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Epigenetic influence of long non-coding RNAs on the development of insulin resistance in metabolically associated fatty liver disease (part 2)

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Abstract. *Understanding the mechanisms of action of long non-coding RNAs (lncR) and their significance in the development of insulin resistance (IR) in patients with metabolically associated fatty liver disease will allow modifying and increasing the effectiveness of methods for diagnosing and treating metabolic disorders. Adipose tissue is insulin-dependent and plays a significant role in glucose metabolism. The stimulation of the insulin receptor (INSR) of white adipose tissue adipocytes activates the transport of glucose, free fatty acids (FFA), and glycerol into the cell, stimulates lipogenesis de novo and adipogenesis, and also inhibits the activity of lipolysis mechanisms. The leading triggers that cause the development of IR in adipocytes are lipotoxicity and low-grade inflammation of adipose tissue. In particular, in the adipose tissue of patients with metabolically associated steatohepatitis, overexpression of TNF-α and IL-6 mRNA is observed. Inflammatory mediators such as TNF-α and IL-1β inhibit INSR, and TNF-α induces phosphorylation of the serine residue of the IRS-1 molecule, disrupting signal transmission to phosphatidylinositol-4,5-bisphosphate-3-kinase. Obesity activates mitochondrial FFA-stimulated adenine nucleotide translocase 2, which leads to hypoxia of adipocytes and stimulates hypoxia-induced factor-1α. Activation of the latter causes inhibition of glucose uptake by adipocytes, enhances the process of glycolysis by affecting numerous enzymes involved in glucose metabolism, also inducing dysfunction and inflammation of adipose tissue. The authors emphasize that insulin-resistant adipose tissue is characterized by a low level of glucose influx into adipocytes, a high level of FFA release after insulin stimulation, which generally leads to hyperglycemia and hyperlipidemia. The following lncRs are involved in the pathogenesis of IR of white adipose tissue: ADIPINT, ASMER, Blnc1, DIO3OS, GAS5, Gm15290, H19, LncOb, MEG3, SRA. Long non-coding RNAs involved in the pathogenesis of IR of muscle tissue are IRLnc, H19, NONMMUT044897.*
Keywords: *obesity; insulin resistance; metabolically associated fatty liver disease; long non-coding RNAs*

The role of long non-coding RNAs in the development of insulin resistance in adipose tissue in metabolically associated fatty liver disease

Features of insulin signal transduction in adipocytes

Adipose tissue is an insulin-dependent tissue and plays a significant role in glucose metabolism. Stimulation of the insulin receptor (INSR) of white adipose tissue adipocytes activates the transport of glucose, free fatty acids (FFA), and glycerol into the cell, stimulates *de novo* lipogenesis and adipogenesis, and inhibits the activity of lipolysis mechanisms [1].

The insulin-associated signaling pathway in adipocytes, unlike the hepatocyte pathway, is characterized by an almost equal participation of the substrates IRS1 and IRS2 in signal transduction to the serine/threonine kinase AKT. AKT activation leads to activation of the transcription factor SREBP1c and γ-receptors activated by peroxisome proliferator-activated receptor gamma (PPARγ), leading to the expression of lipogenic genes and increased adipogenesis [2–5].

Inhibition of lipolysis in adipocytes is mediated by AKT's effects on phosphodiesterase 3B (PDE3B), inorganic pyrophosphatase 1 (PP1), and protein phosphatase 2 phosphatase activator (PTPA).

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Phosphodiesterase PDE3B plays a key role in inhibiting lipolysis. Activated AKT phosphorylates PDE3B, which leads to accelerated degradation of the prolipolytic second messenger, cyclic AMP, which has the ability to induce protein kinase A (PKA), which in turn phosphorylates two key lipogenic enzymes: adipose tissue triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL).

In the first stage of lipolysis, ATGL catalyzes the hydrolysis of triglycerides to diacylglycerol (DAG) and fatty acids in lipid droplets. HSL subsequently hydrolyzes DAG to monoacylglycerol and fatty acids. In the final stage of lipolysis, monoacylglycerol lipase (MGL) hydrolyzes monoacylglycerol to glycerol and fatty acids. Protein phosphatase 2A is an activator of HSL; and PP1 acts as the main perilipin phosphatase in adipocytes (Fig. 1) [6–8].

Manifestations of insulin resistance in adipose tissue

The leading triggers that cause the development of insulin resistance (IR) in adipocytes are lipotoxicity and low-level inflammation in adipose tissue. In particular, overexpression of TNF-α and IL-6 mRNA is observed in adipose tissue of patients with IBS. It has been demonstrated that inflammatory mediators such as TNF-α and IL-1β inhibit INSR, and the key pro-inflammatory cytokine TNF-α induces phosphorylation of the serine residue of the IRS-1 molecule, thereby disrupting signal transduction to phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) [9, 10]. JNK1-dependent IL-6 secretion in adipose tissue has been shown to induce increased expression of suppressor of cytokine signaling 3 (SOCS3), which causes inhibition of insulin signal transduction [11].

Also, obesity and HFD can activate mitochondrial fatty acid-stimulated adenine nucleotide translocase 2 (ANT2), which leads to adipocyte hypoxia and activates hypoxia-inducible factor-1α (HIF-1α). Activation of HIF-1α causes inhibition of glucose uptake by adipocytes, enhances glycolysis by affecting numerous enzymes involved in glucose metabolism. Hypoxia and HIF-1α also induce adipose tissue dysfunction and inflammation [12].

It should be noted that insulin-stimulated protein synthesis is not impaired in insulin-resistant adipocytes [13]. Insulin-resistant adipose tissue is characterized by low glucose influx into adipocytes and high levels of FFA release after insulin stimulation, which generally leads to hyperglycemia and hyperlipidemia [4].

Pool of long non-coding RNAs involved in the development of insulin resistance in adipose tissue

In white adipose tissue adipocytes from HFD-induced obese mice, 234 long non-coding RNAs (lncRs) are differentially expressed, of which 87 lncRs are upregulated and 147 lncRs are downregulated compared to adipocytes from normal weight mice [14]. LncRs have been shown to play a significant role in the development of insulin resistance (IR) in white adipose tissue adipocytes in patients with MAFLD (Table 1).

Long non-coding RNAs, the rate of expression of which advances with the development of insulin resistance of adipose tissue

ADIPINT. It has been demonstrated that in obesity, human white adipose tissue increases the expression of an adipocyte-specific lncR that interacts with homo sapiens (human) adipocyte associated pyruvate carboxylase interacting lncRNA — ADIPINT (CATG00000106343.1; 1,638

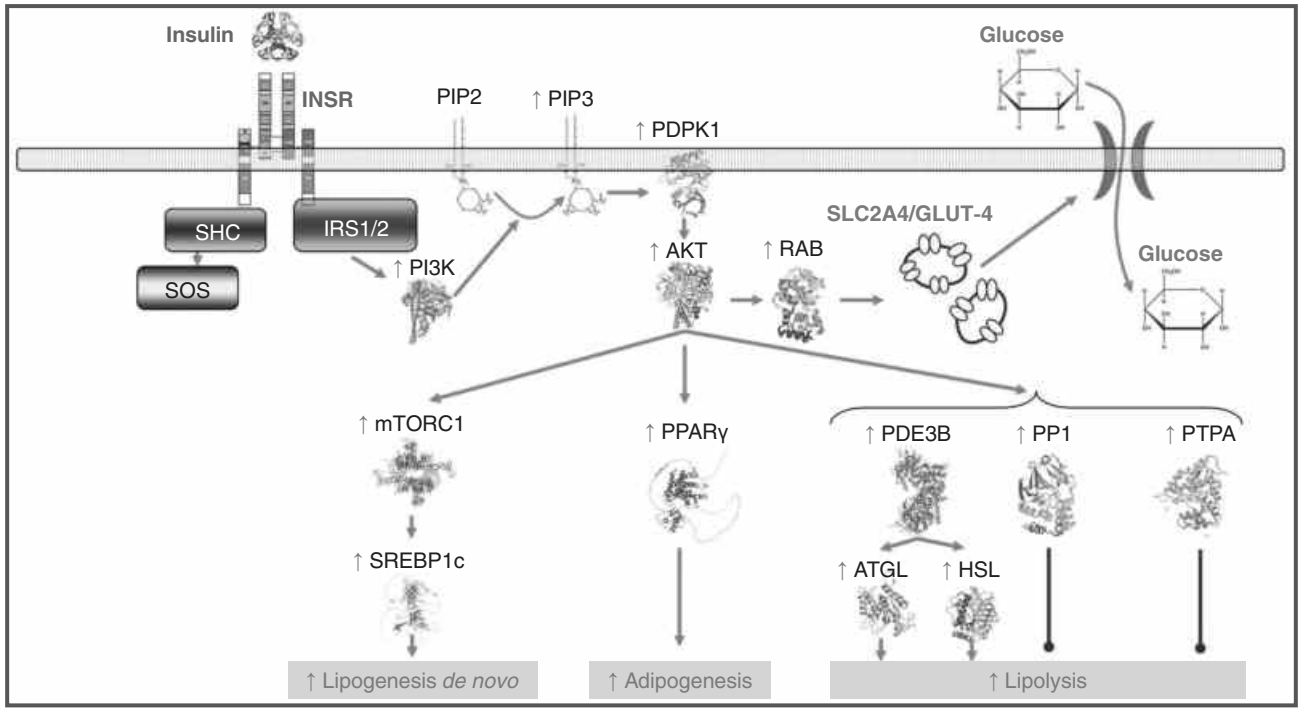

Figure 1. Effect of insulin on glucose and lipid metabolism in adipocytes

Notes: here and in Fig. 2–4: red arrows — activation; blue lines — inhibition. Molecular models adapted from the Protein Data Bank.

Table 1. Long non-coding RNAs associated with adipose tissue IR in MAFLD

LncRs	Action	Literary reference
Increased level of expression in the liver		
ADIPINT	Induces enzymatic activity of pyruvate carboxylase, which stimulates triglyceride synthesis, promotes an increase in lipid droplet size, and induces IR of adipocytes	[15, 16]
ASMER-2	Reduction in ASMER-1 expression inhibits lipolysis and adiponectin release in adipocytes	[17]
Blnc1	Suppresses adipose tissue inflammation through multiple targets, including EBF2, hnRNPU, Zbtb7b, hnRNPA1, and PGC-1β	[15]
Gm15290	Sponges miR-27b, associated with PPARγ-induced stored fat in white adipose tissue	[18]
LincADAL	Promotes lipogenesis and differentiation of adipocytes	[19]
LncASIR	Sprays lipolysis	[20]
LncOb	Couples leptin transcription	[21]
MEG3	Activates FASN and PPARγ in white adipose tissue	[22]
SRA	Activates PPARγ in white adipose tissue	[15]
Decreased level of expression in the liver		
ASMER-1	Decreased ASMER-1 expression suppresses lipolysis and suppresses adiponectin in adipocytes	[16]
DIO3OS	Activates adipogenesis in brown adipose tissue and reduces energy expenditure	[15]
GAS5	Strengthens the transmission of insulin signals	[23]
H19	Overexpression H19 leads to a decrease in body weight, fat weight and an increase in meat weight in mice on aphids HFD	[22]
TUG1	Regulation of the miR-204/SIRT1 axis	[24]
uc001kfc.1	Regulates PTEN expression	[25]

nt URS00025E353D). Moreover, the expression level of lncR ADIPINT is associated with fat cell size, adipose tissue IR and pyruvate carboxylase (PC) activity. The long non-coding RNA ADIPINT physically interacts with PC and promotes its catalytic activity, which enhances lipogenesis *de novo* in adipocytes. The lncR ADIPINT has been shown to primarily function as a mitochondrial gatekeeper for PC, allowing this enzyme to exert multiple effects on glucose metabolism in adipocytes. Knockout of the *ADIPINT* gene has been shown to selectively reduce PC mRNA levels in adipocyte mitochondria; alter the mitochondrial PC interactome; and reduce lipid content in adipocyte fat droplets. ADIPINT-mediated increases in PC activity are thought to induce lipogenesis and gluconeogenesis [16].

ASMER. In white adipose tissue of obese patients, there is an increase in the expression level of adipocyte-specific lncR 1 and 2 (homo sapiens (human) adipocyte associated metabolic related lncRNA 1 and 2 — ASMER-1/ENSG00000235609.4; 8,345 nt URS0000BC4618_9606; ASMER-2/CATG00000111229.1). Long non-coding RNAs ASMER-1 and ASMER-2 regulate the expression of genes of key adipogenic transcription factors, in particular PPARγ. With the development of IR, the expression level of lncR ASMER-1 decreases, and lncR ASMER-2 increases. It has been demonstrated that both ASMER-1 and ASMER-2 have the ability to inhibit lipolysis and adiponectin synthesis in adipocytes of white adipose tissue [17].

Blnc1. The brown adipose tissue long non-coding RNA Blnc1, which is a driver of thermogenesis in brown and beige adipocytes, has been associated with the development of IR [15]. Mice with adipocyte-specific knockout of the *Blnc1* gene (AKO) exhibit hyperglycemia, hyperinsulinemia, and more severe hepatic steatosis after HFD feeding. Also, in these mice, a significant decrease in mRNA expression of uncoupling protein 1 (UCP1), genes involved in *de novo* lipogenesis (*Srebp1c*, *Fasn*, and *Scd*), lipid accumulation (*Dgat2*), and increased expression of several macrophage markers, including galectin 3, carboxypeptidase A3, and TNF-α-induced protein 2, was observed in white adipose tissue adipocytes. In contrast, transgenic mice overexpressing lncR Blnc1 have low serum insulin concentrations, high tissue sensitivity to insulin action, and minimal hepatic steatosis after a course of HFD. It is believed that lncR Blnc1 in white adipose tissue has a protective effect that protects adipocytes from excessive fat accumulation and adipose tissue from the development of inflammation and IR, due to interaction with a partner protein — zinc finger and BTB domain containing 7B (ZBTB7B) [26, 27]. The ZBTB7B protein directly activates the expression of the IRS-1 substrate. ZBTB7B deficiency disrupts the insulin-induced Akt-mTOR-SREBP signaling pathway and lipid biosynthesis [28]. The ZBTB7B protein determines the differentiation of helper T cells. Loss of ZBTB7B expression or disruption of its function inhibits the development of $CD4^+$ T cells [29]. The ZBTB7B protein is also a key factor in the development of brown fat and cold-induced beige fat, as well as the activation of thermogenic gene expression in adipocytes [26].

Gm15290. The long non-coding RNA Gm15290 (mus musculus predicted gene 15290 — Gm15290; 665 nt URS0000CCE0EB_10090) is characterized by a particularly high level of expression in the white adipose tissue of experimental obese mice. It has been demonstrated that lncR Gm15290 activates the expression of key adipogenic genes, such as *PPARG,* the early adipogenic marker gene *C/EBPa*,

and the late adipogenic marker gene fatty acid binding protein 4 (FABP4) [18, 30, 31]. It has been demonstrated that lncR Gm15290 induces miR-27b, which targets INSR and PPARG subunit genes. Overexpression of lncR Gm15290 leads to sequestration of miR-27b, which leads to an increase in the number of both INSR and PPARγ molecules. Silencing of lncR Gm15290 induces a decrease in the rate of body weight gain and the mass of subcutaneous and visceral white adipose tissue in mice fed a HFD. Activation of PPARγ leads to excessive fat deposition in adipocytes and the development of IR. Insufficient increase in lncR Gm15290 expression levels may lead to competition for miR-27b interaction with its target mRNAs. Preferential binding of miR-27b to INSR mRNA leads to the development of IR in combination with excessive lipid accumulation [18, 31].

LincADAL. Long non-coding RNA for adipogenesis and lipogenesis (homo sapiens (human) lincRNA adipogenesis and lipogenesis associated — lincADAL; 523 mt URS0000D780CF_9606), is highly expressed in white adipose tissue and promotes increased expression of SREBP1c, FASN genes, as well as preadipocyte differentiation. The lncR lincADAL exerts its effects on lipogenesis and preadipocyte differentiation through interactions with heterogeneous nuclear ribonucleoprotein U (hnRNPU), insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), and PPARα [18]. The IGF2BP2 protein upregulates the expression of fatty acid elongase 6 (ELOVL6), which catalyzes the elongation of C16 to C18 fatty acids, contributing to the development of MAFLD [32]. *Igf2bp2*$^{(-/-)}$ knockout mice are resistant to the development of HFD-induced AD, insulin resistance, and obesity [33, 34]. It has been demonstrated that lincADAL gene knockout is accompanied by increased PPARα expression in human adipocytes, and lincADAL overexpression is likely to be accompanied by suppression of PPARα receptor mRNA expression activity [19]. Thus, excessive lincADAL generation through its effect on IGF2BP2 and PPARα mRNA expression contributes to the development of IR.

LncASIR. Mice fed a HFD have been shown to have high levels of adipose-specific insulin responsive lncRNA (lncASIR) in white adipose tissue. The lncR LncASIR is thought to be an integral component of the insulin-associated signaling pathway in adipocytes. Thus, silencing lncASIR in cultured primary adipocytes is accompanied by suppression of the expression of diacylglycerol O-acyltransferase (DGAT2), ATP citrate lyase (ACY), thyroid hormone responsive protein (THRSP), acyl-CoA synthetase short-chain family member 2 (ACSS2), 1-acylglycerol-3-phosphate O-acyltransferase 3 (AGPAT3), and aldehyde dehydrogenase 3 family member B2 (ALDH3B2), which are associated with lipolysis [20].

LncOb. In mice on a HFD background, the representation of lncR 1 associated with osteoblastogenesis (mus musculus (mouse) lncRNA osteoblastogenesis associated 1; 618 nt URS00007703E3_10090), which is expressed exclusively in adipocytes of white adipose tissue, is significantly increased. The human *lncOb* gene is located on chromosome 7,21 kb upstream of the leptin (*LEP*) gene [21]. LncOb knockout mice exhibit hyperphagia and faster weight gain, combined with lower leptin expression in primary adipocytes and serum leptin concentrations on a HFD compared to wild-type mice [21, 35, 36]. Studies on experimental animals have shown that leptin deficiency leads to the development of IR in mice regardless of changes in body weight [35, 37, 38]. Obese children with the CC genotype of SNV rs10487505 of the *lncOb* gene, associated with low leptin expression, develop IR. The degree of obesity in children homozygous for the C allele is inversely proportional to the level of leptin in the blood serum and directly proportional to the level of insulin resistance [39]. At the same time, it has been demonstrated that the severity of MAFLD is not associated with either the level of leptin concentration or the SNV rs10487505 genotype of the *lncOb* gene [40].

MEG3. In patients with obesity and IR, increased expression of lncR MEG3 in subcutaneous white adipose tissue is observed. The activity of lncR MEG3 expression correlates with the degree of IR and the level of FASN and PPARγ mRNA concentrations in subcutaneous white adipose tissue adipocytes [22]. Increased expression of lncR MEG3 in vascular endothelial cells isolated from white adipose tissue was also noted, compared with endothelial cells of skeletal muscle or liver vessels of obese mice [41].

SRA. Homo sapiens (human) steroid receptor RNA activator (SRA) is a lncR that has the ability to coordinate the functions of various transcription factors and can act as a scaffold for the assembly of corepressor protein complexes. The long non-coding RNA SRA activates several receptors, such as nuclear receptors for retinoic acid, vitamin D, androgens, estrogens, progesterone, glucocorticoids, and thyroid hormones [42]. Insulin resistance in white adipose tissue is not accompanied by changes in SRA expression in adipocytes, unlike liver and muscle tissues, whose IR is associated with increased SRA expression. At the same time, SRA expression in adipose tissue in patients with type 2 diabetes (T2DM) is inversely proportional to HbA1c values. *Sra1* knockout (SRAKO) mice are characterized by a high degree of insulin sensitivity and resistance to the development of HFD-induced obesity. The increased insulin sensitivity in SRAKO mice is due to increased AKT phosphorylation activity in liver cells, white adipose tissue and calf muscles. SRAKO mice also have lower fasting serum insulin levels than wild-type mice [43–45]. It has been demonstrated that lncR SRA stimulates insulin-induced phosphorylation of both AKT kinase and FoxO1 factor. Overexpression of lncR SRA in white adipose tissue activates PPARγ and promotes differentiation of ST2 adipocyte precursor cells [15, 42].

Long non-coding RNAs whose expression level decreases with the development of insulin resistance in adipose tissue

DIO3OS. The expression of antisense RNA Dio3 (homo sapiens (human) DIO3 opposite strand upstream RNA — DIO3OS; 3,454 nt URS000075DF04_9606), whose gene is localized at the distal end of the imprinted cluster GTL2/DIO3 in region 32.31 of the long arm of chromosome 14, is inhibited in white adipose tissue in female fetuses and newborns born to obese mothers [15, 46]. Inactivation of lncR DIO3OS leads to increased expression of the iodothyronine deiodinase 3 (*Dio3*) gene, which causes a deficiency in the conversion of thyroxine to triiodothyronine and inhibition of the PRDM16/PGC-1a complex, which leads to suppression of brown adipocyte differentiation activity. Conversely, overexpression of lncR DIO3OS activates thermogenesis, adipoge-

nesis of brown adipose tissue, and prevents the development of obesity and metabolic disorders [47]. Triiodothyronine deficiency has been shown to be associated with the development of IR [48, 49]. Thus, decreased expression of the lncR DIO3OS in adipose tissue is accompanied by activation of Dio3, which leads to reduced triiodothyronine formation [50], and triiodothyronine deficiency induces adipose tissue IR.

GAS5. It was found that the expression level of lncR GAS5 in subcutaneous white adipose tissue in patients with type 2 diabetes is significantly lower than in healthy people. The long non-coding RNA GAS5 directly binds to the promoter of INSR subunits and, acting as a transcription activator, stimulates their expression, enhancing insulin signal transmission. According to experimental data, the expression of INSR subunit genes is dramatically reduced upon depletion of lncR GAS5. Thus, an appropriate level of GAS5 transcript concentration is required for normal glucose homeostasis, and insufficient expression of lncR GAS5 leads to the development of IR [23].

H19. According to the results of the study by Javad Daneshmoghadam and colleagues [22], obese women have a reduced level of lncR H19 expression in subcutaneous white adipose tissue compared to women with normal body weight. Moreover, the level of H19 transcript concentration is inversely related to the level of FASN mRNA expression and HOMA-IR values [22]. It has been shown that lncR H19 interacts with polypyrimidine tract binding protein 1 (PTBP1) and stabilizes the mRNA of SERBP1c, a key factor in lipogenesis [51]. At the same time, it has been shown that the suppression of lncR H19 expression is associated with the induction of adipogenesis, as evidenced by the increased activity of PPARγ receptors, C/EBPα proteins, and FABP4 [52].

TUG1. It has been shown that in the white adipose tissue of mice fed a HFD, there is a significant decrease in the concentration of gene 1 transcripts, which is associated with an increased level of taurine expression. Overexpression of lncR TUG1 is accompanied by a significant decrease in body weight, hypoglycemia, inhibition of fat accumulation mechanisms and the activity of the inflammatory reaction in the liver tissue. Long non-coding RNA TUG1, sequestering miR-204, promotes an increase in the expression of the SIRT1 protein, the SLC2A4/GLUT4 transporter, the PPARγ receptor and AKT phosphorylation. A decrease in the level of TUG1 transcripts leads to an increase in the pool of functionally active miR-204, which, interacting with the listed molecular targets, induce lipid accumulation in adipocytes and the development of IR of adipose tissue [24]. The impact of lncR on the insulin-associated signaling pathway leading to the development of adipose tissue IR is presented in Fig. 2.

The role of long non-coding RNAs in the development of insulin resistance in muscle tissue in MAFLD

Features of insulin signal transduction in skeletal muscle myocytes

Skeletal muscle myocytes under physiological conditions respond to the stimulating effect of insulin by activating glycogen synthesis from glucose absorbed from the peripheral blood. Insulin-stimulated glucose consumption is mainly carried out by skeletal muscle cells. In skeletal muscle myocytes, the substrate IRS1 is mainly used for insulin signal transduction, while IRS2 is not a necessary component for insulin-mediated stimulation of glucose transport into the cell. The IRS2 substrate in myocytes is primarily involved in insulin control of lipid metabolism. In skeletal muscle myocytes, AKT activation promotes cellular glucose uptake by inducing the translocation of storage vesicles containing solute carrier family 2 member 4 (SLC2A4/GLUT4) to the plasma membrane. GLUT4 storage vesicle translocation is mediated by induction of the GTP-bound form of Ras-bound substrate 1 of botulinum toxin C3 (Rac family small GTPase 1 — RAC1) and inactivation of the GTPase-activating protein (TBC1 domain family member 4 — TBC1D4). The absence of GLUT4-vesicle-storage translocation in response to insulin stimulation indicates an early stage of IR. In myocytes, glucose undergoes glycolysis, but the majority, approximately 75 %, is used for glycogen synthesis.

Activated AKT kinase stimulates glycogen synthesis mechanisms. On the one hand, it inhibits glycogen synthase kinase 3 (GSK3), which leads to the activation of glycogen synthase 1 (GYS1), and on the other hand, it dephosphorylates phosphorylase kinase (PHK), which reduces the inhibitory effect of glycogen phosphorylase (GP) (Fig. 3) [53, 54].

Manifestations of insulin resistance in muscle tissue

It is known that human skeletal muscle myocytes utilize about 80 % of postprandial glucose, and therefore IR in skeletal muscle myocytes makes a key contribution to the development of MAFLD and T2DM. The constant action of insulin in high concentrations induces phosphorylation of the serine or threonine residue of the IRS1 substrate, which inhibits the functional activity of IRS1 and the mechanisms of translocation of GLUT4 vesicles to the plasma membrane of the cell [55]. Selective IR in muscle tissue, mediated by deletion of the *Irtk* or *Glut4* genes in skeletal muscle myocytes of experimental animals, is accompanied by the development of hepatic steatosis [5]. It has been shown that hepatic steatosis is more associated with skeletal muscle IR than with hepatic IR in patients with MAFLD [11]. Insulin-resistant muscle tissue is characterized by low glucose uptake by cells after insulin stimulation and impaired fatty acid β-oxidation [55].

Pool of long non-coding RNAs involved in the development of muscle insulin resistance

The lncR transcriptome profile of insulin-resistant skeletal muscle myocytes is significantly different from that of myocytes with preserved insulin sensitivity [56]. Long non-coding RNAs are actively involved in the pathogenesis of IR of skeletal muscle myocytes in patients with MAFLD (Table 2).

Long non-coding RNAs whose expression levels are increased in the case of the development of skeletal muscle insulin resistance

IRLnc. Increased expression of long non-coding RNA associated with intramuscular fat related lincRNA (IRLnc) is associated with the development of IR in skeletal muscle myocytes [59]. It has been demonstrated that lncR IRLnc

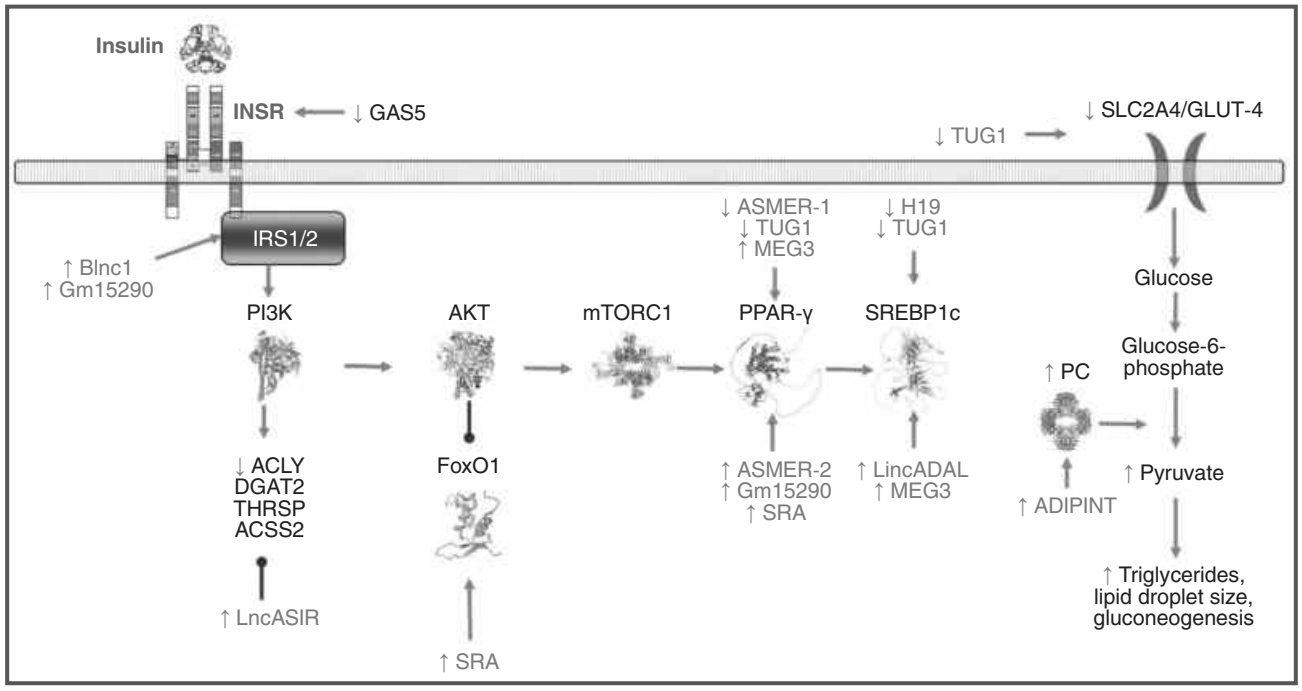

Figure 2. The influence of lncR on the development of insulin resistance in adipose tissue

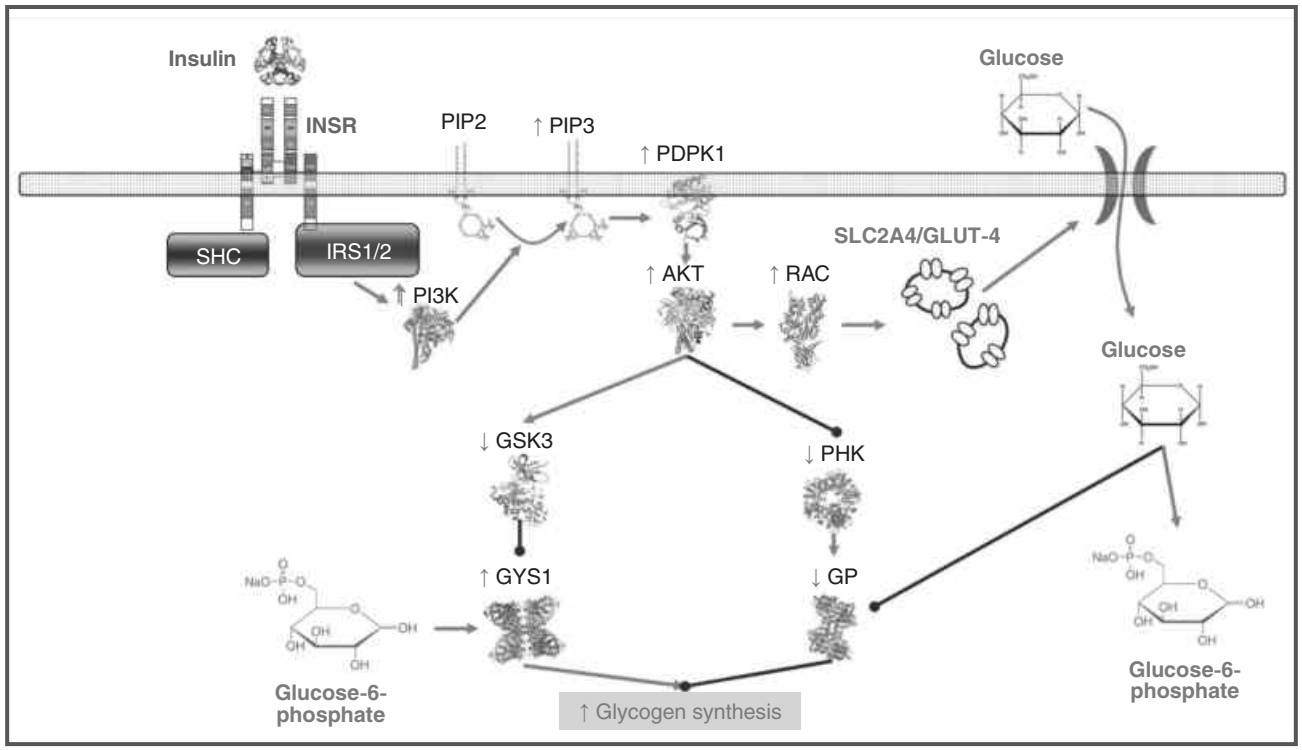

Figure 3. Effect of insulin on glucose metabolism in skeletal muscle myocytes

Table 2. Long non-coding RNAs associated with skeletal muscle insulin resistance in MAFLD

LncRs	Action	Literary reference
Increased level of expression in the liver		
IRLnc	Promotes NR4A3 expression, inhibiting catecholamine catabolism	[57]
NONMMUT044897	Sequesters miR-7051-5p, which inhibits SOCS1, which promotes IR development	[56]
Decreased level of expression in the liver		
H19	Insufficient miR-Let7 silencing leads to DUSP29 inhibition	[58]

directly binds to the mRNA of nuclear receptor subfamily 4 group A member 3 (NR4A3/NOR-1). Silencing lncR IRLnc leads to a decrease in NR4A3 mRNA expression [57]. The NR4A3 protein is a positive regulator of insulin sensitivity. Transcriptional activity of the nuclear receptor NR4A3 enhances glucose transport activity by increasing GLUT4 translocation in both basal and insulin-stimulated L6 cells [60]. It has been demonstrated that overexpression of the NR4A3 gene in 3T3-L1 adipocytes promotes increased insulin-stimulated glucose uptake [61]. At the same time, a decrease in *NR4A3* gene expression levels is observed in insulin-resistant skeletal muscle and adipose tissue of experimental animals [62]. On the other hand, Ligang Wang et al. [57] showed that the lncR IRLnc directly promotes the expression of NR4A3, which inhibits catecholamine catabolism. Overexpression of NR4A3/NOR-1 is accompanied by an increase in catecholamine concentrations, which leads to a decrease in tissue sensitivity to insulin action, including insufficient SLC2A4/GLUT4 translocation activity [60, 63, 64]. Stimulation of β-adrenergic receptors reduces glucose uptake by increasing glucose-6-phosphate concentrations, thereby inhibiting hexokinase, but does not inhibit insulin-stimulated glucose transport in skeletal muscle [65]. It should be noted that lncR IRLnc promotes fat deposition in skeletal muscle fibers, which induces the development of muscle IR [60].

NONMMUT044897. The development of skeletal muscle IR involves lncR NONMMUT044897 (mus musculus long non-coding RNA NONMMUT044897.2; 4,233 te URS-00009B3E3A_10090). It has been shown that IR is accompanied by a significant increase in the expression level of lncR NONMMUT044897, which has the ability to interact with miR-7051-5p. A decrease in the number of functionally active miR-7051-5p leads to an increase in the expression of the *SOCS1* gene, which suppresses the activity of INSR [56, 66, 67].

Long non-coding RNAs whose expression levels are reduced during the development of skeletal muscle insulin resistance

H19. The development of skeletal muscle IR is accompanied by a decrease in the expression level of lncR H19 in myocytes, which contributes to the inhibition of cell sensitivity to insulin. Thus, hyperinsulinemia induces the activation of KH-type splicing regulatory protein (KHSRP), which interacts with primiR Let7 and promotes its maturation to the mature form of miR-Let7, which is a target for lncR H19 [58, 68]. Decreased H19 expression leads to an increase in the pool of functionally active miR-Let7, which leads to the suppression of the activity of dual specificity phosphatase 29 (DUSP29), the mRNA of which is a target of miR-Let7. Decreased DUSP29 levels inhibit protein kinase AMP-activated (PRKA) and the coactivator PGC-1α, which suppress the activity of glucose translocation mechanisms into the cell, activate gluconeogenesis, lipogenesis and inhibit mitochondrial biogenesis, respectively [69, 70]. Also, low levels of the coactivator PGC-1α in hepatocytes lead to impaired expression of the *IRS1* and *IRS2* genes, contributing to the development of liver IR [71]. It should be noted that a decrease in the level of lncR H19 expression in skeletal muscle myocytes contributes to the development of sarcopenia. Knockout of the H19 gene in myoblast cells is accompanied by a decrease in the activity of myocyte differentiation. A decrease in the activity of lncR H19 expression in C2C12 mouse myoblast cells is accompanied by a decrease in the generation of miR-675-3p and miR-675-5p, since they are encoded in exon 1 of the H19 gene. Given that miR-675-3p and miR-675-5p directly inhibit the anti-differentiation transcription factors Smad, a low level of their representation leads to the inhibition of myocyte differentiation and the development of sarcopenia [72, 73].

The effect of lncR on the insulin-associated signaling pathway leading to the development of muscle IR is presented in Fig. 4.

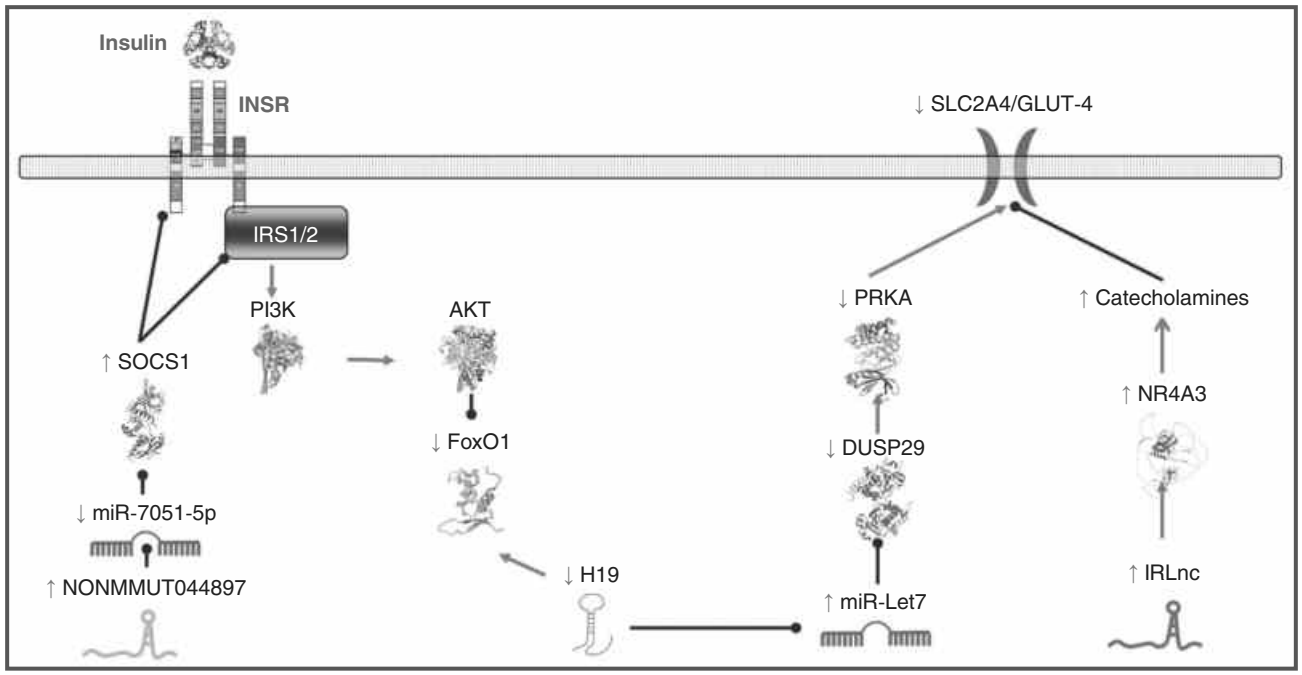

Figure 4. The influence of lncR on the development of insulin resistance in muscle tissue

Conclusions

Thus, IR is a natural consequence of the progression of hepatic steatosis and one of the main pathogenetic factors in the development of various metabolic disorders, which significantly reduce the quality and duration of life of a patient with MAFLD. In the development of IR of the liver, adipose and muscle tissue in patients with MAFLD, lncRs play one of the most important roles, influencing both intracellular insulin-associated signaling pathways and the development of mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation. It has been demonstrated that lncRs such as B4GALT1-AS1, Blnc1, EPB-41L4A-AS1, H19, HCG18, HOTAIR, HOTTIP, HOXB-AS3, LncARSR, MALAT1, MEG3, MIAT are involved in the pathogenesis of hepatic IR; in the pathogenesis of IR of white adipose tissue — ADIPINT, ASMER, Blnc1, DIO3OS, GAS5, Gm15290, H19, LncOb, MEG3, SRA and others, in the pathogenesis of IR of muscle tissue — IRLnc, H19, NONMMUT044897. Understanding the mechanisms of action of lncR and their significance in the development of IR in patients with MAFLD will allow modifying and increasing the effectiveness of methods for diagnosing and treating both IR and other metabolic disorders.

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Епігенетичний вплив довгих некодуючих РНК на розвиток інсулінорезистентності при метаболічно асоційованій жировій хворобі печінки (частина 2)

Резюме. Розуміння механізмів дії довгих некодуючих РНК (long non-coding RNAs — lncR) та їхнього значення в розвитку інсулінорезистентності (ІР) у пацієнтів із метаболічно асоційованою жировою хворобою печінки дозволить модифікувати й підвищити ефективність методів діагностики і лікування метаболічних порушень. Жирова тканина є інсулінозалежною та відіграє істотну роль у метаболізмі глюкози. Збудження інсулінового рецептора (insulin receptor — INSR) адипоцитів білої жирової тканини активує транспортування глюкози, вільних жирних кислот (ВЖК), гліцерину в клітину, стимулює ліпогенез *de novo* й адипогенез, а також пригнічує активність механізмів ліполізу. Провідними тригерами, що викликають розвиток ІР адипоцитів, є ліпотоксичність і неспецифічне запалення жирової тканини. Зокрема, у жировій тканині хворих із метаболічно асоційованим стеатогепатитом спостерігається надекспресія мРНК TNF-α і IL-6. Медіатори запалення, як-от TNF-α та IL-1β, інгібують INSR, а TNF-α індукує фосфорилювання серинового залишку молекули IRS-1, порушуючи передачу сигналу на фосфатидилінозитол-4,5-бісфосфат-3-кіназу. Ожиріння, у свою чергу, активує мітохондріальну ВЖК-стимульовану аденіннуклеотидну транслоказу-2, що призводить до гіпоксії адипоцитів і стимулює індукований гіпоксією фактор 1α. Активація останнього викликає пригнічення поглинання глюкози адипоцитами, посилює процес гліколізу за рахунок впливу на численні ферменти, що беруть участь у метаболізмі глюкози, також індукуючи дисфункцію і запалення жирової тканини. Автори наголошують, що інсулінорезистентна жирова тканина характеризується низьким рівнем інфлюксу глюкози в адипоцити, високим рівнем вивільнення ВЖК після інсулінової стимуляції, що загалом призводить до гіперглікемії та гіперліпідемії. У патогенезі ІР білої жирової тканини беруть участь наступні lncR: ADIPINT, ASMER, Blnc1, DIO3OS, GAS5, Gm15290, H19, LncOb, MEG3, SRA та інші. Довгі некодуючі РНК, що беруть участь у патогенезі ІР м'язової тканини: IRLnc, H19, NONMMUT044897.

Ключові слова: ожиріння; інсулінорезистентність; метаболічно асоційована жирова хвороба печінки; довгі некодуючі РНК