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Epigenetic influence of long non-coding RNAs on the development of insulin resistance in metabolically associated fatty liver disease (part 1)

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Abstract. *Insulin resistance (IR) of metabolic origin is a pathological condition, which is based on a decrease in the metabolic response of insulin-sensitive cells to insulin stimulation. It often accompanies metabolically associated fatty liver disease (MAFLD) and is the pathogenetic basis of type 2 diabetes mellitus (T2DM). MAFLD is associated with a high risk of developing T2DM, its presence increases the likelihood of T2DM by approximately two times during the next five years of the patient's life. Long non-coding RNAs are directly involved in the development of IR, the determination of the level of their expression can significantly increase the effectiveness of diagnosis and prognosis of the disease. Today, among the assumptions explaining the mechanisms of IR development, the lipocentric and glucocentric hypotheses dominate. The lipocentric hypothesis is based on the idea that IR is a consequence of the lipotoxic effect of excessive intracellular content of free fatty acids and their derivatives (diacylglycerol, ceramides). The glucocentric hypothesis postulates that the development of IR is due to recurrent manifestations of hyperglycemia, which are accompanied by the generation of advanced glycation end products. Insulin-resistant liver tissue is characterized by increased activity of gluconeogenesis, depletion of glycogen depot and decreased secretion of triglycerides. Hepatic steatosis leads to the development of IR, which is accompanied by increased activity of gluconeogenesis. Selective hepatic IR is the primary event in the systemic disruption of the insulin-associated signaling pathway, which subsequently leads to the development of IR of peripheral tissues. Numerous long non-coding RNAs, such as H19, MALAT1, MEG3, MIAT, SRA, and others, are involved in the development of hepatic insulin resistance in MAFLD. Long non-coding RNAs, the expression level of which increases in case of the development of hepatic insulin resistance, are Blnc1, EPB41L4A-AS1, H19, HCG18, HOTAIR, HOTTIP, LncARSR, MAYA, MALAT1, MIAT, NONMMUT031874.2. At the same time, long non-coding RNAs, the expression level of which decreases hepatic insulin resistance, are represented by B4GALT1-AS1/LncSHGL, MEG3.*

Keywords: *children; obesity; metabolically associated fatty liver disease; long non-coding RNAs; literature review*

Introduction

Metabolically associated fatty liver disease (MAFLD) usually occurs in obese children and adolescents. Currently, one in three children in the United States is overweight or obese [1]. Metabolically associated fatty liver disease is highly associated with the development of insulin resistance (IR) and gluconeogenesis, which contribute to an unfavorable course of the disease [2–5]. Insulin resistance is characterized by a decrease in cellular sensitivity to insulin. Insulin resistance is characterized by the presence of basal and postprandial hyperglycemia in fasting and after meals, hyperinsulinemia, and elevated levels of glycated hemoglobin, due to the inability of target tissues to adequately utilize glucose in response to insulin stimulation. Insulin resistance often accompanies MAFLD and is the pathogenetic basis of type 2 diabetes mellitus (T2DM) [6]. The development of IR leads to an unfavorable course of MAFLD and the occurrence of metabolic disorders. It has been demonstrated that MAFLD

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is associated with a high risk of developing type 2 diabetes, the presence of MAFLD increases the risk of developing type 2 diabetes during the next five years of the patient's life by approximately two times [7–9]. Long non-coding RNA (lncR) is directly involved in the development of IR, the determination of the level of their expression can significantly increase the efficiency of diagnosis and prognosis of the disease.

1. General ideas about insulin resistance of metabolic origin

Insulin resistance of metabolic origin is a pathological condition, which is based on a decrease in the metabolic response of insulin-sensitive cells to insulin stimulation. There are two types of IR, caused by disorders of insulin reception and signal transduction along intracellular signaling pathways, and IR, the development of which is due to the influence of insulin antagonists or counterinsular hormones [10].

Currently, the lipocentric and glucocentric hypotheses dominate among the hypotheses explaining the mechanisms of IR development [11]. The lipocentric hypothesis is based on the idea that IR is a consequence of the lipotoxic effect of excessive intracellular content of free fatty acids (FFA) and their derivatives (diacylglycerol, ceramides). Lipotoxic effects of fats activate serine/threonine phosphokinase C (PKC) and induce endoplasmic reticulum stress. PKC activation leads to phosphorylation of serine residues of insulin receptor substrate (IRS) molecules, which interrupts insulin signaling via the PI3K/AKT molecular cascade [12–14]. Endoplasmic reticulum stress is accompanied by further activation of the unfolded protein response (UPR), which activates threonine/serine c-Jun-N-terminal kinases (JNK), which inhibit the insulin receptor (INSR) and IRS, and induces an inflammatory response [15–17].

The glucocentric hypothesis postulates that the development of IR is caused by recurrent episodes of hyperglycemia, which are accompanied by the generation of advanced glycation end products (AGE). Advanced glycation end products are a heterogeneous group of chemical compounds that are usually formed by non-enzymatic condensation between carbonyl groups of reducing sugars and free amino groups of nucleic acids, proteins, or lipids (Table 1) [18].

In humans and animals, AGE formation occurs continuously under physiological conditions, but the rate of their formation increases significantly under conditions of high glucose concentration and oxidative stress [18]. Advanced glycation end products exert their inherent effects by interacting with several cellular receptors, which induce numerous intracellular signaling pathways (Table 2) [19].

It has been established that AGE are involved in the development of IR due to their influence on molecular components of the insulin signaling pathway and its regulators, including phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), etc. The interaction of AGEs with their key cellular receptor — receptor for advanced glycation end products (RAGE) activates

Table 1. Classification of AGE [18]

Origin	Precursor	Molecular weight	Toxicity
Endogenous	Glucose derivatives (Glu-AGE)	Low (LMW AGE)	Non-toxic
Exogenous (dietary, dAGE)	Derivatives of fructose (Fru-AGE)		Toxic (TAGEs)
	Derivatives of glycolaldehyde (Glycol-AGE)	High (HMW AGE)	
	Derivatives of glycolaldehyde (Glycer-AGE)		
	Derivatives of methylglyoxal (MGO-AGE)		
	Glyoxal derivatives (GO-AGE)		
	Derivatives of 3-deoxyglucosone (3-DG-AGE)		

Table 2. Human cell surface receptors for AGE [19]

Receptor type	Receptor name	Ligands
RAGE	RAGE	S100A12, S100B, amyloid-β peptide precursor (ABPP), oligonucleotides
Scavenger, class H	Stabilin-1	Acetylated low-density lipoprotein (AcLDL), Gram-positive and Gram-negative bacteria
	Stabilin-2	Hyaluronic acid, heparin, chondroitin sulfate, dermatan sulfate, procollagen propeptides, oligonucleotides, phosphatidylserine, bacteria
Scavenger, class A	SR-AI	Modified low-density lipoproteins
Scavenger, class B	SR-BI	Phospholipids, cholesterol (high-density lipoproteins), cholesterol ester, lipoproteins
Scavenger, class E	OxLDL receptor 1	Oxidatively modified low-density lipoproteins (oxLDL), HSP70 protein
AGE-Rs	AGE-R1	Subunit of the oligosaccharyltransferase complex (48 kDa)
	AGE-R2	Regulatory subunit of β-glucosidase 2
	AGE-R3	Galactose-specific lectin that binds IgE

MAPK/ERK-, TGF-β-, JNK- and NF-κB-associated signaling pathways, which leads to increased oxidative stress and the development of inflammation, increasing the severity of IR [20–22].

2. The role of long non-coding RNAs in the development of insulin resistance in MAFLD

Insulin resistance, as a phenomenon based on impaired insulin signal perception and transduction, can manifest as hepatic IR and peripheral tissue IR (adipose and muscle tissue). IR can also be selective, since different INSR-associated signaling pathways are characterized by different sensitivity to insulin stimulation. Thus, in the case of hepatic IR, insulin does not suppress hepatic glucose production, but stimulates lipogenesis, which leads to hyperglycemia, hyperlipidemia, and hepatic steatosis [16].

2.1. The role of long non-coding RNAs in the development of hepatic insulin resistance in MAFLD

2.1.1. Features of insulin signal transduction in hepatocytes

Elevated blood glucose levels trigger the release of insulin from the pancreas. Insulin subsequently binds to INSR, promoting glucose influx into the cell. The insulin receptor belongs to the type II receptor tyrosine kinase (RTK) family, which also includes the insulin-like growth factor 1 receptor (IGF1R) and the insulin receptor related receptor (INSRR) [23]. The insulin receptor consists of two homodimers formed by α- and β-subunits. Insulin binds to the α-subunit of INSR and causes autophosphorylation of the β-subunit, which induces phosphorylation of tyrosine residues of the insulin receptor substrates IRS1 and IRS2. In hepatocytes, IRS1 plays a more significant role in insulin signaling than IRS2. IRS1 and IRS2 substrates activate phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3). In turn, PIK3 kinase phosphorylates phosphatidylinositol (4,5)-bisphosphate-(PIP2), catalyzing the formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3). Subsequently, PIP3, associated with the inner lipid bilayer of the cell plasma membrane, recruits serine/threonine kinases: 3-phosphoinositide dependent protein kinase-1 (PDPK1) and AKT serine/threonine kinase (AKT/PKB) to the plasma membrane [23, 24]. Having reached the inner surface of the plasma membrane, the PDPK1 kinase phosphorylates AKT, which mediates the enhancement of the process of glucose uptake by the cell, inhibition of glucose synthesis, activation of lipogenesis and glycogen synthesis. Active AKT kinase phosphorylates FoxO (forkhead box O) transcription factors, components of the mTOR-associated signaling pathway, glycogen synthase kinase 3 β, α (GSK3β, GSK3α). Activation of components of IRS-associated signaling pathways, such as the kinase aPRKC, a small G-protein RAB, which is associated with the IRS/PDK1/AKT2 signaling cascade, stimulates the translocation of solute carrier family 2 member 4 (SLC2A4/GLUT4) from intracellular storage vesicles to the plasma membrane of the cell. An increase in the number of SLC2A4/GLUT-4 integrated into the cytoplasmic membrane enhances the flow of glucose into cells and reduces glycemia. In the state of satiety, insulin inhibits the transcription of gluconeogenic genes, especially those mediated by FoxO transcription factors. AKT-dependent phosphorylation of FoxO1 suppresses the expression of glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase 2, mitochondrial (PCK2/PEPCK2), which leads to inhibition of gluconeogenesis. AKT stimulates mechanistic target of rapamycin kinase (mTORC1), which is involved in increasing the activity of *de novo* lipogenesis by activating sterol regulatory element binding protein 1c (SREBP1c). Under the influence of insulin-associated signaling, not only the expression of the *SREBP1c* gene increases, but also its proteolytic cleavage in the liver is activated. After proteolytic cleavage, the mature N-terminal fragment of *SREBP1c* translocates to the cell nucleus, where it binds to the SRE of the promoter of target genes. Increased intracellular glucose induces the activation of the transcription factor ChREBP, which is involved in *de novo* lipogenesis. Phosphorylation of GSK3 kinases converts them into an inactive form, which promotes the activation of glycogen synthase (GS), thereby causing the deposition of glucose as glycogen. Thus, insulin secreted in response to hyperglycemia promotes glycogen synthesis and activation of lipogenesis, but inhibits gluconeogenesis and glycogenolysis (Fig. 1).

Insufficient insulin secretion at low serum glucose concentrations is accompanied by activation of gluconeogenesis and glycogenolysis, contributing to an increase in serum glucose levels [23–29].

2.1.2. Manifestations of hepatic insulin resistance

Hepatic IR is characterized by decreased hepatic glycogen stores and triglyceride secretion from hepatocytes, combined with increased gluconeogenesis. Hepatocyte insulin receptor subunit gene knockout mice exhibit increased expression of gluconeogenic genes, fasting hyperglycemia, and glucose intolerance [15]. The liver plays a central role in glycemic regulation by maintaining the balance between cellular glucose uptake, storage, and release. When serum glucose levels increase in response to insulin, hepatocytes increase the activity of glucose uptake into the cell and its conversion into glycogen and triglycerides, while under conditions of hypoglycemia, the mechanisms of gluconeogenesis and glycogen breakdown are activated in the liver. It should be noted that during prolonged fasting, hepatic gluconeogenesis is the main source of endogenous glucose, which plays a key role in maintaining serum glucose levels. Hepatic steatosis leads to the development of IR, which is accompanied by increased gluconeogenesis activity. In turn, dysregulation of glucose metabolism in the liver contributes to the progression of hepatic steatosis in patients with MAFLD [30–32]. Insulin-resistant liver tissue is characterized by increased gluconeogenesis, glycogen depletion, and decreased triglyceride secretion [16]. Selective hepatic IR is the primary event in the systemic disruption of the insulin-associated signaling pathway, which subsequently leads to the development of peripheral tissue IR [33].

2.1.3. Pool of long non-coding RNAs involved in the development of hepatic insulin resistance

Numerous lncRs, such as H19, MALAT1, MEG3, MIAT, SRA, and others, are involved in the development of hepatic insulin resistance in MAFLD (Table 3) [34–36].

Table 3. Long noncoding RNAs associated with hepatic insulin resistance in MAFLD

LncRs	Action	Literary source
Increased expression in the liver		
Blnc1	Activation of the EDF1/NR1H3/SREBP-1C pathway	[37]
CTD-2517M22.14	Sponging of miR-346; miR-1306-5p; miR-18a-3p; miR-1914-5p, which activates MAPK and induces the development of IR	[38]
CTD-3014M21.1	Sponging of miR-324-5p, miR-2478, which activates MAPK and induces IR development	[38]
CTD-2600O9.2	Sponging of miR-486-3p, which activates MAPK and induces IR development	[38]
EPB41L4A-AS1	Inhibition of expression and increased endocytosis of SLC2A4/GLUT4	[39]
H19	Increasing the activity of gluconeogenesis	[34]
HCG18	Sponging of miR-197-3p, induction of insulin resistance by increasing IL-1β and IL-18 receptor expression	[40]
HOTAIR	Inhibition of SIRT1 signaling pathway	[41]
HOTTIP	Induction of increased WNT7A expression by inhibiting IR	[42]
HOXB-AS3 (homo sapiens (human) HOXB cluster antisense RNA 3; 611 nt URS000075E8D0_9606)	Sponging of PC-5p-36422_6, which activates MAPK and induces IR development, regulates SREBP1 mRNA expression	[38]
LAMA5-AS1 (homo sapiens (human) LAMA5 antisense RNA 1; 838 nt URS000075ED30_9606)	Sponging of miR-18a-3p; miR-516b-5p; miR-763-p3, which activates MAPK and induces the development of IR	[38]
LncARSR	Activation of IRS2 signaling pathway, increasing insulin sensitivity	[43]
MALAT1	Promoting overexpression of IL-1β, IL-6, TNF-α, which induce JNK kinases and PKC, which inhibit insulin signaling	[35]
MIAT	Decreased activity of the PI3K/AKT-associated signaling pathway	[35]
MIR4435-2HG (homo sapiens (human) MIR4435-2 host gene; 3,887 nt URS0000A77756_9606)	Sponging of miR-149-3p_L; miR-1304-3p; miR-452-5p, which activates MAPK and induces IR development	[38]
NONMMUT031874.2	Activation of SOCS3	[44]
RP5-1057I20.5 (homo sapiens (human) novel transcript, antisense to HDAC7; 546 nt URS0000776E03_9606)	Sponging of miR-23b-5p, miR-185-3p, miR-642a-5p, which activates MAPK and induces the development of IR	[38]
Decreased expression in the liver		
B4GALT1-AS1/LncSHGL	Decreased activity of the PI3K/AKT-associated signaling pathway in hepatocytes	[45]
MEG3	Activation of the MEG3-EZH2-SIRT6 axis is associated with suppression of lipid accumulation, inflammation, and insulin resistance	[46]

2.1.3.1. Long non-coding RNAs whose expression levels increase in the event of hepatic insulin resistance

Blnc1. The development of MAH is accompanied by an increase in the expression level of brown fat lncRNA 1 (Blnc1; 759 nt URS0000DBDC4C_9606). It has been shown that the lncR Blnc1 has the ability to directly interact with endothelial differentiation related factor 1 (EDF1), which facilitates the recruitment and coactivation of nuclear receptor subfamily 1 group H member 3/liver X receptor (NR1H3/LXRα), which promotes triglyceride synthesis and causes the development of hepatic IR. In mice with a knockout of the *Blnc1* gene in hepatocytes on a diet enriched with fructose, cholesterol, and trans fats, liver weight and cholesterol and triglyceride content in hepatocytes were lower than in wild-type mice [37].

EPB41L4A-AS1. It was found that the expression of homo sapiens (human) EPB41L4A antisense RNA 1 (EPB41L4A-AS1; 1,194 nt URS000075CCBD_9606) is abnormally increased in liver tissue of patients with T2DM and in skeletal muscle myocytes of individuals with IR. It is believed that lncR EPB41L4A-AS1 suppresses crotonylation of the chromatin site H3K27cr in the promoter region of the glucose transporter SLC2A4/GLUT4, enhances lysine acetylation in the promoter region of the peroxisome proliferator-activated receptor gamma coactivator-1β (PGC-1β) gene, which leads to inhibition of SLC2A4/GLUT4 expression and glucose influx activity into the cell. Also, lncR EPB41L4A-AS1, interacting with lysine acetyltransferase 2A (KAT2A), promotes acetylation of H3K27 and H3K14 sites in the promoter region of the thioredoxin-interacting protein gene, and increases the endocytosis activity of the SLC2A4/GLUT4 transporter and, as a result, reduces glucose transport from the extracellular space into the cell [39].

H19. The long non-coding RNA H19 plays a significant role in regulating the activity of the insulin signaling cascade in hepatocytes, and overexpression of lncR H19, observed

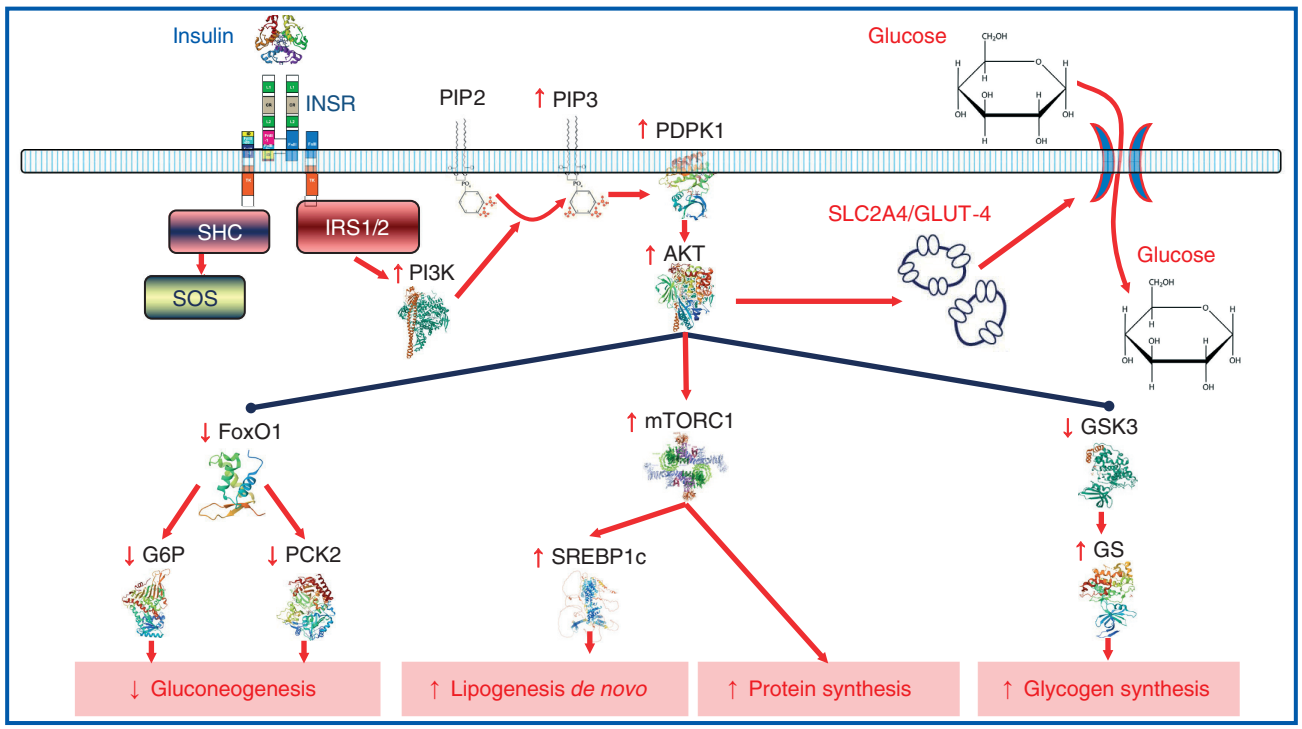

Figure 1. Effect of insulin on glucose and lipid metabolism in hepatocytes

Notes (here and in Fig. 2): red arrows — activation; blue lines — inhibition; molecular models adapted from the Protein Data Bank.

in MAHD, contributes to the development of IR [34]. It has been demonstrated that in patients with type 2 diabetes and in mice with type 2 diabetes induced by a high-fat diet (HFD), there is an increased expression of lncR H19 in the liver, which is due to hypomethylation of CpG islands in the H19 gene promoter and a decrease in folate concentration [47, 48]. Overexpression of lncR H19 in liver tissue increases fasting serum insulin and glucose levels. Long non-coding RNA H19 induces hypomethylation of the hepatocyte nuclear factor 4 alpha (HNF4α) gene promoter, which leads to increased expression of the gene and, as a result, increased expression of the gluconeogenic genes PCK/PEPCK and G6P. The HNF4α factor, directly binding to DNA, regulates the expression of genes involved in the metabolism of bile

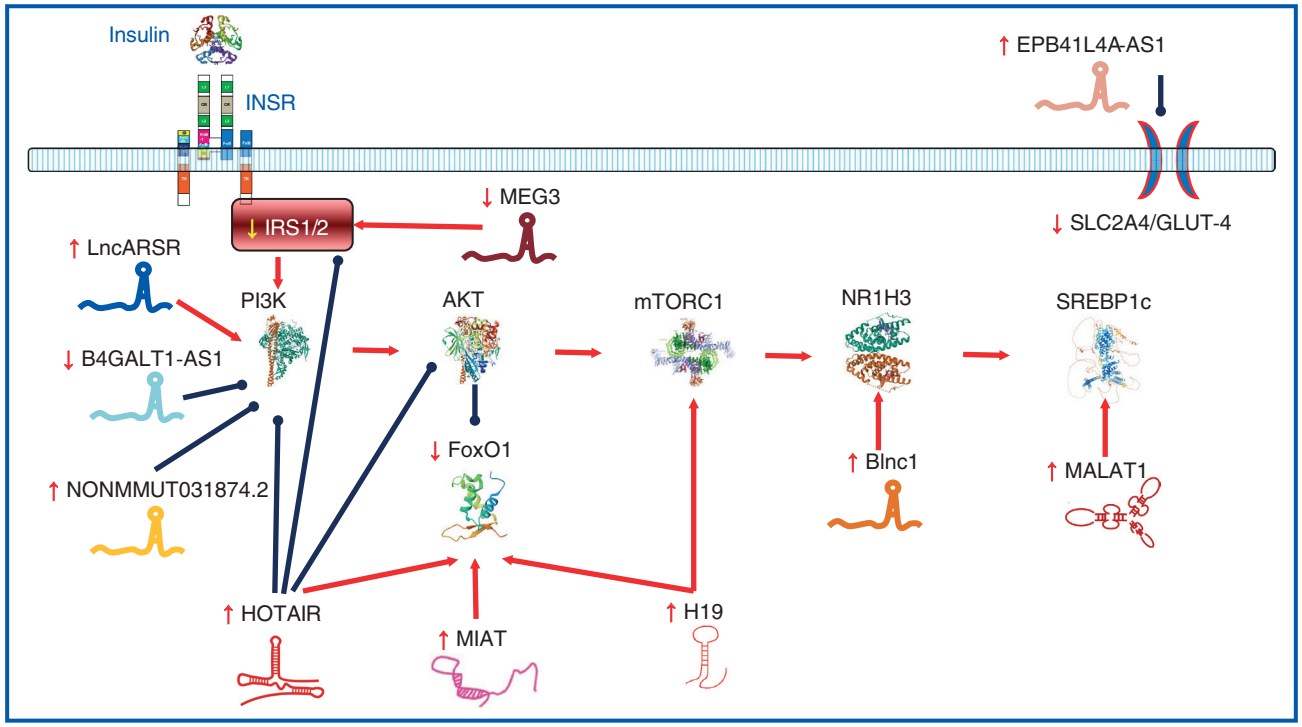

Figure 2. The influence of lncR on the development of hepatic insulin resistance

acids, lipids, and glucose. Mutations in the HNF4α gene induce the development of diabetes in adolescents and adults. It has been shown that the HNF4α factor plays a key role in the proliferation of β-cells of pancreatic islets. The development of IR does not cause β-cell proliferation in mice with a knockout of the Hnf4α gene [49]. Also, overexpression of lncR H19 in Hepa1-6 cells, contributing to the preservation of the FoxO1 factor in the cell nucleus, enhances the expression of PCK1/PEPCK1 and gluconeogenesis [50].

HCG18. The development of IR in patients with MAHCP is accompanied by increased expression of the lncR human leukocyte antigen complex group 18 (HCG18; 6,820 nt URS000075CE1F_9606), which acts as an endogenous sponge for miR-197-3p. Analysis of the luciferase activity of the 3'UTR showed that miR-197-3p directly binds to the IL-1β receptor, which is one of the key molecules of the inflammatory pathways. Also, bioinformatic analysis showed that the target of miR-197 is IL-18. Exogenous expression of miR-197 significantly suppresses the expression of IL-18 at both the mRNA and protein levels in THP-1 cells. It is likely that the lncR HCG18 induces insulin resistance by increasing the expression of the IL-1β receptor and IL-18, which inhibit the reception and transduction of the insulin signal [51, 52].

HOTAIR. Insulin resistance and type 2 diabetes are accompanied by a significant increase in the expression of HOX transcript antisense RNA (HOTAIR). The long non-coding RNA HOTAIR promotes the development of IR, reduces the activity of the PI3K/AKT signaling pathway, enhances the expression of SIRT1 and increases the expression of the factor FoxO1 (forkhead box O1) [53]. Decreased SIRT1 expression leads to: 1) activation of protein tyrosine phosphatase non-receptor type 1 (PTPN1) transcription, which is a negative regulator of the insulin signal transduction cascade; 2) reduction of insulin-induced deacetylation substrate IRS-2; 3) reduction of AKT deacetylation activity, which is required for membrane localization and activation of AKT. HOTAIR-mediated inhibition of SIRT1 mRNA expression activity is believed to play one of the key roles in the pathogenesis of hepatic IR [41, 54–56]. Overexpression of the lncR HOTAIR results in a reduction in the pools of a number of miRs, such as miR-17-5p, miR-20a-5p, miR-214-3p, and miR-222-3p, which target the phosphatase and tensin homolog (PTEN) gene. The reduction in the inhibitory pressure of these miRs leads to the overexpression of the mRNA of the PTEN protein, which has the ability to inhibit the PI3K/AKT signaling pathway and, as a result, to a decrease in the activity of glucose uptake by hepatocytes [56–61]. At the same time, HOTAIR-mediated reduction of FoxO1 activity leads to an increase in gluconeogenesis [62].

HOTTIP. The distal transcript of HOXA distal transcript antisense RNA (HOTTIP) promotes the progression of type 2 diabetes. The lncR HOTTIP has been shown to sequester miR-423-5p, which targets wingless-type MMTV integration site family member 7A (WNT7A). Upregulation of WNT7A expression prevents the development of IR [42]. WNT7A has been shown to inhibit excessive autophagy and inflammation, which contribute to elevated glycemia [63].

LncARSR. In patients with MAJC, increased expression of the lncRNA activated RCC with sunitinib resistance (lncARSR; 1,187 nt URS00026A271B_9606) has been observed [64]. The long non-coding RNA lncARSR binds to yes associated protein 1 (YAP1), inhibits its phosphorylation, and promotes subsequent nuclear translocation of YAP1. YAP1 is a proline-rich phosphoprotein that is a member of the Hippo-associated signaling pathway. Activation of YAP1 translocation results in increased expression of the insulin receptor substrate IRS2. YAP1/TAZ expression has been shown to be positively correlated with IRS2 mRNA expression. Decreased lncARSR expression can lead to a decrease in the IRS2 pool and cause hepatic IR [43, 65]. Thus, increased lncARSR expression in MAJD increases the efficiency of insulin signal perception. However, it should be noted that MAJD is characterized by a significant decrease in IRS2 expression while maintaining adequate IRS1 expression. Maintaining IRS1 expression leads to activation of lipogenesis, and decreased IRS2 expression leads to activation of gluconeogenesis due to increased expression of G6P, PCK2 [66].

MAYA. Long non-coding RNA, lncRNA MIST-1/2 antagonizing for YAP activation (MAYA), the level of which increases with the development of hepatic steatosis, is associated with hepatic IR [67].

MALAT1. In a condition characterized by hyperglycemia and high levels of VFA, overexpression of the three-helical metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is observed. It is likely that hyperglycemia induces a global inhibition of DNMT activity, which leads to hypomethylation of CpG islands in the MALAT1 gene promoter and causes overexpression of the MALAT1 lncR. The MALAT1 transcript indirectly induces the production of pro-inflammatory cytokines IL-1, IL-6, TNF-α, which cause the activation of JNK and PKC, which have the ability to inhibit intracellular insulin signal transduction [11, 35, 68, 69].

MIAT. The homo sapiens (human) myocardial infarction associated transcript (MIAT; 10,078 nt URS00026A259D_9606), or Gomafu transcript, gene is located on chromosome 22q12.1. The evolutionarily conserved MIAT transcript is concentrated exclusively in the nucleus and is not exported to the cytoplasm of the cell [70]. The expression of lncR MIAT is highly sensitive to the influence of various factors, in particular, such as angiotensin II, isoproterenol, hypoxia and various infectious agents. Cardiovascular diseases, including myocardial infarction, myocardial hypertrophy, diabetic, dilated cardiomyopathy, atrial fibrillation, are characterized by the highest level of lncR MIAT concentration in the blood serum [71]. Also, the level of lncR MIAT expression is increased in IR. Overexpression of lncR MIAT in liver tissue leads to basal hyperglycemia even in mice with hypotrophy [72].

The long non-coding RNA MIAT functions as an endogenous sponge for miR-22-3p, miR-29a-3p, miR-29b, miR-29c, miR-139-5p, miR-141, miR-145, miR-150-5p, miR-155-5p, miR-203a, miR-214, miR-302, miR-520d-3p [73].

The decrease in the activity of the miR-29 pool, caused by the sequestering action of lncR MIAT, is accompanied by the activation of PI3K expression and increased activity of gluconeogenesis mechanisms. Thus, in experimental animals with organ-specific knockout of miR-29a, miR-29c, activation of PI3K expression is observed, which leads to

hypoglycemia after exogenous insulin administration [74]. Overexpression of the miR-29 family (miR-29a, miR-29b, miR-29c) in the liver of HFD-induced diabetic and obese mice suppresses the expression of PCK2/PEPCK2, G6P and PGC-1α mRNA [75]. Members of the miR-29 family interact with the transcription factor gene FoxA2, the promoter sequence of which has binding sites for miR-29a and miR-29b. It has been demonstrated that the level of FoxA2 mRNA expression increases together with miR-29 in liver tissues of mice in prediabetic models, and suppression of FoxA2 expression suppresses the expression of miR-29a, miR-29b and miR-29c [76]. Also, a target of miR-29c is lysyl oxidase-like 2 (LOXL2), which catalyzes the oxidative deamination of lysine residues and hydroxylysine in tropocollagen and tropoelastin [77]. The lysyl oxidase LOXL2 is characterized by high levels of expression in the development of hepatic IR. Increased LOXL2 activity is observed in patients with IBD and type 2 diabetes, as well as in experimental animals with IR induced by a high-fructose diet. Increased LOXL2 activity is associated with an increase in the transcriptional activity of the FoxO1 factor and increased gluconeogenesis [78]. MIAT-mediated sequestration of miR-139-5p results in increased expression of the miR-139-5p target, FoxO1, enhancing gluconeogenesis [70]. The reduction in the pool of functionally active miR-150 is accompanied by increased serum concentrations of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, with subsequent activation of JNK kinases, leading to the development of IR [79].

Furthermore, lncR MIAT downregulates anti-inflammatory miRs, which may lead to activation of serine/threonine kinases such as JNK, which inhibits signal transduction through the PI3K/AKT pathway [80].

NONMMUT031874.2. It has been shown that in patients with type 2 diabetes and in mice receiving a HFD, a significant increase in the expression level of mus musculus long non-coding RNA (NONMMUT031874; 22,483 nt URS00009C4056_10090) is noted. The long non-coding RNA NONMMUT031874.2, sequestering miR-7054-5p, promotes an increase in the activity of suppressor of cytokine signaling 3 (SOCS3), which causes the development of IR. SOCS3 protein is thought to mediate hepatic IR; however, the absence of SOCS3 in hepatocytes may induce the production of proinflammatory cytokines, leading to the development of systemic IR. Interestingly, metformin inhibits the expression of NONMMUT031874.2, which increases the sensitivity of cells to insulin. Inhibition of SOCS3 is accompanied by increased activity of the PI3K/AKT signaling pathway, inhibition of gluconeogenesis in the liver, and ultimately, increased sensitivity of hepatocytes to insulin [44, 81].

2.1.3.2. Long non-coding RNAs whose expression levels are reduced during the development of hepatic insulin resistance

B4GALT1-AS1/LncSHGL. Decreased expression of homo sapiens (human) beta-1,4-galactosyltransferase 1 antisense RNA 1 (B4GALT1-AS1) leads to suppression of PI3K expression in hepatocytes, which causes the development of IR [45]. Also, the long non-coding RNA B4GALT1-AS1 can absorb miR-30e and miR-144-3p, the targets of which are the transcription factor SRY-box 9 (SOX9) and Zinc finger E-box binding homeobox 1 (ZEB1), respectively [82]. Metabolic-associated steatohepatitis, which occurs with signs of IR, has been shown to be accompanied by increased expression of SOX9 [83]. In addition, the lncR B4GALT1-AS1 interacts with YAP and human antigen R (HuR) proteins. HuR is a ubiquitously expressed RNA-binding protein that binds and stabilizes AU-rich mRNAs encoding proto-oncogenes, growth factors, and cell cycle regulators. HuR knockout mice on a HFD diet develop IR and obesity with adipocyte hypertrophy in white adipose tissue due to reduced expression of adipose triglyceride lipase (ATGL) [84].

MEG3. The development of metabolic-associated hepatic IR is accompanied by a decrease in the expression level of the maternally expressed gene (MEG3) transcript. Knockout of the Meg3 gene is accompanied by a decrease in the level of phosphorylated AKT in liver and skeletal muscle tissues, but not in white adipose tissue cells in obese mice. Also, in mice with a knockout of the Meg3 gene, a decrease in the level of phosphorylated β-subunits of the insulin receptor of hepatocytes is noted [85]. Overexpression of the lncR MEG3 suppresses the process of lipid accumulation in hepatocytes of mice receiving HFD. The long non-coding RNA MEG3, promoting ubiquitinylation and degradation of EZH2, activates SIRT6, which has hepatoprotective properties [46]. Furthermore, increased expression of MEG3 in HepG2 cells enhances IR by downregulating miR-185-5p, which targets early growth response protein 2 (EGR2). Increased expression of EGR2 mRNA mediated by lncR MEG3 induces JAK2/STAT3/SOCS-1 signaling pathway, leading to decreased efficiency of insulin signal transduction [86].

At the same time, it has been shown that HFD can lead to increased expression of lncR MEG3 in mouse hepatocytes through histone acetylation [87]. Also, lncR MEG3 inactivates miR-302a-3p, which targets CREB-regulated transcriptional coactivator 2 (CRTC2). MEG3-induced inactivation of miR-302a-3p has been shown to increase the expression levels of CRTC2, PGC-1α, and the gluconeogenic genes PCK/PEPCK and G6P in primary hepatocytes [88, 89]. The topical effect of lncR on the insulin-associated signaling pathway leading to the development of hepatic IR is presented in Fig. 2.

Conclusions

Long non-coding RNAs are actively involved in the regulation of various biological processes. Aberrant expression of lncRs may be a key molecular driver of the development of various human pathologies, including metabolic diseases, in particular, obesity, type 2 diabetes, arterial hypertension, dyslipidemia and metabolic-associated fatty liver disease. Selective hepatic insulin resistance is the primary event in the systemic disruption of the insulin-associated signaling pathway, which subsequently leads to the development of IR of peripheral tissues. Numerous lncRs, such as H19, MALAT1, MEG3, MIAT, SRA and others, are involved in the development of hepatic insulin resistance in MAFLD. Long non-coding RNAs, the expression level of which increases in the case of the development of hepatic insulin resistance: Blnc1, EPB41L4A-AS1, H19, HCG18, HOTAIR, HOTTIP, LncARSR, MAYA, MALAT1, MIAT, NONMMUT031874.2. At the same time, long non-coding

RNAs, the expression level of which decreases in the development of hepatic insulin resistance are: B4GALT1-AS1/LncSHGL, MEG3.

It is believed that the development of drugs that regulate the expression of lncR will open new prospects for the prevention and treatment of IR, including in MAFLD [9, 90].

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Епігенетичний вплив довгих некодуючих РНК на розвиток інсулінорезистентності при метаболічно асоційованій жировій хворобі печінки (частина 1)

Резюме. Інсулінорезистентність (ІР) метаболічного генезу є патологічним станом, в основі якого лежить зниження метаболічної відповіді інсулін-чутливих клітин на стимуляцію інсуліном. Вона часто супроводжує метаболічно асоційовану жирову хворобу печінки (МАЖХП) і є патогенетичною основою цукрового діабету (ЦД) 2-го типу. МАЖХП пов'язана з високим ризиком ЦД 2-го типу, її наявність збільшує ймовірність виникнення ЦД 2-го типу протягом наступних п'яти років життя хворого приблизно в два рази. У розвитку ІР безпосередню участь беруть довгі некодуючі РНК, визначення рівня експресії яких може суттєво підвищити ефективність діагностики й прогнозу захворювання. На сьогодні серед припущень, що пояснюють механізми виникнення ІР, домінують ліпоцентрична та глюкоцентрична гіпотези. В основі ліпоцентричної гіпотези лежить уявлення про те, що ІР є наслідком ліпотоксичної дії надлишкового внутрішньоклітинного вмісту вільних жирних кислот та їхніх похідних (діацилгліцерин, цераміди). Глюкоцентрична гіпотеза постулює, що розвиток ІР зумовлений рецидивуючими проявами гіперглікемії, які супроводжуються утворенням кінцевих продуктів глікування. Інсулінорезистентна тканина печінки характеризується підвищенням активності глюконеогенезу, виснаженням глікогенового депо та зниженням секреції тригліцеридів. Стеатоз печінки призводить до розвитку ІР, що асоціюється з посиленням активності глюконеогенезу. Селективна ІР печінки є первинною подією в системному порушенні інсулін-асо-

ційованого сигнального шляху, викликаючи в подальшому ІР периферичних тканин. У розвитку печінкової інсулінорезистентності при МАЖХП беруть участь численні некодуючі РНК, як-от H19, MALAT1, MEG3, MIAT, SRA та інші. Довгі некодуючі РНК, рівень експресії яких підвищується в разі інсулінорезистентності печінки: Blnc1, EPB41L4A-AS1, H19, HCG18, HOTAIR, HOTTIP, LncARSR, MAYA, MALAT1, MIAT, NONMMUT031874.2. У той же час довгі некодуючі РНК, рівень експресії яких знижується при розвитку інсулінорезистентності печінки, представлені B4GALT1-AS1/LncSHGL, MEG3.

Ключові слова: діти; ожиріння; метаболічно асоційована жирова хвороба печінки; довгі некодуючі РНК; літературний огляд