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Developmental origins of type 2 diabetes: Focus on epigenetics

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ABSTRACT

Traditionally, genetics and lifestyle are considered as main determinants of aging-associated pathological conditions. Accumulating evidence, however, suggests that risk of many age-related diseases is not only determined by genetic and adult lifestyle factors but also by factors acting during early development. Type 2 diabetes (T2D), an age-related disease generally manifested after the age of 40, is among such disorders. Since several age-related conditions, such as pro-inflammatory states, are characteristic of both T2D and aging, this disease is conceptualized by many authors as a kind of premature or accelerated aging. There is substantial evidence that intrauterine growth restriction (IUGR), induced by poor or unbalanced nutrient intake, exposure to xenobiotics, maternal substance abuse etc., may impair fetal development, thereby causing the fetal adipose tissue and pancreatic beta cell dysfunction. Consequently, persisting adaptive changes may occur in the glucose–insulin metabolism, including reduced capacity for insulin secretion and insulin resistance. These changes can lead to an improved ability to store fat, thus predisposing to T2D development in later life. The modulation of epigenetic regulation of gene expression likely plays a central role in linking the adverse environmental conditions early in life to the risk of T2D in adulthood. In animal models of IUGR, long-term persistent changes in both DNA methylation and expression of genes implicated in metabolic processes have been repeatedly reported. Findings from human studies confirming the role of epigenetic mechanisms in linking early-life adverse experiences to the risk for T2D in adult life are scarce compared to data from animal studies, mainly because of limited access to suitable biological samples. It is, however, convincing evidence that these mechanisms may also operate in human beings. In this review, theoretical models and research findings evidencing the role of developmental epigenetic variation in the pathogenesis of T2D are summarized and discussed.

1. Introduction

Traditionally, genetics and lifestyle are considered as main determinants of aging-associated pathological conditions. Accumulating evidence, however, suggests that risk of many age-related diseases is not only determined by genetic and adult lifestyle factors but also by factors acting during early development. Type 2 diabetes (T2D) is definitely among such disorders. T2D, also referred to as non-insulin-dependent or adult-onset diabetes, accounts for around 90% of all diabetes cases in both developing and developed societies (Zheng et al., 2018). Currently, this disease causes numerous health and social problems in different countries across the world. In the past few decades, T2D has emerged as a global epidemic, with about 425 000 new cases estimated to occur annually (Jaacks et al., 2016). Risk factors contributing to the risk of this disease include genetic predisposition, sedentary lifestyle, stressful conditions, and unhealthy dietary behavior (Wu et al., 2014). The pathophysiology of T2D is typically characterized by impaired beta cell function and glucose metabolism in the liver, and also by peripheral insulin resistance, a state in which insulin-responsive tissues exhibit lowered responsiveness to normal insulin levels (Wilcox, 2005; Skyler et al., 2017). To compensate for insulin resistance and to maintain normal concentrations of glucose, beta-cells are forced to produce more insulin but eventually fail to do so. Thereafter, T2D can be diagnosed. This form of diabetes is generally manifested after the age of 40 thereby it is regarded as typical age-related disease. Since several age-related conditions, such as pro-inflammatory states, are characteristic of both T2D and aging (Spazzafumo et al., 2013), T2D is conceptualized by many authors as a kind of premature or accelerated aging (Geesaman, 2006).

Genetic predisposition is considered as a factor playing a decisive role in the development of T2D. The dramatic rise in incidence of this pathology during the last decades, however, obviously cannot be explained by predisposing genetic risk factors only, but most likely may be caused by rapid lifestyle changes across the world (Wu et al., 2014).

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Consistent evidence has been obtained that the risk for developing T2D can depend not only on lifestyle factors during adulthood but also on living conditions early in life (Jiang et al., 2013; Berends and Ozanne, 2012; Vaiserman, 2017; Estampador and Franks, 2018). Numerous research findings indicate that epigenetic mechanisms implicated in the control of gene expression play a central role in mediating the link between early-life adverse conditions and the risk of chronic disorders, including T2D, later in life (Bianco-Miotto et al., 2017; Bansal and Simmons, 2018; Cheng et al., 2018). In this review, theoretical models and research findings evidencing the role of developmental epigenetic variation in the pathogenesis of T2D are summarized and discussed.

2. Basic theoretical considerations from ontogenetic and evolutionary perspectives

A causal relationship between disadvantageous developmental conditions and adverse outcomes for health later in life was repeatedly demonstrated in both experimental and observational studies. On the basis of findings from these studies, the Developmental Origins of Health and Disease (DOHaD) concept has been introduced. This concept postulates that both physiology and structure of the developing organism may be adapted to adverse growth conditions in such a way which predisposes to different disease conditions in adult life (Mandy and Nyirenda, 2018). Poor nutritional status during development can, in particular, induce substantial structural and functional changes in key organs, including muscle, liver, pancreas and brain, which may persist across the entire life course, including old age (Vaiserman, 2014a, 2014b). According to the related "predictive adaptive response" (PAR) hypothesis, such ontogenetic adaptive strategy enables the developing organism to use early-life experiences in order to maximize fitness basing on expected environmental conditions in future life (Bateson et al., 2014). For example, poor or unbalanced nutritional status throughout prenatal development may result in impaired fetal growth, thereby causing intrauterine growth restriction (IUGR) accompanied by severe dysfunctions in fetal pancreatic beta cells and adipose tissue. As a result of these processes, fetus adapts to malnutrition by reducing ability to produce insulin and by developing insulin resistance. Such adaptation may, in turn, result in "developmental programming" and subsequently affect appetite and feeding behavior during adult life (Estampador and Franks, 2018). These metabolic adaptations may provide short-term benefits for survival in unfavorable postnatal environmental conditions through enhanced capability to store fat in the conditions of irregular approachability of nutritional resources. Realization of such an adaptive strategy, however, may predispose to higher risk of T2D in conditions of plentiful food supply during the postnatal life.

These considerations altogether formed the conceptual basis for the "thrifty phenotype" hypothesis (Hales and Barker, 2013). This concept followed from the thrifty genotype hypothesis by James Neel, postulating that the same genes which allowed survive famines anciently are being challenged nowadays by current life conditions in that food is usually plentiful (Neel, 1962). The thrifty phenotype hypothesis assumes that adaptations may occur in the fetus malnourished *in utero* following placental dysfunction, inadequate nutrient intake, stress or other disadvantageous factors. These adaptations can be aimed at optimal use and storage of nutrients in order to maximize the metabolic performance. More recently, the thrifty epigenotype hypothesis has been proposed by Reinhard Stöger (Stöger, 2008). This hypothesis postulates that, under normal nutritional conditions, metabolism develops into a healthy norm, while prenatal malnutrition lead to compensatory epigenetic changes in energy and adipogenic metabolism gene networks, thereby programming the metabolism in a way that resulting phenotype may be better adapted for survival under poor nutritional conditions. Such adaptive strategy can be realized through different mechanisms involved in the energy and glucose metabolic pathways. Among them, there are reduced insulin sensitivity of muscle protein synthesis, enhanced insulin sensitivity of peripheral tissues for utilization of glucose, increased production of hepatic glucose and impaired pancreatic development (Thorn et al., 2011). These adaptive processes provide obvious survival benefits for the IUGR fetuses by promoting both energy intake and utilization, lowering the rate of anabolic hormones production and demand for amino acids, and also increasing the glucose production to maintain consumption of glucose by vital organs, especially the brain (Miller et al., 2016). These processes, in total, cause asymmetrical growth of the IUGR fetuses, with severe restriction in subcutaneous tissues and muscles, less severe in bone tissue, and least in the brain (Thorn et al., 2011). Consequently, adaptive alterations may occur in the glucose–insulin metabolism, and these metabolic changes can persist into adulthood. These metabolic modifications commonly include reduced capacity for insulin secretion and/or insulin resistance, and they can lead to an improved ability to store fat. Furthermore, lowered nutrient uptake during prenatal development can result in modified appetite regulation and feeding behavior across the life course (Nielsen et al., 2014). These adaptive changes are generally accompanied by modifying the growth trajectory, i.e., lower birth weight followed by rapid weight gain in postnatal life. Currently, such an ontogenetic scenario is referred to as "catch-up" growth (a linear growth rate greater than expected for chronological age following a period of growth inhibition) (Martin et al., 2017). This adaptive strategy allows tissues of the growing fetus to maintain basic energy flows at the expense of linear growth in conditions of restricted nutrient availability. If such metabolic changes persist until adulthood or if they may be more easily inducible later in life, they, however, may support energy intake beyond metabolic demand in case if energy delivery increases, leading by that to the development of obesity, insulin resistance and T2D throughout adult life (Stöger, 2008).

In early epidemiological research, birth weight has been used as a common proxy for IUGR. Initially, it was assumed on the basis of obtained data that low birth weight (LBW) may be a crucial risk factor for development of T2D. Based on these theoretical considerations, it was suggested for a long time that there is a simple inverse linear association between birth weight and risk for T2D in later life (Whincup et al., 2008). Subsequent meta-analyses, however, have indicated little support for this point. These meta-analyses have demonstrated that a relationship between birth weight and risk for T2D is rather U-shaped with high birth weight (HBW, more than 4000 g) associated with an increased risk for the T2D development to the same extent as LBW (less than 2500 g) (Harder et al., 2007). A more recent meta-analysis by Palatianou et al. (2014), however, showed that HBW is rather associated with a high risk for non-diabetic obesity, but not for T2D as such. This uncertainty could be likely explained by the fact that relationship between LBW and the risk of T2D in adulthood is mediated by catch-up growth throughout postnatal life of IUGR individuals (Berends et al., 2013). An important point in this regard is that catch-up growth typically causes a disproportionately elevated rate of fat gain in comparison with lean tissue gain (Dulloo, 2008). The preferential catch-up fat is commonly driven by complex mechanisms of energy conservation operating through suppression of thermogenesis and resulting in development of so-called "thrifty catch-up fat" phenotype that is generally characterized by insulin and leptin resistance. A consistent evidence for such a causal link has been obtained, e.g., from well-known epidemiological research by David Barker and co-authors. In these studies, LBW individuals whose weight caught up during early infancy in such a way that they had an average or even above average weight from the age of seven showed higher risk for development of hypertension and T2D, and also high rate of death from coronary heart disease later in life compared to age-matched controls (Eriksson et al., 1999, 2000).

3. Mechanistic basis for developmental programming of T2D

Accumulating evidence indicates that persistent structural and functional alterations may be induced in IUGR conditions that

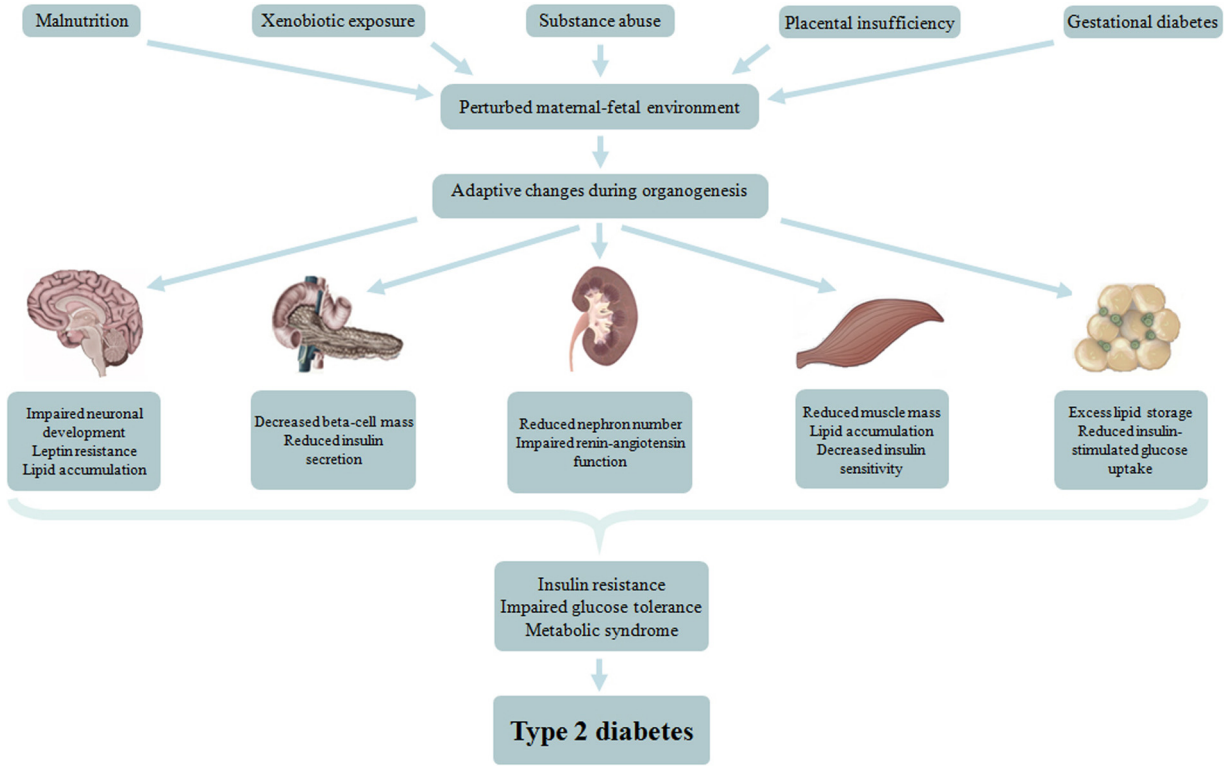

Fig. 1. Schematic representation of main tissue and organ changes involved in developmental programming of energy metabolism in favor of fat storage and to a high risk of developing T2D during adulthood in IUGR individuals.

modulate body functions across the entire life course (Lucas, 1991; Sutton et al., 2016). These changes usually occur during critical periods of early development, when all body organs start to form and processes of cell proliferation and differentiation reach their peak (Gluckman et al., 2005). The restricted organ development during this period has been repeatedly shown to be mediated by a reduction in cell number and a disturbed balance of different cell types within the tissues; such depletion in a set of functional units within certain organs may subsequently restrict their functional performance (Zohdi et al., 2014). Fig. 1 schematically represents main tissue and organ changes involved in developmental programming of energy metabolism in favor of fat storage in IUGR individuals.

The pancreas is an organ especially sensitive to inadequate nutritional status during the stage of organogenesis. Imbalanced nutrient uptake during this period may cause long-term structural/functional changes in pancreatic tissue. In many rodent models, such as maternal calorie/protein restriction and intrauterine artery ligation models, a significant reduction of beta cell mass and islet vascularization has been repeatedly observed (Tarry-Adkins and Ozanne, 2011). The persistent modification of vital organs can evidently result in substantial modifications of different biochemical and hormonal pathways, thus increasing susceptibility to developing various pathological states later in life (Godfrey and Barker, 1995). For instance, prenatal maternal low-protein diet (LPD) was shown to promote cellular differentiation through upregulation of certain transcription factors in a rat model (Rodríguez-Trejo et al., 2012). This stimulation of cell differentiation happened at the expense of proliferation in the neonatal pancreas and resulted in decreased reserve of beta cells, thus apparently contributing to a higher risk for T2D in adulthood. In a rat model, IUGR also caused the reduction in fetal islet cell mass and total pancreatic weight, and also in relative proportion of beta cells within the islets (Snoeck et al., 1990).

Long-term (or even life-long) dysregulation of inflammatory pathways in response to early-life environmental insults is another factor potentially implicated in the etiology and progression of T2D. Chronic low-level inflammation [also commonly referred to as "inflammaging" (Fulop et al., 2018; Franceschi et al., 2018)] is known to be crucially involved in pathogenesis of this disease (Prattichizzo et al., 2018; Tsalamandris et al., 2019). Biomarkers suggestive of chronic inflammatory state include changed levels of specific chemokines and cytokines, and also altered numbers of specific leukocyte populations. Such biomarkers were repeatedly found in diabetic pancreatic islets, livers and adipose tissues, as well as in circulating and vasculature leukocytes, which allows to consider this disease as systemic inflammatory condition (Donath and Shoelson, 2011). Childhood maltreatment and other adversities early in life were consistently demonstrated to be contributed to life-course pro-inflammatory trajectory (Danese et al., 2007; Pollitt et al., 2007; Lacey et al., 2014; Norton et al., 2017; Chen and Lacey, 2018). These data, in aggregate, indicate that early-life adversity-induced dysregulation of immune response may substantially contribute to metabolic programming processes, leading to higher risk for T2D in adulthood.

All the processes above are accompanied by significant epigenetic changes (heritable changes in gene function without alteration in the underlying DNA sequence) (Ong and Ozanne, 2015; Szabó et al., 2018). Particularly, inflammatory pathways mediating the link between early-life adverse experiences and aging-associated phenotypes, including T2D, may be significantly affected by epigenetic factors (Stevenson et al., 2018; Vaiserman, 2018). The immunological memory (an ability to respond more specifically and quickly upon a subsequent exposure to a particular pathogen or antigen) is known to involve alterations in epigenetic transcriptional profiles, including those originating during early development (Balistreri et al., 2019). Indeed, accumulating evidence indicates that gene expression patterns of an organism can be fine-tuned for optimizing cellular activities in actual living conditions. Data are obtained that those genes that were in an active state during previous life stages can be reactivated faster in response to certain environmental challenges (“transcriptional memory” phenomenon)

(Kim et al., 2019). Hyper-repression of particular genes is also possible in certain circumstances (Transcriptional REpression Memory, TREM) (Fabrizio et al., 2019). Gene expression profiles can be optimized in an adaptive manner in rapidly changing environmental conditions due to such transcriptional responses. These epigenetic mechanisms were reported to be critically involved in immune responses. In addition to B- and T-cell immune memory, "trained immunity" response by which innate immune cells become transcriptionally hyperactivated by restimulation with the same or even different pathogens may be also crucially contributed (Netea et al., 2016). Unlike adaptive immunity which is mediated through changes in genetic material (recombination, mutations, etc.), trained immunity is basically orchestrated by epigenomic reprogramming which does not involve changes in DNA structure. Importantly, during the later stages of life, the trained innate immunity, even although advantageous in context of repeating infections, can significantly contribute to chronic inflammation-mediated disorders, including atherosclerosis, obesity and T2D (Nardini et al., 2018; van der Heijden et al., 2018).

An important point is that, whereas DNA structure is relatively stable throughout the development, the epigenome (a totality of epigenetic settings across a genome) is known to be changed dramatically during the fetal development to produce differential gene expression profiles among differentiating cell lines. Basic components of the "epigenetic code" include DNA methylation and histone modification that both contribute to DNA packaging by forming nucleosomes (Fig. 2).

DNA methylation is the most thoroughly investigated mechanism of epigenetic regulation. This molecular mechanism consists of the addition of a methyl group (CH_3-) at the fifth position of the cytosine ring (Ciccarone et al., 2018). The processes of DNA methylation/demethylation occur primarily within CpG islands (short genomic regions rich in cytosine followed by guanine nucleotides), that are generally located near transcription start sites of the gene promoter regions. Methylation of the CpG islands typically lead to a transcriptional silencing, although several transcription factors playing an important role in cell reprogramming during development were recently identified that prefer to bind to CpG-methylated sequences (Yin et al., 2017). Recently, substantial alterations of DNA methylation in tissues such as pancreatic islets, adipose tissue, skeletal muscle and the liver were observed in diabetic patients, highlighting the role of these processes in the pathogenesis of T2D (Davegårdh et al., 2018; Willmer et al., 2018; Zhou et al., 2018).

The posttranslational modification of core histones, including their acetylation, methylation, ubiquitination, phosphorylation and sumoylation of histone tails, is another crucial mechanism of epigenetic regulation (Bannister and Kouzarides, 2011). Histone acetylation, in particular, is associated with transcriptional gene activity, whereas histone deacetylation allows interaction between DNA and histone tails and lead to chromatin compaction and transcriptional silencing. Various combinations of histone modifications, which mark functional chromatin units, form so-called "histone code". Consequently, certain coactivators/cosuppressors and transcription factors are recruited that regulate gene activity and chromatin structure (Zhang et al., 2015). There are two main mechanisms by which histone modifications affect transcriptional activity. The first one is by modifying the structure and conformation of chromatin, and the second one is by providing signals

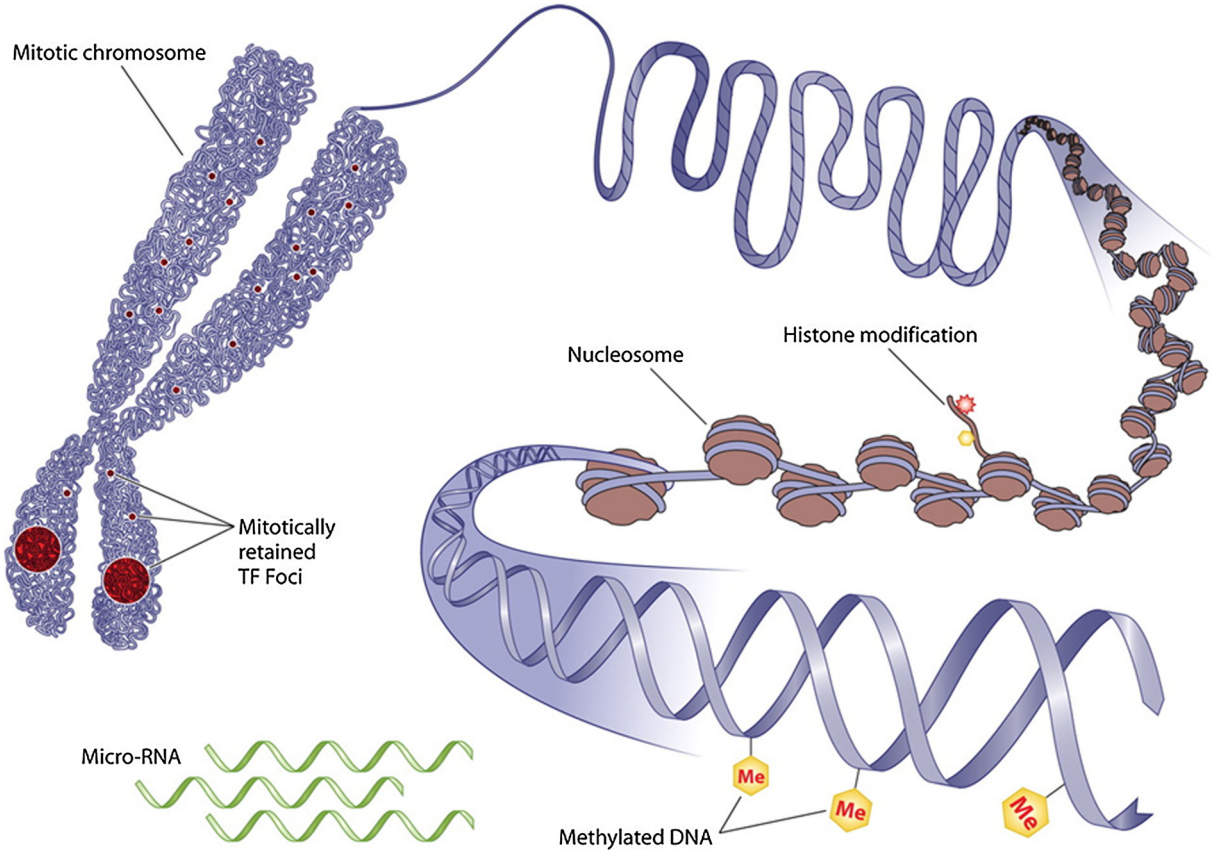

Fig. 2. Mechanisms of inheritable epigenetics. Mammalian gene expression is tightly controlled by genetic as well as epigenetic mechanisms. Epigenetics modifies the phenotype without altering the genotype of a cell. Shown here are some well-defined epigenetic mechanisms that include histone modifications, DNA methylation, and the noncoding RNA-mediated modulation of gene expression. Some of these mechanisms are inheritable through successive cell divisions and contribute to the maintenance of cellular phenotype. Recent studies show that the association of components of transcriptional regulatory machinery with target genes on mitotic chromosomes is a novel epigenetic mechanism that poises genes involved in key cellular processes, such as growth, proliferation, and lineage commitment, for expression in progeny cells. Fig. 2 and its legend are reproduced from Zaidi et al. (2010) with permission from the American Society for Microbiology.

for specific proteins and complexes with specific enzymatic activities to recruit transcriptional repressors or activators (Bannister and Kouzarides, 2011). The dynamic "writing" or "erasing" of histone modifications may be realized, in particular, by specific enzymes catalyzing the processes of removal or addition of acetyl group to lysine residue localized on histone N-terminal tail (Rothbart and Strahl, 2014). The main "writers" include histone acetyltransferases (HATs) and histone methyltransferases (HMTs), while "erasers" include histone deacetylases (HDACs) and lysine demethylases (KDMs) (Hyun et al., 2017). DNA methylation and histone modification are closely interrelated with each other. DNA methylation influences histone modifications and vice versa, by that collectively influencing the chromatin accessibility to RNA polymerase and transcription factors.

Another key component of epigenetic regulation is control of gene activity by non-coding RNAs (ncRNAs) that regulate gene expression at both transcriptional and post-transcriptional levels (Wei et al., 2017). There are regulatory RNA molecules that are transcribed from the DNA sequence but not translated into proteins. Several ncRNAs may interfere with messenger RNA (mRNA) molecules by a mechanism of RNA interference (RNAi) by which gene expression may be regulated in a sequence-specific manner without modifying target sequences (Deng et al., 2014). Presently, microRNAs (miRNAs), short (~18-25 nucleotide) RNA molecules, which may negatively regulate the expression of target genes at the post-transcriptional levels, are the most comprehensively investigated ncRNAs contributing to processes of epigenetic regulation (Morales et al., 2017). There is growing evidence on the importance of miRNAs in pathogenesis of T2D and related cardiovascular disorders (CVDs) (Fig. 3). Each miRNA is able to control multiple mRNAs, whereas each mRNA can be targeted by different miRNAs for precise control of various cellular processes (Christopher et al., 2016). Thus, miRNA-regulated signaling pathways may be extraordinarily complex. Furthermore, the expression of miRNAs may be modulated through DNA methylation and histone modifications and vice versa. Thereby, they may contribute to regulatory feedback loops in epigenetic regulation.

The most important thing in the context of the phenomenon of developmental programming is that epigenome is most sensitive to environmental challenges and plastic throughout early development, especially during establishing differentiation-dependent profiles of gene expression (Burns et al., 2018). The developmentally established epigenetic profiles are steady maintained in various cell types across the life course. In mammalian species, including human beings, the window of developmental epigenetic plasticity extends from preconception through weaning (Hochberg et al., 2011). The epigenetic 'tuning' of phenotype early in life certainly has adaptive value because it allows better match the individual's responses to the environments predicted to be experienced (Vaiserman, 2008, 2010; Hanson et al., 2011). However, if these responses turn out to be mismatched in the real complex environments, it may lead to an elevated risk of disease in later life. Among the prenatal exposures shown to be significantly associated with elevated T2D risk in later life, there are placental dysfunction, malnutrition (both under- and overnutrition), stress, hypoxia, impact of xenobiotics such as endocrine disruptors, and also maternal smoking and intake of alcohol and/or drugs throughout the pregnancy (see Fig. 4 for a schematic illustration).

In the sections below, evidence from animal models and human observational studies is provided for the roles of epigenetic factors in developmental programming of T2D.

4. Evidence from animal models

The compelling evidence for a contributing role of epigenetic factors in developmental programming of T2D came from animal models including mice, rats, guinea pigs, sheep, and primates. A number of animal models have been developed in order to study conditions that may lead to T2D programming. Among them, there are both maternal under-

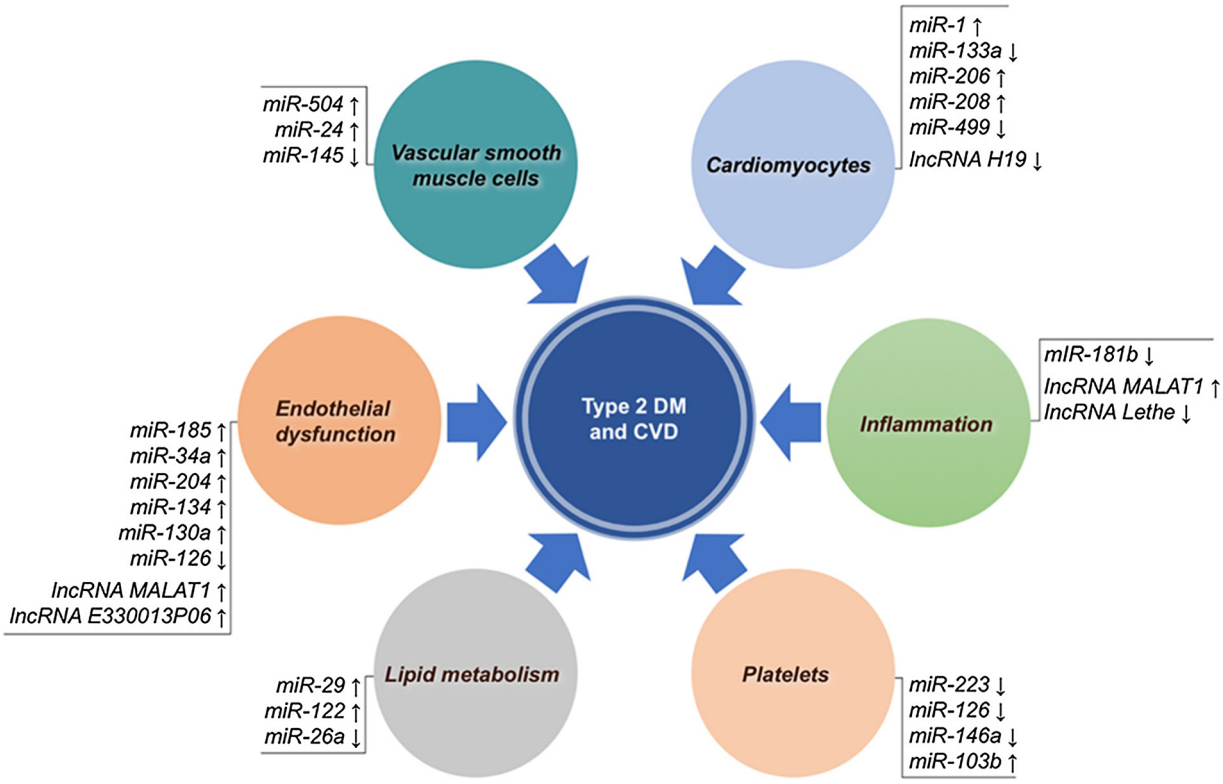

Fig. 3. Non-coding RNAs associated with both type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are grouped according to their main biological mechanism involved in atherosclerotic CVD. Arrows indicate overexpression (↑) or underexpression (↓). Fig. 3 and its legend are reproduced from De Rosa et al. (2018) with permission from the authors.

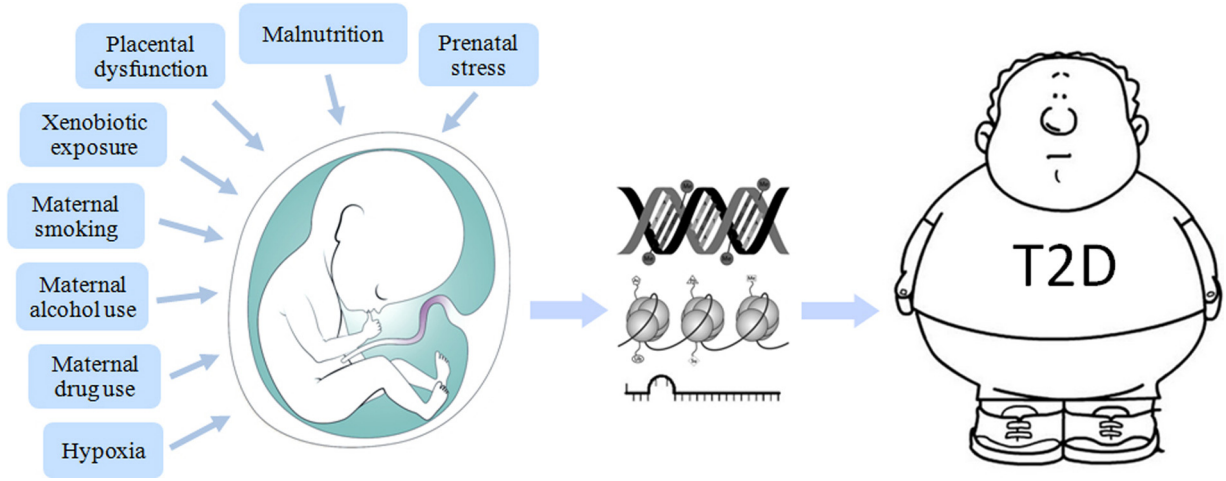

Fig. 4. Schematic representation of the association between adverse environmental exposures early in life and the risk of developing T2D in adult life [adapted from Fig. 3 of Vaiserman and Lushchak (2019)].

and overnutrition, uterine artery ligation, exposure to toxic chemicals such as bisphenol A or phthalates, etc. Furthermore, models of metabolic impairments during intrauterine development induced by maternal obesity or gestational diabetes mellitus have been applied. These prenatal exposures generally led to significant structural/functional changes associated with disturbed glucose homeostasis in the offspring's pancreas, liver, skeletal muscle and adipose tissue. These changes were accompanied by substantially altered expression of genes encoding transcription factors, nutrient receptors/transporters and glucoregulatory enzymes known to play a key role in the development of pancreas and β-cell function, peripheral glucose uptake, as well as in insulin resistance (Bansal and Simmons, 2018). The results from these studies are presented and discussed in the subsequent sections of this review. A brief summary of research evidence from animal models for the role of epigenetic dysregulation in the process of developmental metabolic programming is also given in Table 1.

4.1. Modification of maternal diet during pregnancy

4.1.1. Dietary restriction

An association between undernutrition during development and adult risk for T2D has been intensively investigated by using rodent models of maternal dietary restriction (DR) (Pinney, 2013). Rats prenatally exposed to 50% DR were shown to have reduced β-cell mass both at birth and during the early postnatal development (Garofano et al., 1997, 1998; Dumortier et al., 2007). They were also unable to adaptively increase the mass of beta cells in response to elevated metabolic demands and following insulin resistance during adulthood. As a consequence, T2D-like phenotypes have been developed in these rat offspring, including insufficient expansion of beta-cell mass, failure of beta cells following impaired insulin secretion, fasting hyperglycemia and glucose intolerance (Blondeau et al., 1999; Garofano et al., 1999). These metabolic disturbances have been accompanied by profound epigenetic changes in key genes responsive for beta-cell development. In particular, reduced levels of expression of *Pdx-1* and other genes encoding transcription factors implicated in the regulation of gluconeogenesis, including *FoxO1* and *MafA* genes, as well as changed levels of expression of miRNAs involved in pancreatic development have been found in IUGR rat pancreas (Zhang et al., 2016). The reduced expression level of glucose transporter, *GLUT4*, was also observed in skeletal muscle of adult IUGR rat female offspring (Thamotharan et al., 2005; Raychaudhuri et al., 2008). These changes at the level of gene expression have been shown to be mediated by persistent modifications of histone code, including enhanced activity of HDAC1 and HDAC4, deacetylation of histone 3 lysine 14 (H3K14), increased recruitment of heterochromatin protein 1*α* and dimethylation of H3K9 (H3K9me2), and also elevated binding of DNA methyltransferases, DNMT3a and DNMT3b, throughout adult life (Raychaudhuri et al., 2008).

4.1.2. Low-protein diet

Maternal low-protein diet (LPD) model is one more commonly used rodent model in examining mechanisms contributed to developmental programming of T2D. There is obvious similarity among findings obtained from this model and those from patients with T2D (Ozanne, 2001). In the maternal LPD model, dams fed with a diet containing 5 to 9% protein (casein), i.e., less than half of the standard protein content, but equivalent in energy of the standard control diet containing 18 to 20% protein (Vickers, 2011). It has been demonstrated that maternal LPD can induce profound epigenetic alterations in genes related to metabolic processes. For example, LPD caused decreased transcriptional activity of *Hnf4β*, an important transcriptional factor involved in glucose homeostasis and beta cell differentiation, thereby leading to glucose intolerance in rat pancreatic islets during adult life (Sandovici et al., 2011). In animal models, maternal LPD was also shown to persistently influence the expression levels of key metabolic genes including *Pparα*, *Igf2*, *Nr3c1*, *Cyp2c34* and *GR* (Lillycrop et al., 2005, 2008; Gong et al., 2010; Altmann et al., 2013), and also genes critically implicated in amino acid response pathway in the offspring's livers (Zhou and Pan, 2011). The increased expression of glucoregulatory genes like phosphoenolpyruvate carboxykinase (*PEPCK*) (Zheng et al., 2011) and reduced expression of nutrient transporters including *GLUT4* (Ozanne et al., 2005) have been also observed in LPD offspring, thus predisposing them to insulin resistance in adulthood.

In mouse models, maternal LPD was associated with lowered birth weight, decreased insulin sensitivity and impaired glucose tolerance at weaning (Zheng et al., 2015). Such metabolic impairments have been shown to be mediated by genome-wide epigenetic modifications. In research by Zheng et al. (2015), 253 differentially expressed genes mapped to eleven various pathways were identified in the offspring's livers. Maternal LPD also resulted in DNA demethylation in the promoter region of leptin gene, consequently affecting feeding behavior and metabolic regulation in adulthood (Jousse et al., 2011).

4.1.3. High-fat diet

Experimental evidence for contribution of epigenetic factors in developmental programming of metabolic dysfunction has been also provided from maternal high-fat diet (HFD) model. In these studies, gestational HFD (35–60% of calories coming from fat) resulted in development of abnormal metabolic phenotypes associated with disrupted gene expression patterns in key metabolic tissues of adult offspring

Table 1
Summary of animal evidence for the role of epigenetic dysregulation in developmental metabolic programming.

Condition	Model	Stage(s) of detection	Tissue/ body fluid	Epigenetic outcome(s)	Reference
Dietary restriction during pregnancy	Rat	Embryonic	Pancreas	Downregulation of *Pdx-1, FoxO1* and *MafA* genes. Changed levels of expression of miRNAs involved in pancreatic development	Zhang et al. (2016)
	Rat	Adult	Muscle	Decreased expression and protein concentration of *GLUT4*	Thamotharan et al. (2005)
	Rat	Adult	Muscle	Decreased expression of *GLUT4*. Histone code modifications	Raychaudhuri et al. (2008)
LPD during pregnancy	Rat	Adult	Pancreas	Downregulation of *Hnf4β* gene in pancreatic islets	Sandovici et al., 2011
	Rat	Post-weaning	Liver	Decreased DNA methylation and increased expression of *Pparα* and *GR* genes	Lillycrop et al. (2005)
	Rat	Juvenile and adult	Liver	Decreased *Pparα* promoter methylation in juvenile offspring. Differential changes to the methylation of individual CpG dinucleotides in the *Pparα* promoter in adult offspring	Lillycrop et al. (2008)
	Rat	Neonatal	Liver	Increased *Igf2* and *H19* expression. Increased expression of *Dnmt1* and *Dnmt3a*	Gong et al. (2010)
	Rat	Postnatal d 38	Liver	Increased expression of amino acid response pathway target genes	Zhou and Pan (2011)
	Rat	Adult	Muscle	Reduced expression of *PKCzeta*, *GLUT4* and *p85*	Ozanne et al. (2005)
	Rat	Adult	Muscle	Increased levels of *C/EBPβ* mRNA and protein expression. Increased levels of acetylation of histones H3 and H4 in the *C/EBPβ* promoter region and elevated *PEPCK* gene transcription	Zheng et al. (2011)
	Pig	From gestation to adulthood	Liver	Altered methylation and gene expression of key metabolic genes *Nr3c1*, *Pparα*, and *Cyp2c34*	Altmann et al. (2013)
LPD during pregnancy and lactation	Mice	At weaning	Liver	Altered expression of 253 genes mapped to 11 pathways, including those involved in PPAR signaling	Zheng et al. (2015)
	Mice	Adult	Plasma	DNA demethylation in promoter region of leptin gene. Lower levels of leptin mRNA and protein	Jousse et al. (2011)
HFD during pregnancy and lactation	Mice	At weaning	Liver	Upregulated expression of genes involved in PPAR signaling	Zheng et al. (2014)
	Mice	At weaning	Liver	Upregulation of *miR-143*. Downregulation of *miR-615-5p*, *miR-3079-5p*, *miR-124*, and *miR-101b*	Zheng et al. (2016)
HFD during pregnancy and lactation	Rat	Postnatal d 24	Gut	Altered taste receptor and inflammatory gene expression	Reynolds et al. (2015)
HFD from pre-pregnancy until lactation	Mice	Adult	Liver	Altered expression of lipid and bile acid metabolism-related genes	Tanaka et al. (2018)
Maternal undernutrition or overnutrition	Rat	9 weeks and 6 months of age	Liver	Altered methylation profiles and transcriptional dysregulation of pro-lipogenic genes (*Prkcb* and *Pc*) and genes *Ncor2* and *Smad3* involved in Notch signaling	Heo et al. (2016)
Uterine artery ligation	Rat	Postnatal d 7 and at 3-12 months	Pancreas	Downregulation of *Pdx-1* gene. Increased HAT activity	Pinney et al. (2011)
	Rat	7 weeks of age	Pancreatic islets	1400 differentially methylated loci located mainly near genes regulating cell proliferation, vascularization, apoptosis and insulin secretion. Consistent changes in gene expression patterns	Thompson et al. (2010)
	Rat	Postnatal	Liver	Genome-wide DNA hypomethylation. Increased acetylation of histone H3	MacLennan et al. (2004)
	Rat	Neonatal and adult	Beta cells	Decreased H3K4 trimethylation and increased H3K9 dimethylation in neonatal life. Increased methylation of CpG island in the proximal promoter of the *Pdx1* gene and lowered expression of *Pdx1* gene during adulthood	Park et al. (2008)
	Rat	Neonatal and postnatal d 21	Liver	H3 acetylation in genes encoding (PPAR)-gamma coactivator and carnitine-palmitoyl-transferase I in a site-specific manner	Fu et al. (2004)
	Rat	Neonatal and postnatal d 21	Liver	Enhanced expression of *PGC-1* gene	Lane et al. (2002)
BPA exposure during pregnancy	Mice	F1 and F2 adult offspring	Pancreatic islets	Increased expression of *Igf2* gene in F1 and F2 generations associated with altered levels of DNA methylation	Susiarjo et al. (2015), Bansal et al. (2017)
BPA exposure during pregnancy and lactation	Rat	Postnatal weeks 3 and 21	Liver	Global DNA demethylation. Increased expression of *DNMT3B*, increased methylation of *Gck* gene promoter and reduced *Gck* expression	Ma et al. (2013)
Perinatal paternal BPA exposure	Rat	F1 and F2 adult offspring	Pancreatic islets	Decreased expression and associated hypermethylation of *Igf2* in F2 offspring	Mao et al. (2015)
DEHP exposure during pregnancy	Rat	Postnatal day 60	Muscle	Increased global DNA methylation. Epigenetic alterations in genes critically implicated in the insulin signaling pathway. Downregulation of *Glut4* gene	Rajesh and Balasubramanian (2014)
	Rat	Postnatal day 60	Pancreatic islets	Downregulation of genes involved in the β-cell development and function. Increased global DNA methylation.	Rajesh and Balasubramanian (2015)
Ethanol exposure during gestation	Rat	Neonatal	Fat, plasma	Decreased expression of *PEPCK* and *PGC-1* genes in response to insulin	Chen et al. (2004)
	Rat	Adult	Liver	Impaired insulin response of hepatic gluconeogenic genes	Yao et al. (2006)
	Rat	Adult		Increased expression of *TRB3* and *PTEN* genes. Increased HDAC and decreased HAT activities	Yao and Nyomba (2008)

(*continued on next page*)

Table 1 (*continued*)

Condition	Model	Stage(s) of detection	Tissue/ body fluid	Epigenetic outcome(s)	Reference
Prenatal exposure to nicotine	Rat	Adult	Liver	Increased expression of gluconeogenic genes and HDAC proteins	Yao et al. (2013)
	Guinea pig	Postnatal day 150-200	Liver	Altered expression of genes involved in the insulin and IGF signaling pathways	Dobson et al. (2014)
	Rat	Adult	Hippocampus	Lowered expression of genes encoding hippocampal glucocorticoid receptor and mineralocorticoid receptor	Liu et al. (2012)
	Rat	Before weaning	Pancreas and adipose tissue	Pancreas: decreased gene expression of pancreatic and duodenal homeobox 1, *Pax-6*, and *Nkx6.1*. Adipose tissue: increased gene expression of CAAT-enhancer-binding protein-alpha, *PPAR*-gamma, and sterol regulatory element binding protein-1C	Somm et al. (2008)
Prenatal-to-weaning exposure to nicotine	Rat	Adult	Adipose tissue	Increased expression of genes encoding glucose transporter 4 and leptin. Decreased mRNA level of adiponectin gene	Fan et al. (2016)

(Williams et al., 2014; Glastras et al., 2018). In a mice model, maternal HFD during pregnancy and lactation led to an impaired hepatic glucose and lipid homeostasis, as well as to upregulated expression of genes involved in the PPAR signaling pathway in the early life of offspring (Zheng et al., 2014). Such metabolic dysregulation was associated with altered expression of several hepatic miRNAs. Among them, miR-143 was upregulated, whereas miR-615-5p, miR-3079-5p, miR-124, and miR-101b were downregulated in offspring from HFD-fed dams (Zheng et al., 2016). Functional enrichment analysis demonstrated that target genes of these differentially expressed miRNAs include tumor necrosis factor-α (*TNF-α*) and mitogen-activated protein kinase 1 (*MAPK1*), which are both mapped to inflammatory pathways. In addition, both mRNA and protein levels of TNF-α and MAPK1 were found to be significantly increased in livers of these offspring at weaning. Recently, maternal HFD was found to influence the levels of expression of some lipid and bile acid metabolism-related genes in adult mice offspring in a gender-specific manner (Tanaka et al., 2018). Maternal HFD also resulted in higher serum levels of leptin and obesity in adult female offspring (Keleher et al., 2018). These phenotypic alterations were accompanied by large-scale DNA methylation changes and by expression changes in dozens of genes in the offspring heart and liver. Genes involved in RNA processing, immune response and mitochondria were found to be particularly affected. In a rat model, offspring from HFD-fed dams were significantly heavier at weaning and had impaired insulin sensitivity relative to control animals (Reynolds et al., 2015). Such HFD-induce metabolic impairments were associated with dysregulation of taste receptor, incretin, and with altered pro-inflammatory gene expression in the offspring gut. These changes were gender-specific. In female offspring, the expression levels of *Tas1R1* gene were increased, while those of *PYY* and *IL-10* decreased. In male offspring, the levels of expression of *Tas1R1*, *IL-1β*, *TNFα* and *NLRP3* was increased and *Tas1R3* decreased; these changes were abolished by maternal supplementation with the anti-inflammatory lipid, conjugated linoleic acid. *In-utero* exposure to both maternal undernutrition and overnutrition was associated with non-random dysregulation of DNA methylation profiles in rats (Heo et al., 2016). These changes were similar to those seen in normal aging animals and occurred in regions mapped to genes related to metabolic diseases and aging. Profound epigenetic alterations were observed, among others, in pro-lipogenic genes (*Prkcb* and *Pc*) as well as in genes *Ncor2* and *Smad3* involved in Notch signaling, which plays an important role in pancreatic development. Maternal obesogenic diet from the time they were weaned through breeding at postnatal day 120, delivery and lactation caused substantial changes in insulin, glucose and lipid signaling pathways, thereby resulting in liver dysfunction and insulin resistance in offspring (Lomas-Soria et al., 2018). These metabolic disturbances were accompanied by significantly changed expression levels of 1365 genes in male offspring liver and only 70 genes in female in comparison with controls. In males, many of these genes were associated with key metabolic pathways including insulin signaling (22 genes), glycolysis/gluconeogenesis (7 genes), phospholipase D signaling (14 genes) and non-alcoholic fatty liver disease (13 genes). In contrast, few genes only were changed in these pathways in females.

4.2. Uterine artery ligation

In several studies, uterine artery ligation (UAL) was used in experimental modeling of IUGR. Animal offspring generated via such IUGR model have been found at high risk of developing T2D in adulthood (Wolf, 2003). Development of T2D in this model was accompanied by profound epigenetic modifications revealed at both genome-wide and locus-specific levels. In a genome-wide methylation study by Thompson et al. (2010), 1400 differentially methylated loci were found in pancreatic islets isolated from adult male rats exposed to UAL-induced IUGR. Most of these loci were located mainly near genes regulating processes found to be abnormal in IUGR islets, including cell

proliferation, vascularization, apoptosis and insulin secretion. These methylation changes were associated with consistent changes in expression patterns. In UAL model, epigenetic changes such as genome-wide DNA hypomethylation as well as changed one-carbon metabolism and histone acetylation were also found in postnatal livers (MacLennan et al., 2004). Among the locus-specific changes, the lowered expression levels of *Pdx1* gene encoding the pancreatic homeobox domain 1 critical for beta cell function and development was found in adult rats (Park et al., 2008). These changes were accompanied by epigenetic modifications of histones, such as decrease in H3K4 trimethylation and increase in H3K9 dimethylation in neonatal life, as well as by methylation of CpG island in the proximal promoter of the *Pdx1* gene during adulthood. Bilateral UAL also resulted in substantial reduction in expression levels of genes encoding key transcription factors involved in embryonic beta-cell development such as *Pdx-1* gene (Pinney et al., 2011). These epigenetic alterations have been associated with reduced beta cell formation during the postnatal life, and also with inability to expand mass of beta cells in response to metabolic stress. Uteroplacental insufficiency also increased hepatic H3 acetylation in genes encoding hepatic peroxisome proliferator-activated receptor (PPAR)-gamma coactivator (PGC-1) and carnitine-palmitoyl-transferase I (CPTI) in a site-specific manner. These changes persisted to day 21 of postnatal life (Fu et al., 2004) and were associated with enhanced expression of *PGC-1* gene and development of insulin resistance in male rats (Lane et al., 2002).

4.3. Endocrine-disrupting exposure

While dietary factors obviously play a major role in developmental programming of T2D, non-dietary factors also can significantly affect the risk for developing this disease across modern societies. Among them, there are hazardous to human health environmental pollutants that are constantly present in present-day human environments. The exposure to environmental chemicals with endocrine-disrupting properties is of specific concern because the developing organism is extremely sensitive to perturbation by substances with hormone-like activity (Newbold et al., 2007). Apart from the endocrine-disrupting activity, developmental exposures to these chemicals can potentially contribute to developmental programming of metabolic disorders in offspring, including T2D (Heindel et al., 2017), allowing them to be referred to as “metabolic disrupting chemicals” (Casals-Casas and Desvergne, 2011).

Bisphenol A (BPA), an estrogenic agent widely used in manufacturing of polycarbonate plastics and epoxy resins, is the most thoroughly studied compound among endocrine disruptors. There is accumulating evidence that exposure to BPA early in life enhances the risk for developing metabolic disorders, including T2D and obesity, in adult life, and that epigenetic factors can play a mediating role in this relationship (Vaiserman, 2014a, 2014b; Stel and Legler, 2015). Prenatal exposure to BPA was demonstrated to influence the expression levels of imprinted (parentally expressed) genes including insulin-like growth factor 2 (*Igf2*). This factor has a variety of important biological roles. Among others, it is known to be a key player in early beta cell development, and aberrant imprinting of *Igf2* in early life may potentially affect the normal development of beta cells (Bansal and Pinney, 2017). Recently, Bansal et al. (2017) reported that maternal exposure to BPA throughout the pregnancy can have significant impacts on beta cell development and also on epigenetic status of *Igf2* gene in mice. High BPA exposure caused impairment of mitochondrial function, whereas low BPA exposure substantially reduced beta cell mass and increased the level of apoptotic death of beta cells that persisted to F2 generation. Similar dose-specific changes were observed by the transcriptome analysis of the expression of genes regulating inflammation and mitochondrial function. Maternal BPA exposure resulted in a significantly increased expression of *Igf2* gene in F1 embryos, which persisted in the islets of male offspring up to F2 generation and was associated with altered levels of DNA methylation. The observed changes in levels of DNA methylation and expression of *Igf2* gene were also found to be associated with impaired glucose tolerance and beta cell dysfunction in this model (Susiarjo et al., 2015; Bansal et al., 2017). Interestingly, in a rat model, paternal BPA exposure throughout the perinatal period also caused reduced beta cell mass, impaired glucose tolerance, lowered glucose-stimulated insulin secretion, as well as increased methylation of the *Igf2* gene and reduced *Igf2* expression in islets of the adult male offspring (Mao et al., 2015). In rats, maternal BPA exposure throughout gestation and lactation also lead to global DNA demethylation, increased expression of gene encoding DNA methyltransferase 3B (DNMT3B), increased methylation of glucokinase (*Gck*) gene promoter and reduced *Gck* expression in 3-wk-old male offspring (Ma et al., 2013). These changes were associated with developing insulin resistance in adult offspring.

Similar results were obtained in experimental studying the effects of phthalates, commonly used plasticizers with anti-androgenic properties. Perinatal exposure to di(2-ethylhexyl) phthalate (DEHP) was found to impair pancreatic beta cell function and induce metabolic abnormalities in F1 rat offspring (Lin et al., 2011; Rajesh and Balasubramanian, 2014, 2015; Xu et al., 2018). For example, in the study by Rajesh and Balasubramanian (2014), prenatally DEHP-exposed rat offspring exhibited enhanced blood glucose levels, impaired serum insulin, insulin tolerance and glucose tolerance, and also lowered levels of insulin receptor signaling, glucose uptake and oxidation in the muscle at postnatal day 60. The impaired insulin signaling was associated with an increased global DNA methylation, as well as with downregulation of genes involved in the β-cell development and function. For instance, the glucose transporter 4 (*Glut4*) gene was found to be methylated and down-regulated in DEHP-exposed offspring. Moreover, increased histone deacetylase 2 interaction toward *Glut4* was revealed, indicative of the tight chromatin structure at the *Glut4* promoter. The increased global DNA methylation along with downregulation of genes involved in the β-cell development and function were also observed in DEHP-exposed offspring (Rajesh and Balasubramanian, 2015).

4.4. Prenatal substance abuse

There is accumulating evidence that maternal substance abuse (drinking, smoking, psychoactive drug intake, etc.) during pregnancy and/or breastfeeding is one of the important factors contributing to the present-day epidemic of T2D across the globe (Vaiserman, 2015). It is generally assumed that long-term health outcomes of exposure to psychoactive substances early in life can be mediated by epigenetic mechanisms operating during early development (Vaiserman, 2013). Recently, these mechanisms began to investigate in animal models.

The programming effects of prenatal exposure to alcohol are studied most thoroughly. Rat offspring, prenatally exposed to ethanol, were shown to be at risk for developing insulin resistance and they demonstrated increased gluconeogenesis compared to controls (Chen et al., 2004; Yao et al., 2006). These metabolic changes were found to be mediated by epigenetic alterations in hepatic gluconeogenic genes. The blunted inhibitory response of the gluconeogenic enzymes such as PEPCK and PGC-1 to insulin, manifested in blunted expression of genes encoding these enzymes, was observed in neonatal rats after prenatal ethanol exposure (Chen et al., 2004). The epigenetic alterations induced by ethanol exposure *in utero* have been shown to be able to persist through adulthood (Yao et al., 2006). These alterations included 40–80% higher levels of expression of *PGC-1α* gene and 1.8-fold greater levels of expression of *PEPCK* gene in prenatally exposed offspring. Prenatal ethanol exposure also resulted in an increased expression of gluconeogenic genes and HDACs in adult male rat offspring (Yao et al., 2013), and in an increased expression of genes encoding tribbles 3 (TRB3) and phosphatase and tensin homolog deleted on chromosome ten (PTEN) in the livers of female offspring (Yao and Nyomba, 2008). Maternal alcohol intake from 4 days before conception until day 4 of

gestation resulted in elevated fasting plasma glucose levels, impaired glucose tolerance, decreased insulin sensitivity and increased hepatic gluconeogenesis at 6 months of age (Gårdebjer et al., 2015). These metabolic disturbances were associated with an increased expression of DNMTs 1, 3a, and 3b in fetal liver in late gestation, suggesting that such exposure can cause epigenetic alterations that predispose rat offspring to metabolic dysfunctions in adult life. Confirming evidence for programming effects of prenatal exposure to alcohol was also provided from studies in guinea pig. This is a commonly used animal model in studying alcohol teratogenicity because prenatal development of these animals is much more similar to those in humans in comparison with other rodent models (Dobson et al., 2012). In this model, the offspring of dams exposed to alcohol during their pregnancy were characterized by both pancreatic and whole-body adiposity, and also by altered expression of genes involved in the insulin and IGF signaling pathways at both central and peripheral levels during adulthood (Dobson et al., 2012, 2014).

Prenatal exposure to nicotine, which is the major addictive constituent of tobacco smoke, was shown to inhibit the functional development of the hypothalamic-pituitary-adrenal (HPA) axis, and also to impair glucose and lipid metabolism, resulting in postnatal obesity and altered adipose tissue function in rat models (Gao et al., 2005; Somm et al., 2008; Liu et al., 2012; Fan et al., 2016). These changes were associated with epigenetic alterations in key metabolic genes. For example, prenatal nicotine exposure led to HPA axis-related neuroendocrine metabolic programmed alterations such as increased blood total cholesterol and triglyceride levels in adult offspring; these metabolic changes were related to lowered levels of expression of genes encoding hippocampal glucocorticoid receptor (GR) and mineralocorticoid receptor (Liu et al., 2012). An increased epididymal white adipose tissue weight and marked hypertrophy of adipocytes associated with increased expression of genes encoding proadipogenic transcription factors such as CAAT-enhancer-binding protein-alpha, PPAR-gamma and sterol regulatory element binding protein-1C were also reported at weaning in prenatally exposed rats (Somm et al., 2008). These early tissue changes caused substantial metabolic consequences in adulthood, including enhanced food efficiency on high-fat diet, increased body weight and fat deposition, reduced physical activity, cold intolerance, and also glucose intolerance combined with insulin resistance. In the study by Fan et al. (2016), perinatal nicotine exposure resulted in increased obesity susceptibility in adult male rat offspring and in a modified expression of adipogenic and lipogenic genes. Among them, expression of genes encoding glucose transporter 4 and leptin was increased, while that of adiponectin gene was decreased in the epididymal white adipose tissue; the lipogenic gene expression was increased in the liver in adult male offspring.

4.5. Prenatal exposure to caffeine

In human prospective cohort studies, the link between maternal caffeine intake during pregnancy and risk of metabolic impairments and obesity in offspring has been observed (Li et al., 2015). This relationship was confirmed in animal studies, where prenatal exposure to caffeine caused IUGR and increased risk of abnormal cholesterol metabolism, non-alcoholic fatty liver disease, metabolic syndrome and T2D in adulthood (Sun et al., 2014; Wang et al., 2014; Luo et al., 2015; Kou et al., 2017; Pei et al., 2017). In a rat model, gestational exposure to caffeine resulted in significantly decreased birth weight and postnatal body weight in offspring (Sun et al., 2014). Levels of serum insulin after oral glucose tolerance test were substantially lower in adult offspring who were prenatally exposed to caffeine compared to the control animals. Moreover, 24 proteins mostly involved in energy metabolism were found to be differentially expressed in pancreas of adult offspring between the caffeine-exposed and control groups. Prenatal caffeine exposure reduced the pancreatic beta mass but increased the glucose tolerance in adult offspring rats, especially in females. In these female offspring, such *in-utero* exposure resulted in substantial increase of protein expression of hepatic insulin signaling elements, including insulin receptor (IR), insulin receptor substrate 1 (IRS-1) and elevated phosphorylation of serine-threonine protein kinase (Akt) (Sun et al., 2014).

5. Evidence from human studies

Findings from human studies confirming the role of epigenetic mechanisms in linking early-life adverse experiences to the risk for T2D in adult life are scarce compared to data from animal studies, mainly because of limited access to suitable biological samples. It is, however, convincing evidence that these mechanisms may also operate in human beings (Bianco-Miotto et al., 2017; Nilsson and Ling, 2017; Bansal and Simmons, 2018). Most of these data were obtained in studies conducted using pancreatic samples from deceased T2D donors. In these studies, profound genome-wide epigenetic perturbations were found for all levels of epigenetic regulation, including DNA methylation, histone modifications and miRNA profiling (Stitzel et al., 2010; Morán et al., 2012; van de Bunt et al., 2013; Volkov et al., 2017). A serious methodological problem of these studies is, however, that these perturbations may be induced not only by adverse exposures early in life, but also by various unfavorable events in adulthood. Therefore, results from these studies are rarely used in discussing the developmental epigenetic programming of T2D. The most conclusive evidence for a developmental origin of T2D is obtained using available perinatal tissues, including placenta and umbilical cord blood, with subsequent extrapolation of observed epigenetic effects on corresponding adult tissues. Nevertheless, ultimate conclusions on developmental causality of these epigenetic changes cannot be still made from these studies. Indeed, such epigenetic modifications are cell type- and tissue-specific. Therefore, alterations in certain cell/tissue types may often not reflect the same changes elsewhere, and such extrapolations can be faulty (Bansal and Simmons, 2018). However, even with all these limitations, investigations with this design may provide a feasible option to obtain information regarding epigenetic factors potentially involved in the developmental programming of T2D. The epidemiological evidence for the potential involvement of epigenetic mechanisms in mediating the links between adverse developmental exposures and the risk of T2D in later life is reviewed and discussed in the subsequent subsections. A brief summary of human evidence for the role of epigenetic dysregulation in the process of developmental metabolic programming is also given in Table 2 below.

5.1. Birth weight-discordant twin model

An important evidence for the developmental epigenetic programming of adult-life metabolic health status came from model of monozygotic twins. This study design commonly relies on studying twin pairs raised in the same family environments, which provides control not only for genetic background but also for shared postnatal rearing environment. Therefore, this model provides unique opportunity for investigating associations between intrauterine conditions and adult-life health outcomes. In particular, a supportive evidence for importance of non-genetic factors in early-life etiology of T2D comes from the fact that monozygotic twins who are smaller at birth tend to have increased risk of developing T2D in adulthood (Yajnik, 2013). The long-term persistent differences in both DNA methylation and expression of genes, including those potentially involved in metabolic pathways, were revealed in birth weight-discordant monozygotic twins. Severe intrauterine growth differences (birth weight discordance > 20%) were significantly associated with methylation changes in the *IGF1R* gene in adulthood (Tsai et al., 2015). In the epigenome-wide association study examining adult identical twins discordant for birth weight, the genomic region on chromosome 1 was identified, which was substantially differentially methylated for quantitative birth-weight

Table 2
Summary of human evidence for the role of epigenetic dysregulation in developmental metabolic programming.

Condition /model	Approach	Stage of detection	Population, N	Tissue/ body fluid	Epigenetic outcome(s)	Reference
Birth weight-discordant MZ twin model	MWAS	Adult	71 MZ twin pairs	Blood	Methylation changes in the *IGF1R* gene	Tsai et al. (2015)
	MWAS	Adult	150 MZ twin pairs	Blood	Differentially methylated chromosome 1 region covering metabolism-associated *CRYZ* and *TYW3* genes	Chen et al. (2016)
Gestational diabetes mellitus	q-PCR	Adult	206	Muscle	Lowered levels of *PPAR-γ* coactivator-1α gene expression	Kelstrup et al. (2016)
	q-PCR	Adult	82 exposed individuals, 57 controls	Adipose tissue	Increased adiponectin gene methylation and decreased adiponectin and resistin gene expression	Houshmand-Oeregaard et al. (2017a)
	MWAS	Adult	388 Pima Indians	Peripheral blood	48 differentially methylated CpG sites mapping to 29 genes and 10 intergenic regions	Chen et al. (2017)
Prenatal famine exposure	Mass spectrometry	Adult	311 exposed individuals, 311 same-sex siblings	Peripheral blood	Decreased methylation of the imprinted IGF2 gene	Heijmans et al. (2008)
	MWAS	Adult	313 exposed individuals, 313 same-sex siblings	Peripheral blood	Decreased methylation of the *GNASAS, IL10, LEP, ABCA1, INSIGF* and *MEG3* genes	Tobi et al. (2009)
Seasonality	Pyro-sequencing	Adult	88 healthy heavy smokers	Peripheral blood	Decreased methylation of *LINE-1* retroelements in autumn/ winter-born persons	Ricceri et al. (2014)
	MWAS	Neonatal, adult	367	Peripheral blood	92 differentially methylated regions in adult persons	Lockett et al. (2016)
	MWAS	Neonatal	23 in vitro and 41 naturally conceived children	Cord blood	Decreased stochastic epigenetic variation in autumn-born individuals	Gentilini et al. (2018)
Maternal smoking in pregnancy	MethyLight assay	Adult	90 women	Peripheral blood	Decreased *Sat2* repetitive element methylation	Flom et al. (2011)
	MWAS	Neonatal, age 7, age 17	1018 mother–offspring pairs	Cord blood, peripheral blood	Persisting changes in methylation of *AHRR, MYO1G, CYP1A1* and *CNTNAP2* genes	Richmond et al. (2015)

discordance (Chen et al., 2016). This region covered two genes (*CRYZ* and *TYW3*) both known to be associated with metabolism. Epigenome-wide profiling of DNA methylation in blood samples from 150 pairs of adult monozygotic twins discordant for birth weight did not reveal any epigenetic differences between twins, although several sites displayed age-associated intra-pair differential methylation in highly discordant twin pairs (Tan et al., 2014).

5.2. Gestational diabetes mellitus

The evidence that *in utero* exposure to maternal diabetes mellitus may increase the risk of T2D in adulthood came from the study conducted by Dabelea et al. (2000) with nuclear families of Pima Indians in which at least one sibling was born before and other(s) after the mother was diagnosed with T2D. In this research, those siblings conceived after their mother became diabetic exhibited a 3.7-fold higher risk of T2D in adult life compared to siblings born before the mother has been diagnosed with diabetes, even though their living conditions have been highly similar throughout the rest of life. Adverse metabolic conditions *in-utero* related to gestational exposure to maternal T2D was also shown to induce modifications in epigenetic regulation of genes primarily involved in metabolic diseases. In most of these studies, epigenetic changes were determined in placenta and cord blood samples (Ruchat et al., 2013; Nomura et al., 2014; Finer et al., 2015; Tryggestad et al., 2016; Haertle et al., 2017; Kang et al., 2017; Weng et al., 2018). Data from several studies also suggested that these changes can persist into adulthood (Kelstrup et al., 2016; Houshmand-Oeregaard et al., 2017a, b). For example, lowered levels of PPAR-γ coactivator-1α (*PPARGC1A*) gene expression were found in muscle tissue from adult offspring of mothers with diabetes in pregnancy (Kelstrup et al., 2016). In subcutaneous adipose tissue of adult offspring of such mothers, increased adiponectin (*ADIPOQ*) gene methylation and decreased *ADIPOQ* and resistin (*RETN*) gene expression (Houshmand-Oeregaard et al., 2017a). The increased methylation and decreased expression of *TXNIP* gene were also revealed, but these differences were attenuated after adjustment for confounders (Houshmand-Oeregaard et al., 2017b). In a recent epigenome-wide association study, 48 differentially methylated CpG sites mapping to 29 genes and 10 intergenic regions were identified in Pima Indian individuals exposed to maternal T2D *in utero* (Chen et al., 2017). Methylation status at some of these sites was suggested to impair insulin secretion, increase body weight and increase risk of T2D in adulthood.

5.3. Natural experiments

In human beings, longitudinal designs are obviously not suitable for investigating associations between adverse experiences early in life and the risk for T2D development in adulthood, because of the very long duration of follow-up that is required for such a study. Therefore, most information about these associations came from epidemiological investigations conducted with quasi-experimental designs. Such observational studies ("natural experiments") are referred to as "naturally occurring circumstances in which subsets of the population have different levels of exposure to a supposed causal factor, in a situation resembling an actual experiment where human subjects would be randomly allocated to groups" (Last, 1995). In particular, famines are natural experiments that may provide information about the long-term health effects of poor nutrition and associated stresses in early life. The association between exposure to famine early in life and T2D, among other adverse health outcomes in adult life, was repeatedly found in quasi-experimental studies across many countries such as the Netherlands (Portrait et al., 2011; van Abeelen et al., 2012), China (Wang et al., 2016; Li et al., 2017; Wang et al., 2017; Meng et al., 2018), Austria (Thurner et al., 2013) and Ukraine (Lumey et al., 2015). In investigating long-term health consequences of prenatal exposure to the Dutch famine of 1944–1945, changes in DNA methylation potentially

contributing to these effects have been determined. While no association between the prenatal exposure to the famine and overall DNA methylation level in adult life has been reported (Lumey et al., 2012), the methylation levels of particular genes in the whole blood samples of adult offspring were shown to be clearly associated with prenatal famine exposure. Among them, genes such as *IGF2* (Heijmans et al., 2008) and *GNASAS*, *IL10*, *LEP*, *ABCA1*, *INSIGF* and *MEG3* (Tobi et al., 2009), known to be associated with developing metabolic and cardiovascular phenotypes, have been demonstrated to be differentially methylated among exposed subjects and non-exposed control individuals six decades after exposure to the famine. More recently, a genome-wide analysis of differential DNA methylation in whole blood cells was performed, in which a link between periconceptional exposure to famine and differential methylation of genomic regions extended along pathways associated with growth and metabolism was demonstrated (Tobi et al., 2014). Early, but not mid or late gestation, has been identified to be a critical period for inducing changes in DNA methylation which may persist in whole blood of the perinatally exposed persons into their adulthood (Tobi et al., 2015). Even though it has not been determined whether these changes in DNA methylation were associated with corresponding changes in gene expression, they were apparently associated with disrupted metabolic homeostasis in adult individuals who were prenatally exposed to famine (Lumey et al., 2007). Similar findings were reported in a historical cohort research conducted in Bangladesh (Finer et al., 2016). Those persons who were perinatally exposed to famine have been shown in this study to be at higher risk for developing obesity and T2D during their adult life compared to the unexposed control subjects. The periconceptual exposure to this famine was found to induce significant changes in DNA methylation at metastable epialleles such as *PAX8*, *VTRNA2-1*, *PRDM-9*, *EXD3*, near *ZFP57* and near *BOLA*, which were previously identified as highly sensitive to such exposure.

Seasonality can also be regarded as a kind of natural experiment. In such a quasi-experimental design, month of birth presents an excellent tool for studying effects of early developmental conditions on adult health outcomes regardless of life-course factors. Indeed, in decades past strong seasonal differences existed in nutrition and other factors across different countries. These variations could potentially affect human intrauterine growth depending on the month of gestation. Other potentially triggering factors in disease progression, such as outdoor temperature, sunlight/photoperiod, infections, productions of melatonin and vitamin D also tend to change seasonally (Vaiserman, 2011). Seasonality of birth was revealed for many important ontogenetic characteristics such as birth weight. In the low- and high-latitude regions, lower birth weights tend to be associated with the winter period, and higher mean birth weights tend to be associated with the summer period; in the mid-latitude regions, summer season is generally associated with relatively lower birth weights (Chodick et al., 2009). Seasonal changes were also shown to affect variations in glucose tolerance throughout the pregnancy, with incidence of gestational diabetes mellitus decreasing during cold months and increasing during the summer (Chiefari et al., 2017). In the study by van Hanswijck de Jonge et al. (2003), the evidence was obtained that seasonal variation in postnatal weight gain could be an important indicator for a predisposition to obesity, as well as for other adverse metabolic outcomes later in life. In Hertfordshire (UK), the prevalence of obesity was found to vary as a function of month of birth and was substantially higher among those men who were born in January-June than among those who were born in July-December (Phillips and Young, 2000). In Canada, a relatively lager proportion of the class III obese persons was revealed among those who were born throughout the winter/spring period (Wattie et al., 2008). Seasonal pattern of birth in T2D patients was revealed in several countries, including Slovakia (Mikulecky et al., 2016), Ukraina (Vaiserman et al., 2009) and China (Si et al., 2017), although no evidence for such a pattern was reported in Denmark (Jensen et al., 2015).

The evidence was obtained that basal methylation levels of several genes may be modified by seasonal factors. In particular, the long interspersed nucleotide element-1 (LINE-1) was found to be significantly hypomethylated in autumn/winter season compared to spring/summer season (Ricceri et al., 2014). This finding seems important because lower levels of LINE-1 DNA methylation were shown to be associated with a higher risk of T2D (Martín-Núñez et al., 2014). In the epigenome-wide association study conducted in the Isle of Wight birth cohort, the association of season of birth with DNA methylation was revealed (Lockett et al., 2016). The differentially methylated regions were shown to be enriched in networks contributed to the development, cell cycle regulation and apoptosis. Interestingly, these season of birth-associated methylation changes were largely absent in newborns, suggesting they originate post-natally. The association of epigenetic signatures with season of birth was also recently demonstrated in the study by Gentilini et al. (2018). The number of stochastic epigenetic variations was found to be lower in those individuals who were born in autumn.

5.4. Maternal cigarette smoking

In epidemiological studies, maternal smoking during pregnancy has been repeatedly found to be associated with increased risk of obesity and T2D in offspring (Somm et al., 2008; Maddatu et al., 2017). This association is believed to be mediated by epigenetic changes induced by prenatal nicotine exposure, including those in metabolic pathways. In several studies, the link between maternal smoking in pregnancy and changes in DNA methylation status of specific CpG sites was observed (Flom et al., 2011; Richmond et al., 2015, 2018; Tehranifar et al., 2018). In particular, longitudinal analyses of blood DNA methylation in serial samples at birth, in childhood and in adulthood showed that methylation of some CpG sites can be reversible, while others demonstrated persistently perturbed methylation profiles (Richmond et al., 2015, 2018).

6. Conclusions and prospects

There are a lot of experimental and epidemiological evidence suggesting a relationship between adverse experiences such as stress, malnutrition and xenobiotics early in life and a higher risk of developing T2D and different associated conditions throughout adulthood. Accumulating evidence indicates that mechanisms of epigenetic regulation may play a central role in developmental programming of T2D. Over the last decade, specific epigenetic pathways contributing to these processes have become a subject of comprehensive investigation, and some of these pathways are already unraveled. Consistent findings from animal and human studies suggest that epigenetic dysregulation of important metabolic genes, including those implicated in β-cell development and function, insulin signaling, lipid metabolism (e.g., *PPAR*, resistin), glucose and energy homeostasis (leptin, adiponectin) and also inflammatory response, may contribute to developmental programming of T2D, among other metabolic disorders (see Tables 1 and 2). Epigenetic modifications in miRNA expression could also be crucially involved in these processes.

There are, however, several important outstanding challenges that need to be addressed to a better understanding the causal relationships underlying these processes. In particular, it is not clear yet to what extent developmentally triggered epigenetic modifications may be translated to corresponding changes in gene expression during adulthood. Changes on these levels may indeed co-occur, but it is still unknown if such a link is really causal. Furthermore, it is not fully established yet to what extent alterations in gene expression may be translated into respective changes on the levels of the protein content and activity and, consequently, into particular disease phenotypes. It is also not clear so far whether developmentally induced epigenetic modifications are steadily reproducible and whether they may persist up to late adulthood when T2D typically manifests. There is consistent

evidence that such modifications may really persist life-long, thus determining the risk for developing aging-associated disorders including T2D (Kanherkar et al., 2014; Vaiserman et al., 2018). The research evidence confirming the persistent nature of such epigenetic modifications is, however, scarce. Further studies are therefore needed to a better elucidating the pathways underlying these long-term effects. The other methodological issue is that epigenetic patterns are largely tissue-specific (Sala et al., 2017). Since epigenetic modifications arise both within and between various tissues, the important problem is applicability of results obtained either from peripheral blood or from buccal swab samples to draw any definitive conclusions. The research of tissues/organs most substantially contributing to the pathogenesis of T2D would certainly be of great interest. Such tissues, however, in most cases can be obtained from cadaver donors only. The simultaneous investigation of the epigenetic profiles in both central and peripheral tissues is highly valuable in elucidating epigenetic pathways contributing to developmental programming of T2D. Such studies may be conducted with animal models. Using the animal models, in turn, raises questions about the specificity of these pathways across different mammalian species and also about similarities and distinctions among these pathways in various animal species and man. However, despite these unresolved issues, further research of epigenetic mechanisms involved in developmental programming of T2D seems extremely promising. Since most environmentally induced epigenetic changes, unlike genetic mutations, are potentially reversible (Sinclair and Oberdoerffer, 2009), pharmacological and/or nutritional interventions aimed at correction of developmentally disrupted epigenetic profiles could provide an innovative approach to preventing and treating T2D and associated complications (Vaiserman and Pasyukova, 2012; Pasyukova and Vaiserman, 2017). Prenatal supplementation with folate or its synthetic form, folic acid, has been studied most extensively in this context to date. Folate is an essential component of the one-carbon metabolism, providing methyl groups for DNA methylation (Tserga et al., 2017). Recently, in the Maternal Nutrition and Offspring's Epigenome (MANOE) study, it has been found that prenatal maternal dietary or supplemental intake of methyl-group donors, including folate and folic acid, may significantly influence the buccal DNA methylation in genes related to growth (*IGF2* DMR), metabolism (*RXRA*) and appetite regulation (*LEP*) in infants (Pauwels et al., 2017). In some animal models, evidence was also provided that T2D and associated complications can be prevented by such epigenome-targeted interventions. For example, folic acid supplementation during pregnancy ameliorated maternal LPD-induced epigenetic dysregulation of hepatic genes expression in the rat offspring (Lillycrop et al., 2005, 2008; Gong et al., 2010). Neonatal supplementation with Exendin-4, a long-acting glucagon-like peptide-1 analogue, restored the expression of pancreatic homeobox transcription factor (*Pdx1*) and prevented the development of diabetes in the IUGR rats (Pinney et al., 2011). Based on these theoretical considerations and empirical findings, it can be assumed that implementation of targeted epigenetic therapies to combat T2D would provide new opportunities for clinical practice.

Declaration of Competing Interest

The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Aknowlegements

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