Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2023): 3.1
CiteScore®(2023):7.4
www.biomolbiomed.com | www.blog.bjbms.org

REVIEW ARTICLE

Matarid et al: Gene-environment interaction in diabetes

Exploring the link between environmental chemical exposures and epigenetic modifications in diabetes mellitus

Tasnim R. Matarid[1], Menatallah Rayan[1], Ola J. Hussein[1], Hanan H. Abunada[2], Zaid H. Maayah[1], Hesham M. Korashy[1*]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, QU Health, Qatar University, Doha, Qatar

[2]Biomedical Research Center, QU Health, Qatar University, Doha, Qatar

*****Correspondence to **Hesham M. Korashy**: hkorashy@qu.edu.qa

ABSTRACT

Diabetes mellitus (DM) is a globally prevalent metabolic disorder characterized by impaired glucose homeostasis and insulin secretion. Beyond traditional risk factors like lifestyle and genetics, environmental pollutants, including particulate matter, heavy metals, and persistent organic pollutants, have become significant contributors to DM. One of the key mechanistic pathways through which these pollutants exert their effects is the activation of the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that regulates the expression of cytochrome P450 family 1 (CYP1) enzymes. This cascade contributes to increased oxidative stress and systemic inflammation, hallmarks of metabolic impairment. Importantly, these environmental pollutants are also linked to epigenetic modifications, including aberrant DNA methylation, histone modifications, and microRNA dysregulation, which further disrupt insulin sensitivity and β-cell function. This review explores the possible mechanistic crosstalk between AhR/CYP1 pathway activation and epigenetic alterations in the context of diabetes development. By integrating findings from epidemiology, in vivo, and in vitro studies, we provide a summary of how environmental exposures may influence diabetes risk through epigenetic mechanisms. Understanding these interactions not only advances our knowledge of DM etiology but also highlights novel molecular targets for preventive and therapeutic strategies.

Keywords: Diabetes mellitus; DM; insulin resistance; IR; glucose metabolism; environmental pollutants; Aryl hydrocarbon Receptor; epigenetic modifications

INTRODUCTION

Diabetes mellitus (DM) is one of the most burdensome and widespread metabolic disorders. DM reached epidemic proportions internationally with significant increases in prevalence leading to considerable impacts on the individual's quality of life, and if it is untreated or poorly managed, it contributes to short- and long-term complications (1). According to the latest World Health Organization statistics, about half a billion people globally suffer from DM. Approximately 1.5 million deaths each year are attributed to DM, with the majority of cases occurring in low and middle-income countries. The prevalence of DM has steadily increased over recent decades and is projected to cross 550 million by 2030 (1). DM occurs in two forms; type 1 DM (T1DM) and type 2 DM (T2DM) (2).

T1DM is a chronic autoimmune disease in which activated T lymphocytes mediate an autoimmune process, attacking and destroying pancreatic beta cells (β-cells), considering them as auto-antigens. T1DM is characterized by very little to no insulin secretion by the pancreas (2), and accounts for around 10% of DM cases globally, with the highest incidence detected among younger individuals aged from 10 to 14 years old (3). Epidemiological studies highlighted that family history, age, gender, dietary habits, and other factors such as viral infections contribute to T1DM (2,4). Uncontrolled T1DM can result in diabetic ketoacidosis, a life-threatening condition characterized by fruity-smelling breath, visual fluctuations, heavy breathing, and unconsciousness (5). On the other hand, T2DM is the most common form of DM and accounts for roughly 90% of the cases (6). T2DM is a persistent metabolic disorder in which the pancreas secretes an insufficient amount of insulin in response to systemic insulin resistance (2). T2DM is characterized by elevated blood glucose levels resulting from reduced insulin sensitivity in the liver and peripheral tissues like skeletal muscles and adipose tissue. Moreover, β-cell function declines over time due to prolonged exposure to the associated risk factors and elevated glucose levels impairing insulin secretion. Both genetic and non-genetic factors, such as sedentary lifestyle, obesity, and aging, are associated with increased T2DM risk (7,8). Lack of T2DM management can cause harm not only to micro-blood vessels but also to macro-blood vessels, leading to long-term complications such as retinopathy, neuropathy, and nephropathy (6).

Despite extensive research in the field of DM with the identification and characterization of known traditional risk factors, these conventional risk factors are insufficient to explain the sharp increase in global cases, indicating that other risk factors could contribute to this increase. Among these risk factors, exposure to environmental toxins such as pollutants and chemicals

has been shown to play a significant role in disease development and progression, such as cancer (9,10), autism (11), and cardiovascular disorders (12). Recently, Sayeed et al. have reviewed the physiological and pathological roles of environmental toxins in glucose homeostasis and insulin resistance (13). Although the review highlighted some of the molecular mechanisms involved, such as gluconeogenesis, hypoxia-inducible factor (HIF), oxidative stress, and inflammation (13), the impact of exposure to environmental chemicals and pollutants on the epigenetic modifications in DM remains unrevealed. Therefore, the current review focuses on understanding and further exploring potential molecular mechanisms and the emerging impact of risk factors, particularly the influence of environmental pollutants and epigenetic modifications on the development of diabetes and insulin resistance.

ENVIRONMENTAL POLLUTION AND DM

The impact of environmental pollutants on individuals' health has recently become of increasing concern, particularly after the Industrial Revolution and the growth in human activities. Environmental pollutants or toxins are identified as harmful substances in the surrounding environment that disrupt the biological systems (14). These pollutants, either liquid, solid, or gaseous, can be transported by the air in huge quantities, allowing their spread without barriers (14). Prolonged exposure to toxic substances like air pollutants contributes to the development of many health conditions, including cancer, metabolic, respiratory, neurological, and cardiovascular diseases (10–12,14). For example, endocrine disruptor compounds (EDCs), such as particulate matter (PM), heavy metals, and persistent organic pollutants (POPs), are environmental pollutants that are increasingly recognized as contributing factors to the development of metabolic disorders like obesity and diabetes (15). This section sheds light on the influence of different environmental chemicals on DM development and progression.

Particulate matter (PM)

PM is one of the most common global factors that threaten and influence the development of many diseases (15,16). PM is small air pollutants of microscopic solid particles or liquid droplets composed of organic compounds, diesel exhaust, polycyclic aromatic hydrocarbons (PAH), and reactive heavy metals. PM is classified into three categories based on its diameter size: PM_{10} (10 μm diameter), $PM_{2.5}$ (2.5 μm diameter), and $PM_{0.1}$ (0.1 μm diameter). PM_{10} is less dangerous and is typically produced directly from sources such as construction work and dust, whereas $PM_{2.5}$ and $PM_{0.1}$ are hazardous because they can penetrate deep into tissues and

bloodstreams and are produced directly from natural or man-made sources such as vehicle exhaust and combustion activities. PMs enter the body via inhalation and potentiate the development of several health conditions, including metabolic disorders like diabetes (17).

Zorena et al. have recently reported in a comprehensive review that exposure to $PM_{2.5}$, PM_{10}, and associated pollutants like nitrogen dioxide, sulfur dioxide, and heavy metals contribute to T1DM through oxidative stress, inflammation, and potential disruptions to the gut microbiome (16). In addition, a longitudinal study that involved more than 44,000 children and adolescents with T1DM was conducted to evaluate the association between PM_{10} and $PM_{2.5}$ with the averages of the hemoglobin A1c (HbA1c) levels, a marker for three-month cumulative blood glucose levels. The study demonstrated that PMs were highly correlated with elevated HbA1c levels (18), possibly due to systemic inflammation and metabolic dysregulation, endothelial dysfunction, and dyslipidemia (18,19). For T2DM, a retrospective study from 1990 to 2019 assessed the global burden trend of T2DM due to exposure to $PM_{2.5}$ and showed a significant increase in the trend in countries with low-middle socioeconomic levels (20). Furthermore, a systematic review and meta-analysis study conducted to assess the association between air pollutants and DM prevalence and incidence in developing countries revealed that long-term exposure to $PM_{2.5}$ was linked to a 25% higher risk of developing T2DM, while no significant association has been found with gestational diabetes during the entire pregnancy period (21). These were further supported by Puett et al., who conducted a prospective epidemiological study to investigate the relationship between PM exposure and the incidence of T2DM and found a weak association between PM exposure and T2DM, however, a slight increase in risk linked to proximity to roadways was observed, especially among women (22).

Several *in vivo* animal studies have investigated the effect of exposure to PM and demonstrated an association with DM development. For example, Miranada et al have shown that exposure of Wistar rats to PM_{10} daily during pregnancy and lactation period increased insulin levels, and body weight, and changed the pancreatic structure in the male offspring. On the other hand, female offspring showed resilience to the adverse effects of maternal exposure to PM and seemed protected due to the placenta's enhanced adaptability against *in utero* environmental insults (23,24). In mice, exposure of male C57BL/6 mice to concentrated ambient $PM_{2.5}$ for 10 weeks induced a non-alcoholic steatohepatitis (NASH)-like phenotype,

characterized by hepatic lipid accumulation, inflammation, disrupted glucose regulation (25), inflammation of the adipose, oxidative stress, and insulin resistance (26).

Collectively, these research findings suggest a link between PM exposure and increased risk of DM.

Heavy metals

Heavy metals are a group of high atomic weight elements that induce toxicity at very low concentrations (15,27). Heavy metals, such as arsenic (As), lead (Pb), mercury (Hg), and cadmium (Cd), are ranked among the topmost hazardous and toxic substances according to the Agency for Toxic Substances and Disease Registry (28). They commonly originate from natural, industrial, or agricultural sources, such as drinking contaminated water or ingestion of contaminated food (27,29). Heavy metals are not biodegradable and tend to increase in developing and industrial cities, which can lead to diseases development due to prolonged exposure and accumulation in the human body (14).

Arsenic (As) is one of the natural toxins found in the environment, either in organic or inorganic forms, that have been correlated with neurological disorders, DM, and respiratory complications (30–32). The high load of As leads to progression and exaggerates the severity of many disorders, including DM. This effect is mediated through alteration in the function of the pancreatic islets and disruption of glucose uptake by inducing reactive oxygen species (ROS) and affecting the Akt-related signaling pathways (30,33). An *in vivo* study on adult male NMRI mice exposed to different doses of As revealed a reduction in insulin secretion in pancreatic islets and increased oxidative stress in liver mitochondria (34). Using the adipocytes 3T3-L1 cell line, it has been reported that treatment of the cells with toxic concentrations of As metabolites, trivalent arsenicals like arsenite, methylamine oxide, and iododimethylarsine, inhibits the insulin-stimulated glucose uptake (ISGU) (35). This diabetogenic effect of As metabolites is mediated through the inhibition of phosphorylation of 3-phosphoinositide-dependent kinase-1, protein kinase B, and AKT pathways, leading to impaired glucose tolerance (35). In this context, it has been reported that activation of Akt plays a vital role in insulin signaling regulation, translocating the glucose transporter type 4 (GLUT4) to the cellular membrane in response to insulin (35, 36).

Lead (Pb) is another toxic heavy metal that is widely distributed in the environment due to natural and anthropogenic sources, such as Pb-based paints, industrial emissions, and contaminated water (37). It is highly persistent and not biodegradable, leading to long-term

contamination (38). According to ATSDR, Pb can cause severe health issues, including neurological, cardiovascular, hematological, and immunological disorders (38). Blood Pb levels below 5 μg/dL have been linked to neurological and developmental impairments, as well as cognitive deficits, especially in children (38,39). Importantly, exposure to Pb is well linked with an elevated risk of DM (29,37). A repeated-measure longitudinal study that included 5505 Chinese, with a 5-year follow-up, showed a significant association between blood Pb level and increased fasting plasma glucose levels and reduced homeostatic model assessment of β-cell function (HOMA-B) (29,40). This association predominately existed in women, but not men, suggesting a gender-dependent response (40). Another human study, including 110 industrial workers in the United Arab Emirates who were exposed to Pb in their workplace, showed a positive association between blood Pb levels and fasting blood glucose and lipid levels, consequently increasing the risk of DM and heart diseases (41). In addition, an *in vivo* animal study on Wistar rats treated with various Pb doses for 32 days showed marginally elevated blood glucose levels, fasting insulin levels, and HOMA-IR (42). Furthermore, the isolated pancreatic islet cells of the Wistar rats treated with Pb exhibited low cell viability and impaired glucose-stimulated insulin secretion (GSIS), which was associated with an increase in ROS levels and glycogen synthase kinase-3 beta (GSK-3β), leading to insulin resistance (42).

Organic pollutants

Organic pollutants are human-made, long-lasting, and toxic lipophilic substances that pose significant environmental health concerns (43, 44). These compounds are classified as either persistent organic pollutants (POPs) or non-persistent organic pollutants (NPOPs) based on their capacity to persist in the environment. While POPs are known for their long-term bioaccumulation, even NPOPs are toxic and can disrupt physiological pathways, despite their relatively transient presence in biological systems (11, 45). POPs include polycyclic aromatic hydrocarbons (PAHs), halogenated aromatic hydrocarbons (HAHs), organochlorine pesticides, polychlorinated biphenyls (PCBs), and chemical by-products like dioxins (45–47). PAHs, such as benzo[a]pyrene (BaP), and HAHs, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (11,13,28,39) have prolonged half-life and are commonly formed through cigarette smoking, consumption of grilled and smoked foods, and fossil fuels (48).

The association between prolonged human exposure to POPs and elevated risk of T2DM has been recently explored (44). For example, Ruzzin and his group have reported that Sprague-Dawley rats fed for 28 days with a high-fat diet (HFD) containing POPs developed

impaired insulin action, reduced ISGU in the skeletal muscle and adipose tissue, and suppressed insulin-mediated glucose production in the liver compared to control rats (49). These observations have been confirmed at the *in vitro* levels, in which treating differentiated 3T3-L1 adipocytes with a POPs mixture for 48 h reduced ISGU (49). Human studies also support the link between POP exposure and T2DM prevalence. A cross-sectional prospective study involving 2,016 adults demonstrated a strong correlation between serum concentration of POPs and T2DM risk, with organochlorines and PCB-153 showing the strongest association (50). Similarly, a nested case-control study of 300 American Indians reported a positive, but not significant, association between the serum concentration of POPs, particularly PCB-151, and the incidence and risk of diabetes (46). An interesting study conducted on Chinese females investigating the impact of exposure to PAHs, kitchen ventilation, and exhaled nitric oxide (NO) showed that the prolonged inhalation of PAHs and NO fractions emitted during cooking was associated with an increase in T2DM prevalence among cooking females, highlighting the impact of occupational and environmental exposure to the development of diabetes (51). This outcome may be mediated by triggering systemic inflammatory responses and oxidative stress, which disrupt the insulin signaling pathway and glucose metabolism (28,51). Another supporting evidence is the observations of Alshaarawy et al., who analyzed 2,769 participants in the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2006 to examine the relationship between urinary monohydroxy-PAH (OH-PAH) metabolites and DM (52). The study found a positive link between specific PAH metabolites (e.g., 1-hydroxy naphthalene, 2-hydroxynaphthalene, and 2-hydroxyphenanthrene) and both HbA1c levels and DM prevalence (52). Consistent with Alshaarawy's observations, a study using the Korean National Environmental Health Survey (KoNEHS) data from 2015 to 2017 demonstrated associations between PAHs (e.g., 2-hydroxyfluorene) and diabetes (53). The study revealed that urinary concentrations of PAHs, along with benzene metabolite trans, trans-muconic acid (t,t-MA), were positively associated with an increased risk of DM and obesity (53). While these findings collectively highlight the potential role of PAHs in the development of diabetes, suggesting that urinary PAH metabolites could be a reliable biomarker of DM, these studies also emphasize the need for further research to understand the causal relationship between PAHs and DM (51–53).

ARYL HYDROCARBON RECEPTOR (AHR) AND DM

AhR regulation

Several studies reinforce the hypothesis that exposure to environmental contaminants contributes to the development of DM. However, the underlying mechanisms and pathways by which these toxins induce impairment of glucose metabolism and insulin resistance remain unclear. In this context, previous related studies have demonstrated that the toxic effects of environmental pollutants, such as HAHs and PAHs, are mediated through the activation of a transcription factor, the aryl hydrocarbon receptor (AhR) (9,13,54,55). AhR is a xenobiotic-activated cytosolic transcriptional factor that is expressed in various body tissues, with the highest levels in the liver, lungs, bone marrow, urinary, and gall bladder (13). In pancreatic cells, the AhR is expressed at varying levels. Studies have demonstrated that AhR exhibits low expression levels in normal pancreatic tissue, with predominant localization in acinar and ductal cells. However, its expression is moderately elevated in conditions like chronic pancreatitis and significantly upregulated in pancreatic cancers, highlighting its potential role in pancreatic cell responses and disease pathophysiology (56–58). AhR is an active member of the basic-helix-loop-helix (bHLH)/Per-ARNT-Sim (PAS) family, which has regulatory roles including differentiation, proliferation, and tumor growth (11,54,59). In addition, it induces the transcription and expression of certain cytochrome P450 family 1 (CYP1) including CYP1A1, CYP1A2, and CYP1B1, which are responsible for xenobiotic metabolism into highly reactive metabolites (54,60,61). Studies reported the mechanistic role of AhR in various medical conditions such as cancer, cardiovascular diseases, autoimmune, and metabolic disorders (10,54,55,61–64). AhR is a target for multiple ligands, some are endogenous, such as tryptophan and indole amino acid metabolites, and plant-source ligands like resveratrol (9,11,65). In addition to exogenous triggers, including PAH molecules such as B[a]P, dioxins like TCDD that exist in the air or foods as complex mixtures, are highly stable compounds and accumulate in the body in adipose tissues (9,66).

A series of molecular events is activated following xenobiotic binding to the AhR receptor in the cell cytoplasm (Fig. 1). Initially, the receptor disconnects from its inhibitory proteins, heat shock protein (HSP90) and p23, allowing the translocation into the nucleus. Once in the nucleus, the activated AhR receptor heterodimerizes with the transcription factor AhR nuclear translocator (ARNT). The complex of AhR and ARNT then binds specifically to the xenobiotic responsive element (XRE) on the DNA of specific genes, such as the genes of the CYP1 family, and initiates their transcription (54,59). Since these environmental toxins rely on the AhR to

produce their toxic effects, AhR likely has a possible role in diabetes development, insulin resistance, and glucose homeostasis.

Role of AhR in glucose metabolism and insulin resistance

The bioactivation of AhR and its regulated genes, CYP1A1, CYP1A2, and CYP1B1, plays a role in metabolic functions involving glucose homeostasis, insulin sensitivity, and lipid metabolism (67). Many studies demonstrated an association between AhR/CYP1 genes' expression and diabetes-related dysfunctions. It has been reported that chronic exposure to low levels of dioxins is associated with insulin resistance and the development of T2DM (68). Moreover, epidemiological studies revealed that dioxin-mediated activation of the AhR is linked with a high risk of T2DM and obesity (60). The Brazilian Longitudinal Study of Adult Health (ELSA-Brazil), conducted in 2061 participants, demonstrated a significant increase in the incidence of DM among participants who have higher AhR ligand bioactivity and increased mitochondrial inhibition (67)

In animal studies, it has been shown that injecting wild-type (WT) and AhR-knockout (KO) C57BL/6J mice with TCDD, a potent AhR/CYP1 inducer, caused impaired GSIS and decreased plasma insulin levels, inhibited insulin response in the WT mice compared to the KO group (69,70), whereas AhR-deficient mice showed enhanced insulin sensitivity and improved glucose tolerance compared to WT mice (69,70), indicating an AhR-dependent mechanism. In addition, Xu et al. have demonstrated that AhR-deficient mice had a protective role against HFD-induced obesity, insulin resistance, inflammation, and hepatic steatosis (69). Similarly, Liu et al. have reported that the deficiency of CYP1B1 in C57BL/6J mice prevents adult mice from HFD-induced obesity and glucose intolerance compared to WT mice, suggesting an important role of CYP1B1 in energy metabolism and insulin sensitivity (71). An additional animal study in zebrafishes showed that 24-48 hpf zebrafishes exposed to PCB-126 at concentrations of 2-5 nM exhibited dysmorphology in the pancreatic islet that resulted in the manifestation of ectopic β-cells and islet fragmentation (72). Collectively, animal studies suggest the possible role of AhR/CYP1 activation in glucose intolerance, impairment of insulin secretion, pancreatic islet dysfunction, and consequently the development of DM. One of the possible underlying mechanisms is the ability of AhR activation to inhibit the function of effector T cells while inducing regulatory T cells (Treg cells) that contribute to the pancreatic β-cells dysfunction, and subsequent development of DM (13). This postulation is based on the fact that AhR and target genes are expressed in innate and adaptive immune and anti-

inflammatory cells, which are involved in immune responses and regulation of inflammatory cytokine secretion, which might influence the autoimmune reaction of T1DM (73). At the *in vitro* cell line levels, it has been reported that exposure of human hepatoma HepG2 cells and multiple rodent pancreatic endocrine cell lines (MIN6, βTC-6, INS1, α-TC1, α-TC3) to the AhR activator TCDD leads to increasing β-cell death, suppression of insulin secretion, and subsequently lowers plasma insulin levels (62).

CROSSTALK BETWEEN AHR/CYP1 PATHWAY AND EPIGENETIC MODIFICATIONS IN INSULIN RESISTANCE AND GLUCOSE HEMOSTASIS

While previous studies and reviews have highlighted several mechanisms that mediate the involvement of the AhR/CYP1 pathway in the pathogenesis of DM (13)To our knowledge, there is a scarcity and lack of a clear understanding of the crosstalk between the AhR/CYP1 pathway and the epigenetic modifications in the context of insulin resistance and diabetes.

Epigenetics studies the complex interaction between environmental stimuli, genetics, and the onset of diseases (74). Disease vulnerability depends on the complexity between individual genetic profiles and epigenetic modifications influenced by environmental factors (75). It explores reversible heritable alterations in gene expression that independently occur away from any changes in the original DNA sequence, leading to misinterpretation of the genes by the cell. The three primary acknowledged epigenetic mechanisms are DNA methylation, histone modifications, and non-coding RNA (ncRNA) (2,6). Environmental pollutants are well known to mediate epigenetic change in the development of various diseases, including metabolic disorders and diabetes (74,76). These pollutants increase the production of ROS which leads to DNA damage and altered methylation and affects multiple inflammatory signaling pathways, including the nuclear factor kappa-B (NF-κB). This, in turn, results in metabolic dysregulation, including insulin resistance, glucose intolerance, and dyslipidemia (15,77). This section explores the possible links between epigenetic alteration and AhR/CYP1 activation by environmental toxins in the risk of developing insulin resistance and diabetes as summarized in Fig. 2.

DNA methylation

DNA methylation is one of the most important epigenetic mechanisms that is involved in many disorders, including cardiovascular disease, obesity, cancer, and diabetes (9,66,74). During the methylation process, a methyl group is transferred by DNA-methyl transferase

enzymes (DNMTs) and covalently binds to the cytosine of CpG dinucleotides within the CpG islands, which are generally found on 5' regulatory sites within the promoter, intragenic, and enhancer regions (78). Hypermethylation is typically responsible for gene silencing, whereas hypomethylation leads to an increase in gene expression (7,79–81).

DNA methylation has been reported to be induced by various environmental pollutants, including bisphenol A (BPA), PAHs, PM, and heavy metals (9,74). A wide genome study in 400 adult individuals revealed a significant association between blood and urine As levels and gene-specific DNA methylation (82,83). The higher As exposure was linked with a reduction in methylation levels at the Sequestosome 1 (*SQSTM1)* gene, which encodes the sequestosome-1 protein that binds ubiquitin and regulates the activation of the NF-κB pathway (82). Additionally, *SQSTM1* has been implicated in several diseases, including insulin resistance. These findings suggested that toxicity could be mediated by epigenetic modifications, particularly DNA methylation (82).

A recent paper has linked exposure to environmental pollutants, particularly $PM_{10,}$ with DNA methylation genes related to cardiovascular diseases, respiratory diseases, immune responses, and oxidative stress (84). In the context of oxidative stress, it has been reported that an increase in the production of ROS can lead to epigenetic alterations of the nuclear methylation/demethylation actions through either modifying the sites of methylated CpG or by changing the enzymatic expression (15,84). A human study reported that exposure to air pollutants in the first trimester was associated with DNA hypomethylation of the long interspersed nuclear element (*LINE-1*) gene in newborns, whereas hypermethylation occurs in the last months of pregnancy (83,85). The epigenetic alteration of the *LINE-1* gene in response to exposure to environmental pollutants influences glucose metabolism and is associated with a higher risk of DM during the developmental stage (85–87). An animal study demonstrated that exposure to EDCs such as BPA during prenatal development disrupts the genetic imprinting of genes like Insulin-like Growth Factor 2 *(Igf2)*, which is a critical regulator of early pancreatic β-cell development (74,88). Prenatal BPA exposure increases DNA methylation of *Igf2* differentially methylated region 1 (DMR1), which is normally an unmethylated regulatory region, preventing the binding of the GC-binding Factor 2 (GCF2) repressor protein and allowing activation of *Igf2* expression from both maternal and paternal alleles. The loss of imprinting leads to abnormal *Igf2* expression, which may hinder β-cell maturation and lead to glucose intolerance in later life (74,88). Kubi et al. have investigated early embryonic exposure to low-dose TCDD and alteration in the DNA methylome, which affects early pancreatic lineage development using human Embryonic stem cells (hESCs) as

the study model to mimic early pancreatic development (89). Interestingly, they have reported that treatment of the cells with TCDD (10 and 100 PM) for two weeks resulted in disruption of DNA methylation profiles, causing hypermethylation of key genes involved in pancreatic development and function such as protein kinase AMP-activated non-catalytic gamma 1 (*PRKAG1)*, Calpain-10 (*CAPN10)*, and hepatocyte nuclear factor 1 homeobox B (*HNF-1B)*. These epigenetic alterations negatively affected hESCs differentiation toward pancreatic progenitor cells and reduced the expression of critical developmental markers such as Sex-determining Region Y-Box 17(*SOX17*), Forkhead Box A2 (*FOXA2*), and Pancreatic and Duodenal Homeobox 1(*PDX1*)(89). For example, the hypermethylation of *PRKAG1* remained persistent throughout the differentiation stages, indicating that initial exposure to TCDD can activate permanent epigenetic changes and potentiate the risk for T2DM later in life (89). Linking this observation with the AhR/CYP1 pathway, it has been reported that TCDD exposure for 24 h induced the demethylation of two CpGs at the Cyp1a1 proximal promoter in the liver of C57BL/6J mice (75,90). This, in turn, results in metabolic dysregulation, involving glucose intolerance and dyslipidemia (15,84). These results suggest a novel crosstalk between AhR and DNA methylation for glucose metabolism and insulin secretion. Further experimental studies are encouraged to further explore the crosstalk and the molecular mechanisms involved.

Histon modification

Histones are a group of globular proteins, including H1, H2A, H2B, H3, and H4, that surround DNA to form chromatin. Conformational changes in the structure of post-translational histone might occur due to enzymatic alterations in lysine and arginine residues in the amino terminus (78). These alternations, such as methylation, acetylation, ubiquitination, lactylation, or phosphorylation, regulate the silencing or expression of certain genes based on the mechanism of modification (7,81,91). For example, trimethylation of lysine 4 on histone H3 (H3K4me3) is linked with gene expression, however, lysine 9 dimethylation (H3K9me2) leads to gene silencing (92). H3K4me3, in particular, is essential in maintaining the functions of pancreatic β cells, and its restructuring is associated with gene expression changes implicated in diabetes pathogenesis (93). For example, overexpression of the *Fxyd3* gene, an FXYD domain-containing ion transport regulator 3 gene, reduced glucose-induced insulin secretion of β-cells in diabetic mice (94). In this context, a chromatin immunoprecipitation (ChIP) assay revealed that upregulation of H3K4me3 at the transcriptional start site of the *Fxyd3* gene in the islets of *Glp1r*$^{-/-}$*; Gipr*$^{-/-}$ double knockout (dKO) mice was associated with a reduction in the expression of *Fxyd3* gene (94).

Another ChIP study involved H3K4me3, H3K27me3, H3K9me3, H3K9Ac, and H4K16Ac, showing an elevation in the level of H3K9Ac of T1DM susceptible genes, such as HLA class II histocompatibility antigen, DRB1 β chain (HLA-DRB1), and HLA-DQB1, in the T1DM group of patients compared to the normal cohort (95). Moreover, the acetylation of the Forkhead box protein O1 (*FOXO1*) gene, which controls thePDX1 gene, and hence the development of pancreatic β-cells and glucose homeostasis. Furthermore, it has been reported that deacetylation of histone 3 lysine 9 (H3K9) via histone deacetylase 6 (HDAC6) leads to suppression of the insulin receptor substrate 2 (IRS2) protein, which sequentially leads to the development of insulin resistance (8, 96).

Histone lysine lactylation (Kla) is a novel post-translational histone modification that was first recognized in 2019 (97–100). It involves the addition of the lactyl group to the lysine residue of the histone protein, mostly located on H3 and H4, such as H3K18la, H3K14la, and H4K12la (97, 101). This modification is derived from lactate, a byproduct of glycolysis, that has been implicated in various biological processes (97,101). Similar to other histone modifications, histone Kla activates gene expression and thus is involved in a variety of disease progression, such as cancer (102,103), cardiovascular disorders (97,100,104), and insulin resistance (105). A recent study that included 15 lean and 14 obese adults who underwent oral glucose tolerance tests and muscle biopsies showed that higher levels of lactylation occur in the human skeletal muscle of obese individuals, especially females. The findings were further supported at the *in vitro* levels using human skeletal muscle cells (HSkMCs). The results showed that lactate exposure led to a dose-dependent rise in IRS-1 serine phosphorylation, which is a marker of insulin resistance (105).

In correlation with the AhR/CYP1 pathway, Kubi et al. have demonstrated an association between the upregulation of HDAC7 with β-cell dysfunction and impaired insulin secretion in hESCs treated with a low dose of AhR inducer, TCDD, suggesting that inhibition of HDAC7 could be a promising targeted therapy for treating T2DM (89). In addition, a ChIP assay conducted in HepG2 and human breast cancer MCF-7 cells treated with 100 nM TCDD showed induction of different types of histone modifications, including H3K9Ac, H3K14Ac, H4Ac, and H3K4me3 at the CYP1A1 and CYP1B1 promoters in MCF-7 cells and only the CYP1A1 promoter region in HepG2 cells (93,106). Given that histone restructuring involved H3K4me3 and H3K9Ac are associated with changes in gene expression relevant to diabetes, and the AhR/CYP1 pathway also induces the modification of certain histones such as H3K9Ac and

H3K4me3, it is believable that histone-mediated epigenetic regulation could act as a potential mechanistic link between AhR/CYP1 activity and β-cell dysfunction in diabetes. However, further studies are needed to further explore the pathways and the mediating mechanisms.

MicroRNAs (miRNA)

Non-coding miRNA consists of 22 nucleotides of single-stranded RNA (107). miRNAs are one of the most common clusters of molecules involved in gene expression regulation that control various biological activities. In addition, they regulate the production of many protein-coding genes by targeting mRNAs for cleavage, causing translational repression. Dysregulation of miRNAs has been observed in many diseases, such as Alzheimer's disease, diabetes, and cancer. DNA methylation, histone, and RNA modifications can regulate the action of miRNAs (80,108).

A genome-wide study of the miRNA expression in patients with T1DM revealed a significant increase in the miR-510 and a reduction of miR-342 and miR-191 levels compared with the non-diabetic group (4). In addition, a high miR-326 level was found in the peripheral blood lymphocytes of T1DM patients, which was directly associated with the severity of the disease (109). A case-control study including 326 patients with T2DM and 342 healthy controls explored the association between two genetic variants of miR-143 (rs4705342 and rs353292) and the risk of T2DM in the Chinese population. In this study, higher serum expression levels of miR-143 were observed in subjects with the CC genotype of rs4705342, which was associated with higher levels of low-density lipoprotein cholesterol (LDL-C), FBG, HbA1C, and increased T2DM risk (110). These results support a role for the rs4705342 CC genotype of miR-143 in the pathogenesis of T2DM associated with increased miR-143 expression, thereby introducing it as a possible biomarker and therapeutic target of T2DM (110).

The miR-29 family, which includes miR-29a, miR-29b1, miR-29b2, and miR-29c, plays a negative role in glucose tolerance and insulin resistance (111). While the miR-29 family is expressed in many organs such as the liver, adipose tissues, and skeletal muscles, it was among the most abundant miRNAs expressed in the pancreatic cells of NOD mice. Overexpression of miR-29 has been shown to downregulate the GSIS of the primary islet cells of the mouse (112). In Goto-Kakizaki diabetic rats, it has been reported that elevated levels of miR-29 family members are associated with insulin resistance in skeletal muscle, liver, and adipose tissues of the rats (113). In addition, transfection of the adipocytes 3T3L1 cells with adenovirus-mediated overexpression of miR-29a/b/c resulted in significant repression in insulin-stimulated glucose uptake through deactivation of the Akt signal (113).

On the other hand, miR-375 was shown to be the most abundantly expressed in pancreatic β-cells, where it is required for insulin secretion regulation (114). Data from an experimental study where miR-375 Knockout (KO) and miR-375/obese KO mice were used revealed hyperglycemia due to an increase in the mass of pancreatic α-cell, impairment in the glucose tolerance, and reduced insulin secretion, which represents an insulin resistance condition in the miR-375 KO group (115). The study by Kumar et al. showed that ginger-derived nanoparticles (GDNPs) up-regulated miR-375 and markedly enhanced glucose tolerance and insulin sensitivity (116). This microRNA inhibited the overexpression of AhR and decreased the production of AhR ligand indole from gut bacteria. Additionally, miR-375 targeted genes involved in hepatic insulin signaling, resulting in improved systemic insulin sensitivity. These findings shed light on the importance of miR-375 in gut and liver homeostasis and suggest that miR-375 might be a novel target for the treatment of metabolic disorders (116).

In a separate experimental study, researchers explored the relationship between miR-375 and AhR expression in airway epithelial cells with exposure to air pollutants, including diesel exhaust particles (DEP) and PM (117). The study found that treatment with DEP or PM in primary human bronchial epithelial cells (BEC) resulted in a significant overexpression of miR-375 and thymic stromal lymphopoietin (TSLP), in a signaling pathway where miR-375 may negatively regulate AhR. Additional validation with a miR-375 mimic showed a modest, yet statistically significant decrease in AhR mRNA in pHBEC. In particular, DEP exposure inhibited AhR expression in pHBEC, which was reversed through anti-miR-375 transfection, identifying miR-375 as a regulator of AhR. These results suggest that air pollutants induce upregulation of miR-375 and TSLP through the AhR pathway in pHBEC. (117).

To the best of our knowledge, the association between environmental pollutant exposure and miRNA expression, specifically in the context of diabetes, remains an unexplored area. Collectively, studies suggest that pollutants may chronically upregulate miR-375, potentially disrupting its regulatory role in pancreatic cells and contributing to diabetes pathogenesis. Additionally, epigenetic variations appear to correlate with AhR/CYP1 pathway-related gene expression, highlighting a complex dual relationship. However, the precise mechanisms linking AhR/CYP1 pathways, epigenetic modifications, and glucose intolerance remain unclear. Therefore, further detailed investigations are needed to unravel these interactions and their role in the development of diabetes.

CONCLUSION

This review underscores the critical role of environmental toxins in the pathogenesis of DM through epigenetic modifications and AhR activation. It supports evidence linking environmental exposures such as heavy metals, air pollutants, and POPs with disruptions in glucose homeostasis and insulin resistance. The AhR/CYP1 pathway emerges as a central player, mediating the diabetogenic effects of these pollutants and influencing DNA methylation, histone modifications, and microRNA expressions. Although the research and the significant advancements that have been achieved to understand these pathways, the precise mechanisms underlying their interplay remain incompletely understood. Future research focusing on this critical intersection could enhance our understanding of diabetes etiology and drive the development of innovative therapeutic strategies to address the effects of environmental pollutants on metabolic health.

ACKNOWLEDGMENTS

This study was supported by Qatar University Internal Grant No. QUCG-CPH-23/24-154 to HMK, Qatar University Graduate Assistantship to TRM, Qatar University-Royal College of Surgeons of Ireland PhD dual degree scholarship to MR, and Qatar Foundation Graduate Studies Research Assistantship no. GSRA8-L-1-0506-21033 to OJH.

Conflicts of interest: There are no financial or other interests in this study that might be construed as a conflict of interest. All the authors are aware of and agree to the content of the study and their being listed as authors in the manuscript. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Funding: Qatar University Internal Grant No. QUCG-CPH-23/24-154 to HMK. Qatar University Graduate Assistantship to TRM, Qatar University-Royal College of Surgeons of Ireland PhD dual degree scholarship to MR. Qatar Foundation Graduate Studies Research Assistantship no. GSRA8-L-1-0506-21033 to OJH.

Data availability: The data is available upon request.

Submitted: 8 December 2024

Accepted: 27 December 2024

Published online: 21 May 2025

REFERENCES

1. Diabetes [Internet]. [cited 2024 Jan 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes

2. A. Alhazzaa R, Heinbockel T, B. Csoka A. Diabetes and Epigenetics. In: Anwar M, Farooq Z, Ahmad Rather R, Tauseef M, Heinbockel T, editors. Biochemistry [Internet]. IntechOpen; 2022 [cited 2024 Jan 18]. Available from: https://www.intechopen.com/chapters/81647

3. Forga L. Epidemiología en la diabetes tipo 1: ayudando a encajar las piezas del puzle. Endocrinol Nutr [Internet]. 2015 Apr [cited 2024 May 12];62(4):149–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1575092215000571

4. Cerna M. Epigenetic Regulation in Etiology of Type 1 Diabetes Mellitus. Int J Mol Sci [Internet]. 2019 Dec 19 [cited 2024 Jan 18];21(1):36. Available from: https://www.mdpi.com/1422-0067/21/1/36

5. Uncontrolled diabetes: 10 symptoms [Internet]. 2019 [cited 2024 May 12]. Available from: https://www.medicalnewstoday.com/articles/317465

6. Kowluru RA, Mohammad G. Epigenetic modifications in diabetes. Metabolism [Internet]. 2022 Jan [cited 2024 Jan 18];126:154920. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0026049521002201

7. Hossan T, Kundu S, Alam SS, Nagarajan S. Epigenetic Modifications Associated with the Pathogenesis of Type 2 Diabetes Mellitus. Endocr Metab Immune Disord - Drug Targets [Internet]. 2019 Sep 3 [cited 2024 Jan 18];19(6):775–86. Available from: http://www.eurekaselect.com/170377/article

8. Ling C. Epigenetics in Human Obesity and Type 2 Diabetes. Cell Metab.

9. Akhtar S, Hourani S, Therachiyil L, Al-Dhfyan A, Agouni A, Zeidan A, et al. Epigenetic Regulation of Cancer Stem Cells by the Aryl Hydrocarbon Receptor Pathway. Semin Cancer Biol [Internet]. 2022 Aug [cited 2024 Jan 18];83:177–96. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1044579X2030184X

10. Rayan M, Sayed TS, Hussein OJ, Therachiyil L, Maayah ZH, Maccalli C, et al. Unlocking the secrets: exploring the influence of the aryl hydrocarbon receptor and microbiome on cancer development. Cell Mol Biol Lett [Internet]. 2024 Mar 6 [cited 2024 Nov 24];29(1):33. Available from: https://cmbl.biomedcentral.com/articles/10.1186/s11658-024-00538-0

11. Dhulkifle H, Agouni A, Zeidan A, Al-Kuwari MS, Parray A, Tolefat M, et al. Influence of the Aryl Hydrocarbon Receptor Activating Environmental Pollutants on Autism Spectrum Disorder. Int J Mol Sci [Internet]. 2021 Aug 26 [cited 2024 May 9];22(17):9258. Available from: https://www.mdpi.com/1422-0067/22/17/9258

12. Sagheer U, Al-Kindi S, Abohashem S, Phillips CT, Rana JS, Bhatnagar A, et al. Environmental Pollution and Cardiovascular Disease. JACC Adv [Internet]. 2024 Feb [cited 2024 Nov 24];3(2):100805. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2772963X23008529

13. Sayed TS, Maayah ZH, Zeidan HA, Agouni A, Korashy HM. Insight into the physiological and pathological roles of the aryl hydrocarbon receptor pathway in glucose homeostasis, insulin resistance, and diabetes development. Cell Mol Biol Lett [Internet]. 2022 Dec [cited 2024 Jan 18];27(1):103. Available from: https://cmbl.biomedcentral.com/articles/10.1186/s11658-022-00397-7

14. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. Front Public Health [Internet]. 2020 Feb 20 [cited 2024 May 14];8:14. Available from: https://www.frontiersin.org/article/10.3389/fpubh.2020.00014/full

15. Khalil WJ, Akeblersane M, Khan AS, Moin ASM, Butler AE. Environmental Pollution and the Risk of Developing Metabolic Disorders: Obesity and Diabetes. Int J Mol Sci [Internet]. 2023 May 17 [cited 2024 May 14];24(10):8870. Available from: https://www.mdpi.com/1422-0067/24/10/8870

16. Zorena K, Jaskulak M, Michalska M, Mrugacz M, Vandenbulcke F. Air Pollution, Oxidative Stress, and the Risk of Development of Type 1 Diabetes. Antioxidants [Internet]. 2022 Sep 27 [cited 2024 Nov 10];11(10):1908. Available from: https://www.mdpi.com/2076-3921/11/10/1908

17. Adams K, Greenbaum DS, Shaikh R, Van Erp AM, Russell AG. Particulate matter components, sources, and health: Systematic approaches to testing effects. J Air Waste Manag Assoc [Internet]. 2015 May 4 [cited 2024 Nov 10];65(5):544–58. Available from: https://www.tandfonline.com/doi/full/10.1080/10962247.2014.1001884

18. Lanzinger S, Altug H, Schikowski T, Khodaverdi S, Rosenbauer J, Rathmann W, et al. Longitudinal relationship of particulate matter and metabolic control and severe hypoglycaemia in children and adolescents with type 1 diabetes. Environ Res [Internet]. 2022 Jan [cited 2024 Nov 10];203:111859. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0013935121011531

19. Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. Atherosclerosis [Internet]. 2009 Mar [cited 2024 Nov 25];203(1):311–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021915008004528

20. Liu C, Wang B, Liu S, Li S, Zhang K, Luo B, et al. Type 2 diabetes attributable to PM2.5: A global burden study from 1990 to 2019. Environ Int [Internet]. 2021 Nov [cited 2024 Nov 24];156:106725. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0160412021003500

21. He D, Wu S, Zhao H, Qiu H, Fu Y, Li X, et al. Association between particulate matter 2.5 and diabetes mellitus: A meta-analysis of cohort studies. J Diabetes Investig [Internet]. 2017 Sep [cited 2024 Nov 10];8(5):687–96. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jdi.12631

22. Puett RC, Hart JE, Schwartz J, Hu FB, Liese AD, Laden F. Are Particulate Matter Exposures Associated with Risk of Type 2 Diabetes? Environ Health Perspect [Internet]. 2011 Mar [cited 2024 Nov 24];119(3):384–9. Available from: https://ehp.niehs.nih.gov/doi/10.1289/ehp.1002344

23. Miranda RA, da Silva Franco CC, Previate C, Alves VS, Francisco FA, Moreira VM, et al. Particulate Matter Exposure During Perinatal Life Results in Impaired Glucose Metabolism in Adult Male Rat Offspring. Cell Physiol Biochem [Internet]. 2018 [cited 2024 Nov 10];49(1):395–405. Available from: https://karger.com/CPB/article/doi/10.1159/000492901

24. Aiken CE, Ozanne SE. Sex differences in developmental programming models. REPRODUCTION [Internet]. 2013 Jan [cited 2024 Nov 24];145(1):R1–13. Available from: https://rep.bioscientifica.com/view/journals/rep/145/1/R1.xml

25. Zheng Z, Xu X, Zhang X, Wang A, Zhang C, Hüttemann M, et al. Exposure to ambient particulate matter induces a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. J Hepatol [Internet]. 2013 Jan [cited 2024 Nov 24];58(1):148–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827812006320

26. Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. Ambient Air Pollution Exaggerates Adipose Inflammation and Insulin Resistance in a Mouse Model of Diet-Induced Obesity. Circulation [Internet]. 2009 Feb 3 [cited 2024 Nov 24];119(4):538–46. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.108.799015

27. Briffa J, Sinagra E, Blundell R. Heavy metal pollution in the environment and their toxicological effects on humans. Heliyon [Internet]. 2020 Sep [cited 2024 May 15];6(9):e04691. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405844020315346

28. El-Sikaily A, Helal M. Environmental pollution and diabetes mellitus. 2021;9(3).

29. Wang X, Karvonen CA, Herman WH, Mukherjee B, Harlow SD, Park SK. Urinary metals and incident diabetes in midlife women: Study of Women's Health Across the Nation (SWAN). Health Serv Res.

30. Chen YW, Yang CY, Huang CF, Hung DZ, Leung YM, Liu SH. Heavy metals, islet function and diabetes development. Islets [Internet]. 2009 Nov [cited 2024 May 15];1(3):169–76. Available from: http://www.tandfonline.com/doi/abs/10.4161/isl.1.3.9262

31. Hong Y seoub, Ye B jin, Kim Y mi, Kim B gwon, Kang G hui, Kim J jin, et al. Investigation of Health Effects According to the Exposure of Low Concentration Arsenic Contaminated Ground Water. Int J Environ Res Public Health [Internet]. 2017 Nov 27 [cited 2024 May 15];14(12):1461. Available from: http://www.mdpi.com/1660-4601/14/12/1461

32. Arsenic Toxicity: What Are the Standards and Regulation for Arsenic Exposure? | Environmental Medicine | ATSDR [Internet]. 2023 [cited 2024 Nov 9]. Available from: https://www.atsdr.cdc.gov/csem/arsenic/standards.html

33. Yen C, Lu F, Huang C, Chen W, Liu S, Linshiau S. The diabetogenic effects of the combination of humic acid and arsenic: In vitro and in vivo studies. Toxicol Lett

[Internet]. 2007 Aug 10 [cited 2024 May 15];172(3):91–105. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378427407001397

34. Ahangarpour A, Oroojan AA, Rezaei M, Khodayar MJ, Alboghobeish S, Zeinvand M. Effects of butyric acid and arsenic on isolated pancreatic islets and liver mitochondria of male mouse.

35. Paul DS, Harmon AW, Devesa V, Thomas DJ, Stýblo M. Molecular Mechanisms of the Diabetogenic Effects of Arsenic: Inhibition of Insulin Signaling by Arsenite and Methylarsonous Acid. Environ Health Perspect [Internet]. 2007 May [cited 2024 May 15];115(5):734–42. Available from: https://ehp.niehs.nih.gov/doi/10.1289/ehp.9867

36. Walton F. Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes. Toxicol Appl Pharmacol [Internet]. 2004 Aug [cited 2024 May 15];198(3):424–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0041008X04000845

37. Leff T, Stemmer P, Tyrrell J, Jog R. Diabetes and Exposure to Environmental Lead (Pb). Toxics [Internet]. 2018 Sep 6 [cited 2024 Nov 25];6(3):54. Available from: https://www.mdpi.com/2305-6304/6/3/54

38. Lead (Pb) Toxicity: What Are U.S. Standards for Lead Levels? | Environmental Medicine | ATSDR [Internet]. 2023 [cited 2024 Nov 9]. Available from: https://www.atsdr.cdc.gov/csem/leadtoxicity/safety_standards.html

39. Alonso-Magdalena P, Tudurí E, Marroquí L, Quesada I, Sargis RM, Nadal A. Toxic Effects of Common Environmental Pollutants in Pancreatic β-Cells and the Onset of Diabetes Mellitus. In: Encyclopedia of Endocrine Diseases [Internet]. Elsevier; 2019 [cited 2024 Nov 7]. p. 764–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128012383643258

40. Wang B, Zhang W, Chen C, Chen Y, Xia F, Wang N, et al. Lead exposure and impaired glucose homeostasis in Chinese adults: A repeated measures study with 5 years of follow-up. Ecotoxicol Environ Saf [Internet]. 2022 Sep [cited 2024 Nov 25];243:113953. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014765132200793X

41. Bener A, Obineche E, Gillett M, Pasha MAH, Bishawi B. Association between blood levels of lead, blood pressure and risk of diabetes and heart disease in workers. Int Arch Occup Environ Health [Internet]. 2001 Jul 1 [cited 2024 Nov 25];74(5):375–8. Available from: http://link.springer.com/10.1007/s004200100231

42. Mostafalou S, Baeeri M, Bahadar H, Soltany-Rezaee-Rad M, Gholami M, Abdollahi M. Molecular mechanisms involved in lead induced disruption of hepatic and pancreatic glucose metabolism. Environ Toxicol Pharmacol [Internet]. 2015 Jan [cited 2024 Nov 9];39(1):16–26. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1382668914002592

43. Ibrahim MM, Fjære E, Lock EJ, Naville D, Amlund H, Meugnier E, et al. Chronic Consumption of Farmed Salmon Containing Persistent Organic Pollutants Causes Insulin Resistance and Obesity in Mice. Fadini GP, editor. PLoS ONE [Internet]. 2011

Sep 23 [cited 2024 May 15];6(9):e25170. Available from: https://dx.plos.org/10.1371/journal.pone.0025170

44. Lee DH, Porta M, Jacobs DR, Vandenberg LN. Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes. Endocr Rev [Internet]. 2014 Aug 1 [cited 2024 May 15];35(4):557–601. Available from: https://academic.oup.com/edrv/article/35/4/557/2354641

45. Bresson SE, Isom S, Jensen ET, Huber S, Oulhote Y, Rigdon J, et al. Associations between persistent organic pollutants and type 1 diabetes in youth. Environ Int [Internet]. 2022 May [cited 2024 May 15];163:107175. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0160412022001015

46. Grice BA, Nelson RG, Williams DE, Knowler WC, Mason C, Hanson RL, et al. Associations between persistent organic pollutants, type 2 diabetes, diabetic nephropathy and mortality. Occup Environ Med [Internet]. 2017 Jul [cited 2024 May 15];74(7):521–7. Available from: https://oem.bmj.com/lookup/doi/10.1136/oemed-2016-103948

47. Kim YA, Park JB, Woo MS, Lee SY, Kim HY, Yoo YH. Persistent Organic Pollutant-Mediated Insulin Resistance. Int J Environ Res Public Health [Internet]. 2019 Feb 3 [cited 2024 Nov 9];16(3):448. Available from: https://www.mdpi.com/1660-4601/16/3/448

48. Mallah MA, Basnet TB, Ali M, Xie F, Li X, Feng F, et al. Association between urinary polycyclic aromatic hydrocarbon metabolites and diabetes mellitus among the US population: a cross-sectional study. Int Health [Internet]. 2023 Mar 1 [cited 2024 May 15];15(2):161–70. Available from: https://academic.oup.com/inthealth/article/15/2/161/6617857

49. Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, et al. Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome. Environ Health Perspect [Internet]. 2010 Apr [cited 2024 May 15];118(4):465–71. Available from: https://ehp.niehs.nih.gov/doi/10.1289/ehp.0901321

50. Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, et al. A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes. Diabetes Care [Internet]. 2006 Jul 1 [cited 2024 Nov 26];29(7):1638–44. Available from: https://diabetesjournals.org/care/article/29/7/1638/28580/A-Strong-Dose-Response-Relation-Between-Serum

51. Hou J, Sun H, Zhou Y, Zhang Y, Yin W, Xu T, et al. Environmental exposure to polycyclic aromatic hydrocarbons, kitchen ventilation, fractional exhaled nitric oxide, and risk of diabetes among Chinese females. Indoor Air [Internet]. 2018 May [cited 2024 May 15];28(3):383–93. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ina.12453

52. Alshaarawy O, Zhu M, Ducatman AM, Conway B, Andrew ME. Urinary polycyclic aromatic hydrocarbon biomarkers and diabetes mellitus. Occup Environ Med [Internet]. 2014 Jun [cited 2024 Nov 30];71(6):437–41. Available from: https://oem.bmj.com/lookup/doi/10.1136/oemed-2013-101987

53. Lee I, Park H, Kim MJ, Kim S, Choi S, Park J, et al. Exposure to polycyclic aromatic hydrocarbons and volatile organic compounds is associated with a risk of obesity and diabetes mellitus among Korean adults: Korean National Environmental Health Survey (KoNEHS) 2015–2017. Int J Hyg Environ Health [Internet]. 2022 Mar [cited 2024 Dec 1];240:113886. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1438463921002017

54. Larigot L, Juricek L, Dairou J, Coumoul X. AhR signaling pathways and regulatory functions. Biochim Open [Internet]. 2018 Dec [cited 2024 May 9];7:1–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214008518300038

55. Korashy HM, El-Kadi AOS. The Role of Aryl Hydrocarbon Receptor in the Pathogenesis of Cardiovascular Diseases. Drug Metab Rev [Internet]. 2006 Jan [cited 2024 Nov 24];38(3):411–50. Available from: http://www.tandfonline.com/doi/full/10.1080/03602530600632063

56. Gunton JE, Kulkarni RN, Yim S, Okada T, Hawthorne WJ, Tseng YH, et al. Loss of ARNT/HIF1␣ Mediates Altered Gene Expression and Pancreatic-Islet Dysfunction in Human Type 2 Diabetes.

57. Koliopanos A. Increased arylhydrocarbon receptor expression offers a potential therapeutic target for pancreatic cancer.

58. Clarke J, Flatt PR, Barnett CR. Cytochrome P450 1A-like proteins expressed in the islets of Langerhans and altered pancreatic β -cell secretory responsiveness. Br J Pharmacol [Internet]. 1997 May [cited 2024 Apr 16];121(3):389–94. Available from: https://bpspubs.onlinelibrary.wiley.com/doi/10.1038/sj.bjp.0701139

59. Rejano-Gordillo CM, Marín-Díaz B, Ordiales-Talavero A, Merino JM, González-Rico FJ, Fernández-Salguero PM. From Nucleus to Organs: Insights of Aryl Hydrocarbon Receptor Molecular Mechanisms. Int J Mol Sci [Internet]. 2022 Nov 29 [cited 2024 May 9];23(23):14919. Available from: https://www.mdpi.com/1422-0067/23/23/14919

60. Bock KW. Human and rodent aryl hydrocarbon receptor (AHR): from mediator of dioxin toxicity to physiologic AHR functions and therapeutic options. Biol Chem [Internet]. 2017 Apr 1 [cited 2024 May 10];398(4):455–64. Available from: https://www.degruyter.com/document/doi/10.1515/hsz-2016-0303/html

61. Kim K. The Role of Endocrine Disruption Chemical-Regulated Aryl Hydrocarbon Receptor Activity in the Pathogenesis of Pancreatic Diseases and Cancer. Int J Mol Sci [Internet]. 2024 Mar 29 [cited 2024 Nov 30];25(7):3818. Available from: https://www.mdpi.com/1422-0067/25/7/3818

62. Ibrahim M, MacFarlane EM, Matteo G, Hoyeck MP, Rick KRC, Farokhi S, et al. Functional cytochrome P450 1A enzymes are induced in mouse and human islets following pollutant exposure. Diabetologia [Internet]. 2020 Jan [cited 2024 Apr 16];63(1):162–78. Available from: http://link.springer.com/10.1007/s00125-019-05035-0

63. Hoyeck MP, Angela Ching MaE, Basu L, Van Allen K, Palaniyandi J, Perera I, et al. The aryl hydrocarbon receptor in β-cells mediates the effects of TCDD on glucose

homeostasis in mice. Mol Metab [Internet]. 2024 Mar [cited 2024 Nov 30];81:101893. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2212877824000243

64. O'Driscoll CA, Mezrich JD. The Aryl Hydrocarbon Receptor as an Immune-Modulator of Atmospheric Particulate Matter-Mediated Autoimmunity. Front Immunol [Internet]. 2018 Dec 6 [cited 2024 Nov 30];9:2833. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2018.02833/full

65. Liu WC, Chen PH, Chen LW. Supplementation of endogenous Ahr ligands reverses insulin resistance and associated inflammation in an insulin-dependent diabetic mouse model. J Nutr Biochem [Internet]. 2020 Sep [cited 2024 Jan 18];83:108384. Available from: https://linkinghub.elsevier.com/retrieve/pii/S095528631930957X

66. Wajda A, Łapczuk-Romańska J, Paradowska-Gorycka A. Epigenetic Regulations of AhR in the Aspect of Immunomodulation. Int J Mol Sci [Internet]. 2020 Sep 3 [cited 2024 Jan 18];21(17):6404. Available from: https://www.mdpi.com/1422-0067/21/17/6404

67. Duncan BB, Castilhos CD, Bracco PA, Schmidt MI, Kang S, Im S, et al. Aryl-hydrocarbon receptor binding and the incidence of type 2 diabetes: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Environ Health [Internet]. 2020 Dec [cited 2024 Jan 18];19(1):105. Available from: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-020-00658-y

68. Jaeger C, Tischkau SA. Role of Aryl Hydrocarbon Receptor in Circadian Clock Disruption and Metabolic Dysfunction. Environ Health Insights [Internet]. 2016 Jan [cited 2024 May 21];10:EHI.S38343. Available from: http://journals.sagepub.com/doi/10.4137/EHI.S38343

69. Xu CX, Wang C, Zhang ZM, Jaeger C, Krager S, Bottum K, et al. Aryl hydrocarbon receptor deficiency protects mice from diet-induced adiposity and metabolic disorders through increased energy expenditure. Int J Obes. 2015;

70. Kurita H, Yoshioka W, Nishimura N, Kubota N, Kadowaki T, Tohyama C. Aryl hydrocarbon receptor-mediated effects of 2,3,7,8-tetrachlorodibenzo- *p* -dioxin on glucose-stimulated insulin secretion in mice. J Appl Toxicol [Internet]. 2009 Nov [cited 2024 Nov 9];29(8):689–94. Available from: https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/jat.1459

71. Liu X, Huang T, Li L, Tang Y, Tian Y, Wang S, et al. CYP1B1 deficiency ameliorates obesity and glucose intolerance induced by high fat diet in adult C57BL/6J mice.

72. Timme-Laragy AR, Sant KE, Rousseau ME, diIorio PJ. Deviant development of pancreatic beta cells from embryonic exposure to PCB-126 in zebrafish. Comp Biochem Physiol Part C Toxicol Pharmacol [Internet]. 2015 Dec [cited 2024 Nov 9];178:25–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1532045615001210

73. Yue T, Sun F, Yang C, Wang F, Luo J, Yang P, et al. The AHR Signaling Attenuates Autoimmune Responses During the Development of Type 1 Diabetes. Front Immunol [Internet]. 2020 Aug 7 [cited 2024 Jan 18];11:1510. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2020.01510/full

74. Bansal A, Pinney SE. DNA methylation and its role in the pathogenesis of diabetes: BANSAL AND PINNEY. Pediatr Diabetes [Internet]. 2017 May [cited 2024 Nov 30];18(3):167–77. Available from: https://onlinelibrary.wiley.com/doi/10.1111/pedi.12521

75. Patrizi B, Siciliani De Cumis M. TCDD Toxicity Mediated by Epigenetic Mechanisms. Int J Mol Sci [Internet]. 2018 Dec 18 [cited 2024 May 21];19(12):4101. Available from: http://www.mdpi.com/1422-0067/19/12/4101

76. Wang Z, Xie Z, Lu Q, Chang C, Zhou Z. Beyond Genetics: What Causes Type 1 Diabetes. Clin Rev Allergy Immunol [Internet]. 2017 Apr [cited 2024 Dec 1];52(2):273–86. Available from: http://link.springer.com/10.1007/s12016-016-8592-1

77. Liu J, Han X, Zhang T, Tian K, Li Z, Luo F. Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: from mechanism to therapy. J Hematol OncolJ Hematol Oncol [Internet]. 2023 Nov 30 [cited 2024 Dec 24];16(1):116. Available from: https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01512-7

78. Soeatmadji DW. The Role of Epigenetic Changes in The Development of Diabetes Mellitus. Acta Med Indones. 2019;51(1).

79. Szabó M, Máté B, Csép K, Benedek T. Epigenetic Modifications Linked to T2D, the Heritability Gap, and Potential Therapeutic Targets. Biochem Genet [Internet]. 2018 Dec [cited 2024 Jan 18];56(6):553–74. Available from: http://link.springer.com/10.1007/s10528-018-9863-8

80. Mannar V, Department of Medicine, Aarupadai Veedu Medical College, Puducherry, India, Boro H, Department of Endocrinology and Metabolism, Aadhar Health Institute, Hisar, India, Patel D, Department of Endocrinology, Mediheal Hospital, Nairobi, Kenya, et al. Epigenetics of the Pathogenesis and Complications of Type 2 Diabetes Mellitus. Eur Endocrinol [Internet]. 2023 [cited 2024 Jan 18];19(1):46. Available from: https://www.touchendocrinology.com/diabetes/journal-articles/epigenetics-of-the-pathogenesis-and-complications-of-type-2-diabetes-mellitus/

81. Soeatmadji DW. The Role of Epigenetic Changes in The Development of Diabetes Mellitus. Acta Med Indones. 2019;51(1).

82. Argos M, Chen L, Jasmine F, Tong L, Pierce BL, Roy S, et al. Gene-Specific Differential DNA Methylation and Chronic Arsenic Exposure in an Epigenome-Wide Association Study of Adults in Bangladesh. Environ Health Perspect [Internet]. 2015 Jan [cited 2024 Nov 10];123(1):64–71. Available from: https://ehp.niehs.nih.gov/doi/10.1289/ehp.1307884

83. Martin EM, Fry RC. Environmental Influences on the Epigenome: Exposure-Associated DNA Methylation in Human Populations. Annu Rev Public Health [Internet]. 2024 Apr 1 [cited 2024 Nov 10];39(1):309–33. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-publhealth-040617-014629

84. Poursafa P, Kamali Z, Fraszczyk E, Boezen HM, Vaez A, Snieder H. DNA methylation: a potential mediator between air pollution and metabolic syndrome. Clin Epigenetics [Internet]. 2022 Dec [cited 2024 Nov 10];14(1):82. Available from: https://clinicalepigeneticsjournal.biomedcentral.com/articles/10.1186/s13148-022-01301-y

85. Alvarado-Cruz I, Alegría-Torres JA, Montes-Castro N, Jiménez-Garza O, Quintanilla-Vega B. Environmental Epigenetic Changes, as Risk Factors for the Development of Diseases in Children: A Systematic Review. Ann Glob Health [Internet]. 2018 Jul 27 [cited 2024 May 21];84(2):212–24. Available from: https://annalsofglobalhealth.org/articles/10.29024/aogh.909

86. LINE-1 in type 2 diabetes mellitus.pdf.

87. Katsanou A, Kostoulas C, Liberopoulos E, Tsatsoulis A, Georgiou I, Tigas S. Retrotransposons and Diabetes Mellitus. Epigenomes [Internet]. 2024 Sep 6 [cited 2024 Nov 10];8(3):35. Available from: https://www.mdpi.com/2075-4655/8/3/35

88. Susiarjo M, Sasson I, Mesaros C, Bartolomei MS. Bisphenol A Exposure Disrupts Genomic Imprinting in the Mouse. Kelsey G, editor. PLoS Genet [Internet]. 2013 Apr 4 [cited 2024 Dec 1];9(4):e1003401. Available from: https://dx.plos.org/10.1371/journal.pgen.1003401

89. Kubi JA, Chen ACH, Fong SW, Lai KP, Wong CKC, Yeung WSB, et al. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the differentiation of embryonic stem cells towards pancreatic lineage and pancreatic beta cell function. Environ Int [Internet]. 2019 Sep [cited 2024 Nov 30];130:104885. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0160412019304611

90. Amenya HZ, Tohyama C, Ohsako S. Dioxin induces Ahr-dependent robust DNA demethylation of the Cyp1a1 promoter via Tdg in the mouse liver. Sci Rep [Internet]. 2016 Oct 7 [cited 2024 Nov 10];6(1):34989. Available from: https://www.nature.com/articles/srep34989

91. Su R, Sarmiento-Andrade Y, Verde L, Frias-Toral E, Sarno G. Epigenetics in Obesity and Diabetes Mellitus: New Insights. 2023;

92. Black JC, Van Rechem C, Whetstine JR. Histone Lysine Methylation Dynamics: Establishment, Regulation, and Biological Impact. Mol Cell [Internet]. 2012 Nov [cited 2024 Jan 18];48(4):491–507. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1097276512009379

93. Vanderkruk B. Methylation of histone H3 lysine 4 is required for maintenance of beta cell function in adult mice. 2023;

94. Vallois D, Niederhäuser G, Ibberson M, Nagaray V, Marselli L, Marchetti P, et al. Gluco-Incretins Regulate Beta-Cell Glucose Competence by Epigenetic Silencing of Fxyd3 Expression. Alquier T, editor. PLoS ONE [Internet]. 2014 Jul 24 [cited 2024 Oct 14];9(7):e103277. Available from: https://dx.plos.org/10.1371/journal.pone.0103277

95. Miao F, Chen Z, Zhang L, Liu Z, Wu X, Yuan YC, et al. Profiles of Epigenetic Histone Post-translational Modifications at Type 1 Diabetes Susceptible Genes. J Biol Chem

[Internet]. 2012 May [cited 2024 May 21];287(20):16335–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925820607712

96. Dalfrà MG, Burlina S, Del Vescovo GG, Lapolla A. Genetics and Epigenetics: New Insight on Gestational Diabetes Mellitus. Front Endocrinol [Internet]. 2020 Dec 1 [cited 2024 Apr 16];11:602477. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2020.602477/full

97. Xu K, Zhang K, Wang Y, Gu Y. Comprehensive review of histone lactylation: Structure, function, and therapeutic targets. Biochem Pharmacol [Internet]. 2024 Jul [cited 2024 Dec 25];225:116331. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006295224003149

98. Afthab M, Hambo S, Kim H, Alhamad A, Harb H. Particulate matter-induced epigenetic modifications and lung complications. Eur Respir Rev [Internet]. 2024 Oct [cited 2024 Dec 25];33(174):240129. Available from: http://publications.ersnet.org/lookup/doi/10.1183/16000617.0129-2024

99. Chen AN, Luo Y, Yang YH, Fu JT, Geng XM, Shi JP, et al. Lactylation, a Novel Metabolic Reprogramming Code: Current Status and Prospects. Front Immunol [Internet]. 2021 Jun 10 [cited 2024 Dec 25];12:688910. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2021.688910/full

100. Li X, Cai P, Tang X, Wu Y, Zhang Y, Rong X. Lactylation Modification in Cardiometabolic Disorders: Function and Mechanism. Metabolites [Internet]. 2024 Apr 12 [cited 2024 Dec 25];14(4):217. Available from: https://www.mdpi.com/2218-1989/14/4/217

101. Wang J, Wang Z, Wang Q, Li X, Guo Y. Ubiquitous protein lactylation in health and diseases. Cell Mol Biol Lett [Internet]. 2024 Feb 5 [cited 2024 Dec 25];29(1):23. Available from: https://cmbl.biomedcentral.com/articles/10.1186/s11658-024-00541-5

102. De La Cruz-López KG, Castro-Muñoz LJ, Reyes-Hernández DO, García-Carrancá A, Manzo-Merino J. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front Oncol [Internet]. 2019 Nov 1 [cited 2024 Dec 25];9:1143. Available from: https://www.frontiersin.org/article/10.3389/fonc.2019.01143/full

103. Li F, Si W, Xia L, Yin D, Wei T, Tao M, et al. Positive feedback regulation between glycolysis and histone lactylation drives oncogenesis in pancreatic ductal adenocarcinoma. Mol Cancer [Internet]. 2024 May 6 [cited 2024 Dec 25];23(1):90. Available from: https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-024-02008-9

104. Wang N, Wang W, Wang X, Mang G, Chen J, Yan X, et al. Histone Lactylation Boosts Reparative Gene Activation Post–Myocardial Infarction. Circ Res [Internet]. 2022 Nov 11 [cited 2024 Dec 25];131(11):893–908. Available from: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.122.320488

105. Maschari D, Saxena G, Law TD, Walsh E, Campbell MC, Consitt LA. Lactate-induced lactylation in skeletal muscle is associated with insulin resistance in humans. Front

Physiol [Internet]. 2022 Aug 30 [cited 2024 Dec 25];13:951390. Available from: https://www.frontiersin.org/articles/10.3389/fphys.2022.951390/full

106. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther [Internet]. 2022 Jul 6 [cited 2024 Oct 14];7(1):216. Available from: https://www.nature.com/articles/s41392-022-01073-0

107. The Profiling and Role of miRNAs in Diabetes Mellitus. J Diabetes Clin Res [Internet]. 2019 Jul 22 [cited 2024 Dec 1];1(1). Available from: https://www.scientificarchives.com/admin/assets/articles/pdf/the-profiling-and-role-of-mirnas-in-diabetes-mellitus-20190910070943.pdf

108. Ling C. Epigenetic regulation of insulin action and secretion – role in the pathogenesis of type 2 diabetes. J Intern Med [Internet]. 2020 Aug [cited 2024 Jan 18];288(2):158–67. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.13049

109. Sebastiani G, Grieco FA, Spagnuolo I, Galleri L, Cataldo D, Dotta F. Increased expression of microRNA miR-326 in type 1 diabetic patients with ongoing islet autoimmunity. Diabetes Metab Res Rev [Internet]. 2011 Nov [cited 2024 May 21];27(8):862–6. Available from: https://onlinelibrary.wiley.com/doi/10.1002/dmrr.1262

110. Kong D, Duan Y, Wang J, Liu Y. A functional polymorphism of microRNA-143 is associated with the risk of type 2 diabetes mellitus in the northern Chinese Han population. Front Endocrinol [Internet]. 2022 Sep 23 [cited 2024 May 21];13:994953. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2022.994953/full

111. Afsharmanesh MR, Mohammadi Z, Mansourian AR, Jafari SM. A Review of micro RNAs CHANGES in T2DM in animals and humans. J Diabetes [Internet]. 2023 Aug [cited 2024 Oct 21];15(8):649–64. Available from: https://onlinelibrary.wiley.com/doi/10.1111/1753-0407.13431

112. Roggli E, Gattesco S, Caille D, Briet C, Boitard C, Meda P, et al. Changes in MicroRNA Expression Contribute to Pancreatic b-Cell Dysfunction in Prediabetic NOD Mice.

113. He A, Zhu L, Gupta N, Chang Y, Fang F. Overexpression of Micro Ribonucleic Acid 29, Highly Up-Regulated in Diabetic Rats, Leads to Insulin Resistance in 3T3-L1 Adipocytes. Mol Endocrinol [Internet]. 2007 Nov 1 [cited 2024 Oct 22];21(11):2785–94. Available from: https://academic.oup.com/mend/article/21/11/2785/2738506

114. Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, MacDonald PE, et al. A pancreatic islet-specific microRNA regulates insulin secretion. Nature [Internet]. 2004 Nov [cited 2024 Oct 21];432(7014):226–30. Available from: https://www.nature.com/articles/nature03076

115. Poy MN, Hausser J, Trajkovski M, Braun M, Collins S, Rorsman P, et al. miR-375 maintains normal pancreatic. Med Sci.

116. Kumar A, Ren Y, Sundaram K, Mu J, Sriwastva MK, Dryden GW, et al. miR-375 prevents high-fat diet-induced insulin resistance and obesity by targeting the aryl

hydrocarbon receptor and bacterial tryptophanase (*tnaA*) gene. Theranostics [Internet]. 2021 [cited 2024 Oct 9];11(9):4061–77. Available from: https://www.thno.org/v11p4061.htm

117. Bleck B, Grunig G, Chiu A, Liu M, Gordon T, Kazeros A, et al. MicroRNA-375 Regulation of Thymic Stromal Lymphopoietin by Diesel Exhaust Particles and Ambient Particulate Matter in Human Bronchial Epithelial Cells. J Immunol [Internet]. 2013 Apr 1 [cited 2024 Nov 11];190(7):3757–63. Available from: https://journals.aai.org/jimmunol/article/190/7/3757/87063/MicroRNA-375-Regulation-of-Thymic-Stromal

TABLES AND FIGURES WITH LEGENDS

Table 1: Impact of the AhR-activating environmental pollutants on DM

Species	Types	Toxic substance	Epigenetic mechanisms	Affected Gene	Impact in Diabetes	Ref.
Human		As	DNA hypomethylation	SQSTM1	↑ in Insulin resistance	(82)
		PM	DNA methylation /demethylation		↑ ROS production, ↑ glucose intolerance ↑ dyslipidemia	(84)
		Air pollutants (PM, DDE, and PBDEs)	DNA methylation	LINE-1	↑ incidence of T2DM	(86)
***In vivo* model**	F1 hybrid progeny from C57BL/6 (B6), and CAST/(C7)	BPA (prenatal exposure)	DNA methylation	Igf2	↓ Igf2 imprinting ↓ β-cell development ↓ glucose tolerance	(74,88)
	C57BL/6 mice (Liver)	TCDD	DNA demethylation	Cyp1ba1	↑metabolic dysregulation, ↑glucose intolerance	(15,75, 84,90)
***In vitro* model**	hESCs cell line	TCDD	DNA hypermethylation	PRKAG1, CAPN10, HNF-1B MAFA	↓ pancreatic lineage differentiation ↑ risk of T2D	(89)
		TCDD	DNA hypomethylation	HDAC7	↑ β-cell dysfunction ↓ insulin secretion	(89)
	HepG2 cell line	TCDD	Histon modification (H3K9Ac, H3K14Ac, H4Ac, and H3K4me3)	CYP1A1 and CYP1B1	↑ incidence of DM	(93,106)
	pHBEC cell lines	Air pollutants (PM, DDE)	miRNA-375	AhR	↑ incidence of DM	(117)

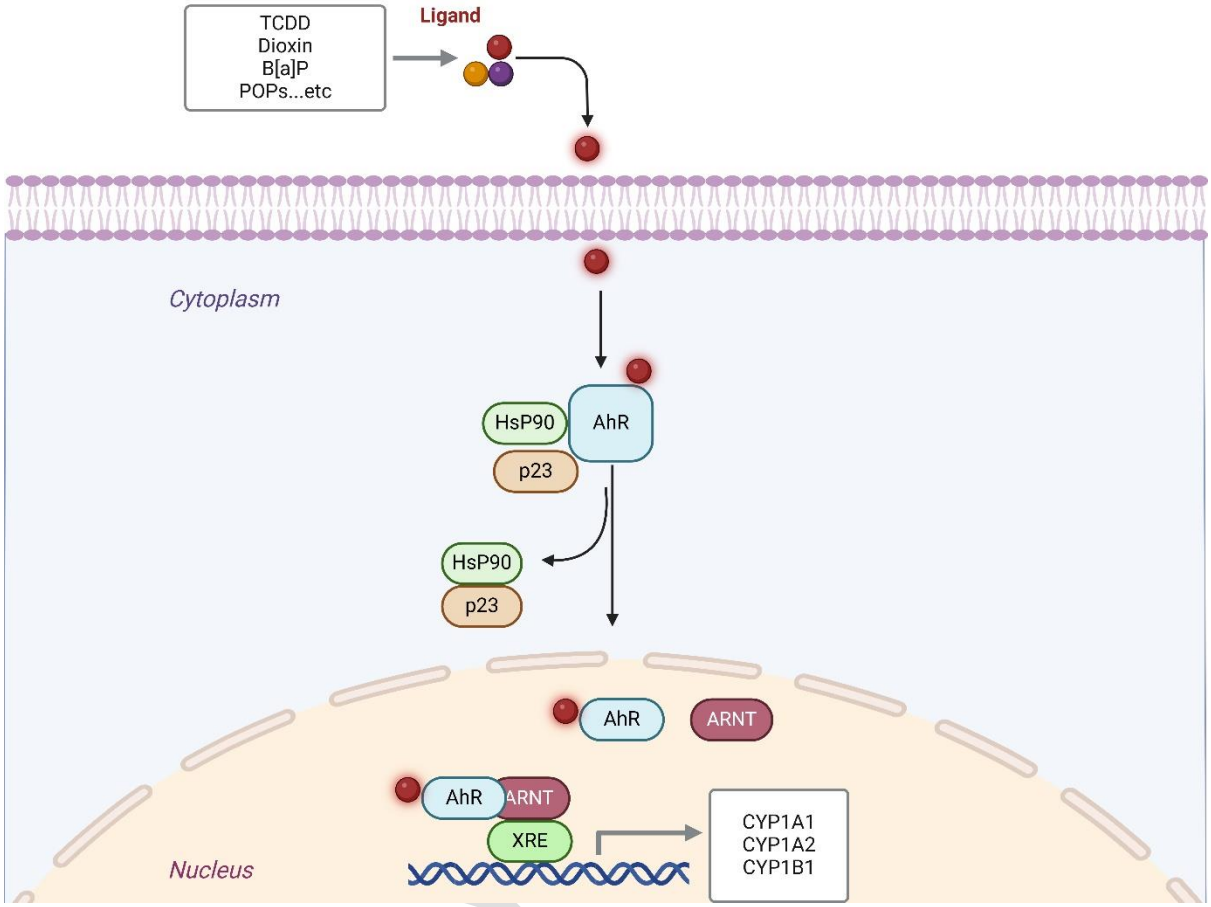

Figure 1. AhR/CYP1 signaling pathway: AhR is a ligand-activated transcription factor that forms a complex with Hsp90 and p23 in the cytoplasm. Ligand-induced conformational shifts of AhR lead to its nuclear translocation, forming a complex with aryl hydrocarbon receptor nuclear translocator (ARNT), and binding to xenobiotic response elements (XREs) in regulatory regions of the genome. This regulates the expression of target genes such as cytochrome P450 family 1 (CYP1) enzymes, such asCYP1A1, CYP1A2, and CYP1B1.

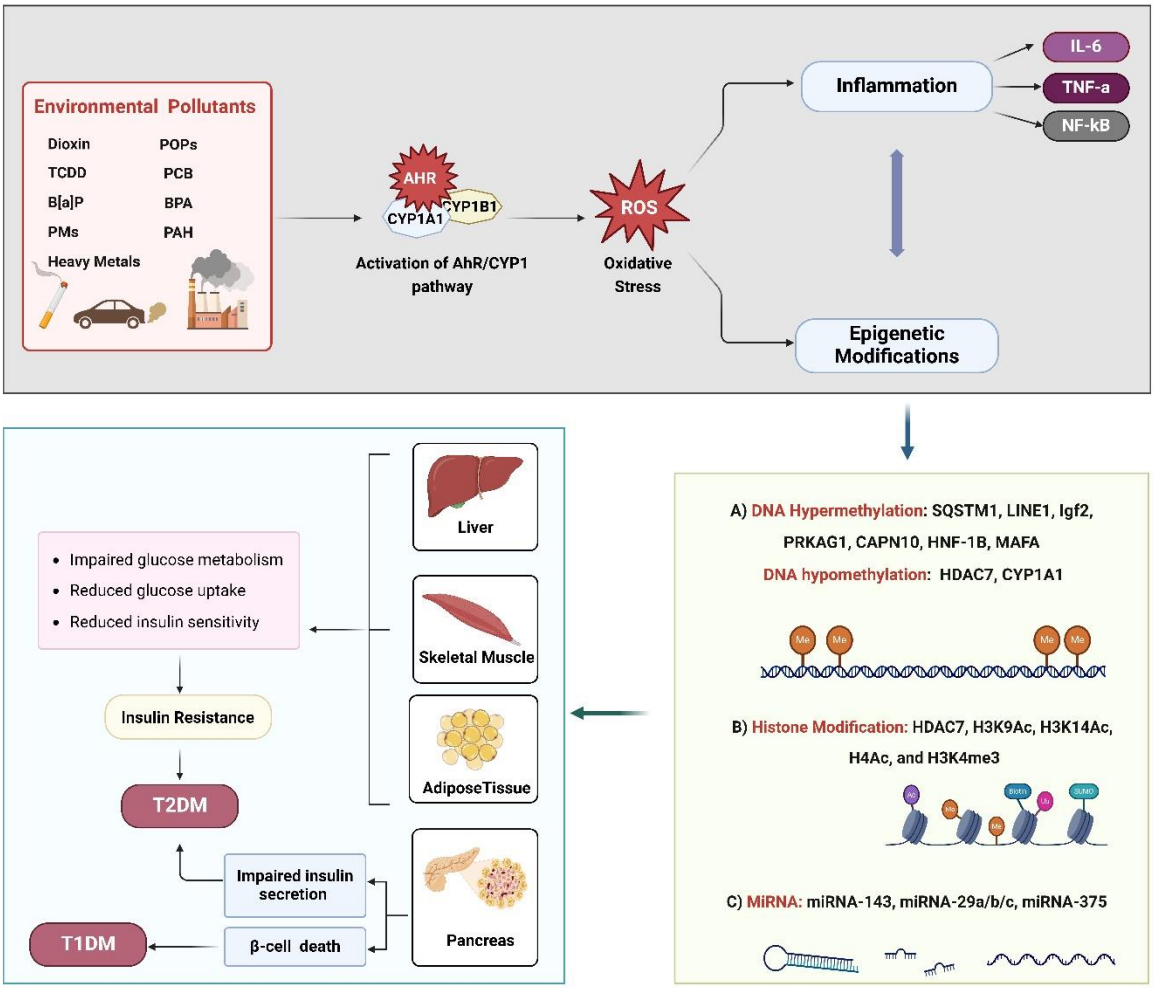

Figure 2. This schematic diagram highlights the connection between epigenetic modifications and activation of the AhR/CYP1 pathway by environmental pollutants, illustrating their contribution to insulin resistance and diabetes risk. Environmental pollutants such as dioxins and heavy metals activate AhR/CYP1, leading to oxidative stress and systemic inflammation (e.g., IL-6, TNF-α, NF-kB). This results in aberrant DNA methylation (e.g., *SQSTM1*, *LINE1*, *Igf2*), histone modifications (e.g., HDAC7, H3K9Ac), and miRNA dysregulation (e.g., miRNA375, miRNA-143). These epigenetic changes disrupt insulin signaling and glucose metabolism and contribute to DM.