory therapies targeting the epigenome during infectious diseases have emerged in the past years [142]. In this context, histone H3 modulation in macrophages was proposed as a strategy to attenuate the NF- $\kappa$ B/NLRP3-mediated inflammatory response during infection by the parasite *Leishmania donovani* [143]. Also, in vitro inhibition of the epigenetically

active bromodomain and extraterminal domain (BET) proteins suppressed inflammation induced by the fungal pathogens *Candida albicans* and *Aspergillus fumigatus* [144]. Moreover, the pharmacological inhibition of the histone Lys demethylase JMJD3 protected mice against early septic death and reduced pro-inflammatory cytokine production via up-regulation of miR-146a [145]. Similarly, histone demethylase KDM3C demonstrated an anti-inflammatory effect by suppressing NF- $\kappa$ B signaling against oral bacterial infection in mice [146].

## Smoking and excessive alcohol drinking

Smoking and urban particulate air pollution may alter systemic immunologic and inflammatory reactions. Cigarette smoke-induced inflammation was related to significant changes in active and repressive gene markers on histone 3 and histone 4 involving the regulation of the NLRP10 molecule, both in vivo and in vitro [147]. In bronchoalveolar lavage cells, tobacco smoke exposure increased the activity of inflammatory pathways by inducing continuous active demethylation processes [148]. Also, exposure of human macrophages to cigarette smoke extract promoted pro-inflammatory cytokine release by activation of the NF- $\kappa$ B pathway and concomitant posttranslational modifications of HDACs [149]. Remarkably, the prenatal environmental tobacco smoke exposure in mice increased the risk of pulmonary inflammation in the offspring through altered DNA methylation patterns [150]. In humans, the smoking-induced hypomethylation of the *GPR15* gene (a chemoattractant receptor involved in systemic inflammation) has been proposed as an epigenetic biomarker underlying the potential role of smoking in chronic inflammatory pathologies [151]. Bioinformatic analyses revealed that long-term chronic smoking in African American women was associated with altered promoter DNA methylation of genes mapped to critical sub-networks modulating inflammation and immune function [152].

Excessive alcohol drinking causes inflammation and impairs the body's ability to regulate the inflammatory response. Integrative epigenetic profiling analysis in blood samples from individuals with chronic alcohol consumption identified DNA methylation changes in genes related to inflammation (including *HERC5*) [153]. Nevertheless, the treatment with *S*-adenosyl-L-methionine (SAM), the methyl donor for all methylation reactions, did not improve the histopathology scores for hepatocyte inflammation and damage in patients with alcohol liver disease [154].

Notably, alcohol exposure decreased miR-148a expression in human hepatocytes, leading to NLRP3 inflammasome activation and liver injury [155]. Molecular analyses identified a regulatory role for miR-155 in chronic

alcohol-induced intestinal inflammation and barrier dysfunction in a knockout animal model [156]. In this regard, up-regulation of miR-155 by chronic alcohol-intake triggered the production of the inflammatory cytokine TNF- $\alpha$  in macrophages [157]. Similarly, alcohol-induced miR-155 and HDAC11 increased the responsiveness of Kupffer cells to LPS by disinhibiting the TLR4 inflammatory pathway [158]. Furthermore, chronic ethanol intake up-regulated miR-155 and contributed to neuro-inflammation in mice [159], whereas miR-339-5p had an inhibitory effect in this patho-phenotype [160].

## Sleep patterns

Experimental and clinical observational studies suggest that disturbed sleep patterns may contribute to inflammatory processes linked to CVD and other metabolic diseases through a complex network of autonomic, endocrine, and cytokine signals [161]. Epigenetic signatures may be an important biological mechanism linking poor sleep to inflammation, although limited evidence exists. In this context, sleep deprivation (deprived of restful REM sleep using the flowerpot technique) was associated with a significant unbalance in histone activity as well as oxidative stress and ongoing inflammation in rat hippocampus [162]. Moreover, differentially expressed genes involved in inflammatory pathways and declined fertility were detected in male rats exposed to chronic sleep restriction, which was not related to DNA methylation mechanisms [163]. Also, sleep-disordered breathing (a common disorder inducing oxidative stress and inflammation) was associated with epigenetic age acceleration among individuals at high cardiovascular risk [164]. Furthermore, epigenetic modifications have been proposed to constitute an important determinant of inflammatory phenotype in obstructive sleep apnea [165].

## Chronic stress and social features

Chronic stress has been linked to negative health outcomes, including increased inflammation. Findings from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that chronic stress by living in unfavorable neighborhood conditions was associated with methylation changes in genes related to stress reactivity (*AVP*, *BDNF*, *FKBP5*, *SLC6A4*) and inflammation (*CCLI*, *CD1D*, *F8*, *KLRG1*, *NLRP12*, *SLAMF7*, *TLR1*) [166]. In this same sample, life course measures of socioeconomic status also correlated with the methylation status of stress- and inflammation-related genes using a multi-level modeling approach [167]. Indicators of socioeconomic status were also associated with DNA methylation of genes involved in inflammation in healthy Italian

individuals [168]. Likewise, social environments (including household socioeconomic condition in childhood) predicted DNA methylation patterns of inflammatory genes in young adulthood in Asians [169]. Moreover, it was reported that exposure to trauma and adversity during early life (i.e. neighborhood violence during childhood) amplified the adult pro-inflammatory response to stress in African American men, which was related to epigenetic phenomena involving *IL6* promoter hypomethylation [170]. Additionally, the miR-106b~25 cluster seems to play a role in mediating inflammatory and behavioral responses to repeated social defeat stress in a mouse model of stress vulnerability [171].

Interestingly, a brief yoga intervention (8 weeks of twice-weekly, hour-long yoga classes) modified the methylation levels of inflammatory markers in a community population of women with psychological distress [172]. Indeed, a day of intensive practice of mindfulness meditation reduced the expression of chromatin modulatory and inflammatory genes in PBMCs from experienced meditators [173]. Further research confirmed a relationship between a short meditation intervention (a day of intensive meditation practice for 8 h) in trained subjects and methylated sites in genes involved in immune cell metabolism and inflammation [174]. Remarkably, life satisfaction was prospectively associated with promoter methylation of the inflammatory *TLR2* gene [175].

## Climate

Climatological conditions such as air pollution and oxygen level may be associated with susceptibility to chronic inflammatory diseases by affecting the epigenome. Regarding the effects of air pollution on inflammation by epigenetic modulation, it was reported that the long-term exposure (annual average in the preceding year) to fine particulate matter (PM<sub>2.5</sub>) was associated with increased TNF- $\alpha$  expression through a reduction in *TNF- $\alpha$*  gene methylation in women [176]. In addition, changes in *TNF* methylation were proposed to mediate acute inflammation following personal exposure to fine particulate air pollution [177]. Consistently, adverse cardiac autonomic dysfunctions by PM<sub>2.5</sub> exposure was partially related to methylation changes in the inflammatory *TLR2* gene [178]. Increases in primary and secondary air pollutant concentrations also involved *TLR2* methylation modifications, which could be an epigenetic biomarker underlying the adverse effects of air contamination on health [179, 180]. Noteworthy, exposure to urban particular matter interacted with obesogenic nutrition to regulate inflammation and oxidative stress pathways involving tissue-differential DNA methylation effects [181]. Also, whole-genome analyses detected altered DNA methylation patterns in oxidative and inflammatory pathway genes associated with both air pollution and vascular disease risk in Italians [182]. An

inverse association was correspondingly reported between the daily exposure to particulate matter (specifically PM<sub>10</sub>) and the DNA methylation status of inflammatory genes in peripheral blood of obese subjects [183].

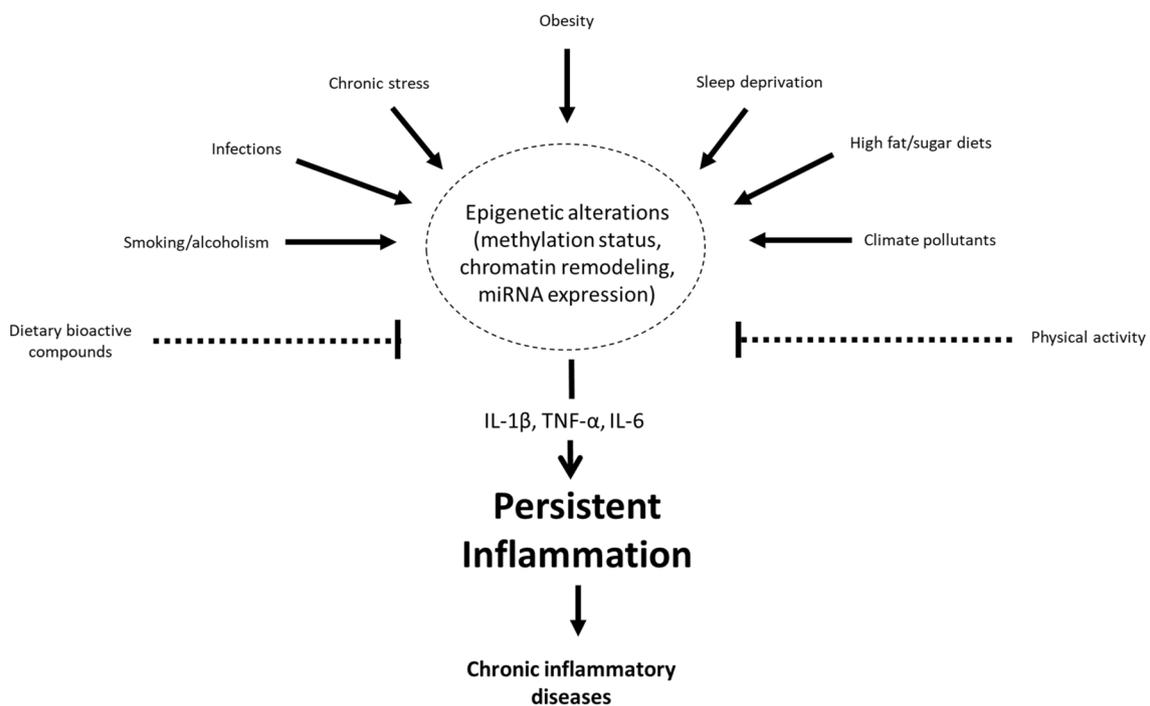
Besides, it was evidenced that the adverse cardiovascular and metabolic effects as consequence of air pollution inhalation may be mediated by miRNAs targeting key factors orchestrating coagulation and inflammatory pathways [184]. Later work disclosed positive correlations between PM<sub>2.5</sub> exposure and the expression of several miRNAs (miR-21-5p, miR-187-3p, miR-146a-5p, miR-1-3p, and miR-199a-5p) predicted to target inflammatory markers [185]. Microarray analyses uncovered an underlying mechanism of PM<sub>2.5</sub>-induced airway inflammation involving regulation of non-coding RNAs co-targeting miR-3607-5p in bronchial cells [186]. Furthermore, inhalation of ozone (O<sub>3</sub>), another criteria air pollutant, disrupted the expression of miRNA profiles associated with inflammatory and immune response signaling [187]. Intriguingly, it was reported that particulate matter air pollution might attenuate the inflammatory response in Chinese children, in some extent mediated by miRNAs regulating pro-inflammatory genes [188]. These findings support the involvement of epigenetic phenomena in the induction of inflammatory processes after the exposure to environmental air pollutants (Fig. 1).

The role of hypoxia as a main inducing factor of inflammation has been elucidated in recent years [189]. For example, low oxygen consumption was associated with *IL6* gene

hypomethylation and increased serum IL-6 concentrations in obese subjects with sleep apnea–hypopnea syndrome [190]. A mechanistic role of inflammasome activation in determining aerobic capacity (measured by peak oxygen uptake) was suggested since the percentage of methylation of the *ASC* gene and plasma IL-1 $\beta$  levels correlated with aerobic capacity in stable outpatients with heart failure [191]. Also, response to hypoxia in adipocytes was related to gene promoter hypomethylation and up-regulation of pro-inflammatory cytokines [192]. Moreover, gestational intermittent hypoxia induced endothelial dysfunction, triggered pro-inflammatory gene expression, and caused epigenetic changes in adult male offspring to increase the risk of developing cardiometabolic disease [193]. Similarly, epigenetic programming of pro-inflammatory phenotype in the heart development and vulnerability to disease later in life were associated with fetal hypoxia in rats [194]. Furthermore, hypoxia drove cardiac miRNAs profiles and inflammation processes in the right and left ventricle in a murine model [195].

## Concluding remarks

Obesity and unhealthy diet as well as adverse environmental stimuli including sleep deprivation, chemical exposure, alcohol abuse, smoking, and climate pollution promote inflammatory processes in the host through epigenetic alterations,



**Fig. 1** The interplay of obesity, infections, diet, stress, and environmental factors in inflammation through epigenetic mechanisms

**Table 4** Role of some external environmental stimuli in several inflammatory processes involving epigenetic regulation

Type of stimuli	Dose/time	Study model	Epigenetic signatures	Modification types	Reference
<i>Endocrine disrupting chemicals exposure</i>					
Mono-(2-ethylhexyl) phthalate	50 $\mu$ M	RAW 264.7 Cells	SIRT activity and protein expression	↓	[117]
butyl benzyl phthalate	3 $\mu$ g/ml	murine transgenerational asthma model	Global DNA methylation	↑	[118]
Bisphenol A	50 ng/kg diet 50 $\mu$ g/kg diet 50 mg/kg diet	bone marrow-derived mast cells of adult mice	Global DNA methylation	↑	[119]
Bisphenol A	0.5 mg/kg	Sheep placentomes	DNA methyltransferase 3A and histone deacetylase 1 expressions	↑	[120]
<i>Smoking</i>					
Cigarette smoke exposure	250 or 1000 ng/ml	Lungs of C57Bl/6 mice	Histone 3 and histone 4 acetylation	↑	[147]
Cigarette smoke exposure	At least 5 cigarettes per day	Human bronchoalveolar lavage cells	5hmC differentially methylated positions	DMRs	[148]
Cigarette smoke extract	1% and 2.5%	Human macrophages	HDAC activity and protein levels	↓	[149]
Environmental tobacco smoke	1.0 mg/m(3)	Offspring of pregnant C57BL/6 mice	Global and IL13 DNA methylation	↓	[150]
Cigarette smoke exposure	Current smokers	Human peripheral blood	<i>GPR15</i> methylation	↓	[151]
Cigarette smoke exposure	Active smokers	Human PBMCs	<i>AHRR</i> and <i>GPR15</i> gene methylation	DMRs	[152]
<i>Excessive alcohol drinking</i>					
Alcohol dependence	$\geq$ 80 g of alcohol intake/day	Human PBMCs	<i>HERC5</i> gene methylation	↑	[153]
Alcohol exposure	> 60 g/day	Human hepatocytes	miR-148a expression	↓	[155]
Acute alcohol binge	5 g/kg 50% alcohol/day	Small bowel in mice	miR-155 expression	↑	[156]
Alcohol exposure	25 mm alcohol	RAW 264.7 cells	miR-155 expression	↑	[157]
Alcohol exposure	32.4% alcohol-derived calories	Mice Kupffer cells	miR-155 and HDAC11 expressions	↑	[158]
Alcohol exposure	5% ethanol	Mouse cerebellum	miR-155 expression	↑	[159]
Alcohol exposure	15% alcohol	Mouse brain tissue	miR-339-5p expression	↓	[160]
<i>Sleep disturbances</i>					
REM sleep deprivation	Three sessions of 48 h each	Rat's hippocampus	HAT/HDAC activity	↑	[162]
Sleep-disordered breathing	Apnea-hypopnea index	Human whole blood samples	DNA methylation-age acceleration	↑	[164]
Obstructive sleep apnea	With and without high levels of hsCRP (1.50 mg/dL)	Human whole blood samples	<i>FOXP3</i> and <i>IRF1</i> gene methylation	↑	[165]
<i>Climate (air pollution)</i>					
PM <sub>2.5</sub> exposure	Annual average exposition	Human whole blood samples	<i>TNF-<math>\alpha</math></i> methylation	↓	[176]
PM <sub>2.5</sub> exposure	Continuously for 72 h	Human whole blood samples	<i>TNF-<math>\alpha</math></i> methylation	↓	[177]
PM <sub>2.5</sub> exposure	10 $\mu$ g/m(3)	Human whole blood samples	<i>TLR2</i> gene methylation	↑	[178]
Traffic-related pollutants exposure	28 days cumulated exposure	Human whole blood samples	<i>TLR2</i> gene methylation	↓	[179]
Traffic-related pollutants exposure	One-week exposure	Human whole blood samples	<i>F3</i> gene methylation	↓	[180]
Urban PM exposure	One-week exposure	Mouse lung samples	Dnmt3a2 expression	↑	[181]

**Table 4** (continued)

Type of stimuli	Dose/time	Study model	Epigenetic signatures	Modification types	Reference
NO <sub>2</sub> and PM <sub>2.5</sub> exposure	17 years before cerebrovascular disease diagnosis	Human whole blood samples	DNA methylation of inflammatory pathways	DMRs	[182]
PM <sub>10</sub> exposure	Mean of 1 and 14 days	Human peripheral blood samples	<i>CD14</i> and <i>TLR4</i> methylation levels	↓	[183]
PM and metal exposure	4 days of steel production work	Human peripheral blood samples	miR-302b, miR-200c and miR-30d expressions	↑	[184]
PM <sub>2.5</sub> exposure	Two-week periods	Human whole blood samples	miR-21-5p, miR-187-3p, miR-146a-5p, miR-1-3p and miR-199a-5p expressions	↓	[185]
PM <sub>2.5</sub> exposure	75 µg/ml	Human bronchial epithelial cell line	circRNA104250 and lncRNAuc001.dgp.1 expressions	↑	[186]
O <sub>3</sub> exposure	0.4 ppm O <sub>3</sub> for 2 h	Sputum samples	miR-132, miR-143, miR-145, miR-199a*, miR-199b-5p, miR-222, miR-223, miR-25, miR-424, and miR-582-5p expressions	↑	[187]

DMRs Differentially methylated regions

involving predominantly DNA methylation modifications in animal studies (Table 4). However, further studies in humans focused on other epigenetic mechanisms, such as histone acetylation/deacetylation processes and miRNA regulation affecting pro-inflammatory gene expression are required.

Scientific advances concerning the epigenetic mechanisms underlying inflammation-related chronic diseases such as diabetes, cardiovascular diseases, cancer, and neurodegenerative disorders are providing a better understanding of the molecular bases for the implicated pathological processes, and the prediction of individual disease risk based on the epigenotype. Nevertheless, it is necessary to integrate this knowledge with other emerging factors influencing the susceptibility/resistance to inflammation including the genetic background, microbiota composition, and metabolic profiles using systems biology and large-scale bioinformatics tools.

Also, the fact that diverse pathogens, including respiratory viruses, induce epigenome modifications to promote systemic infection, opens opportunities for the development of efficient medications for specific targets. This finding is of current relevance for emerging widespread viral infections such as SARS-CoV-2/COVID-19, with a common fatal inflammatory lung condition without current effective therapies or available vaccine. Moreover, the suppressive effect of obesity and other environmental mediators of the immune function also needs to be addressed.

Progress in the identification of epigenetically active dietary components and lifestyle factors will contribute to the design of therapeutic interventions alleviating persistent

inflammation by targeting the epigenome. In this regard, dietary bioactive compounds (i.e. polyphenols), *n*-3 PUFA, and regular physical activity have demonstrated anti-inflammatory properties through epigenetic phenomena. Nevertheless, the heterogeneity of the existing literature and the scarcity of studies in humans makes it difficult to propose specific recommendations about the amounts of polyphenols and *n*-3PUFA consumptions as well as the type, intensity, or duration of exercise that could counteract inflammatory processes. However, current available knowledge highlights the importance of anti-inflammatory dietary and exercise patterns for health and evidence the need of performing more nutriepigenetic investigations through randomized controlled clinical trials in order to prescribe precision nutritional and lifestyle recommendations for specific population and diseased groups.

Although further scientific advances in these research areas are needed, these insights are paving the way for the design of innovative strategies aimed to the prevention, management, prognosis, and treatment of chronic inflammatory diseases through personalized approaches (including precision nutrition) based on inflammatory epigenetic signatures.

## Conclusions

Obesogenic and health-damaging environments can drive persistent inflammation by modifying some specific epigenetic mechanisms and negatively impact the development of chronic inflammatory diseases. The prescription

of nutritional therapies using epigenetically active nutrients and physical activities with anti-inflammatory properties may help to revert the adverse effects of chronic inflammation.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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