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Research Article

The role of polymorphism of redox-sensitive genes in the mechanisms of oxidative stress in obesity and metabolic diseases

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ABSTRACT
The review summarizes ideas about the role of polymorphic variants of redox-sensitive genes that regulate the development of oxidative stress in obesity and associated metabolic diseases. The concept of oxidative stress, activated oxygen metabolites (AOM), which include reactive forms of oxygen, nitrogen, and chlorine, is considered, and an idea of the antioxidant system and its enzymatic link is given. The important role of gene polymorphism of AOM-producing enzymes — *CYBA*, *CYBB*, *MT-ND1/2/4L*, *MT-CO1/3*, *XOR*, *CYP*, *NOS2/3*, *MPO* — in the induction of oxidative stress in obesity has been shown. The dualism of AOM in obesity is emphasized: on the one hand, they are necessary for normal adipogenesis and signaling, and, on the other hand, they play a trigger role in the development of oxidative stress. It has been demonstrated that an imbalance in antioxidant system in obesity and metabolic disorders may be associated with variability in the genes of key antioxidant enzymes and proteins — *SOD1/2/3*, *CAT*, *GPX1-8*, *GSR*, *GSTP1*, *GSTM1*, *GSTT1*, *PRDX3*, *TXNIP*, *HMOX1*, *NQO1*, *NFE2L2*, *KEAP1*. The critical role of polymorphism in the Nrf2 transcription factor gene, the main regulator of redox homeostasis under physiological conditions and in obesity, has been demonstrated. It has been demonstrated that disruption of redox homeostasis due to genetic variability of the prooxidant-antioxidant system contributes to the development of the pathological obesity phenotype. Understanding the genetic mechanisms underlying oxidative stress in obesity and metabolic diseases is necessary to expand knowledge about the mechanisms of pathogenesis of these diseases and to develop effective methods for their correction.

Keywords: obesity; metabolic diseases; oxidative stress; gene polymorphism.

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Научная статья

Роль полиморфизма редокс-чувствительных генов в механизмах окислительного стресса при ожирении и метаболических заболеваниях

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АННОТАЦИЯ

В обзоре обобщены представления о роли полиморфизма редокс-чувствительных генов, регулирующих развитие окислительного стресса, при ожирении и ассоциированных метаболических заболеваниях. Рассмотрена концепция окислительного стресса, активированных кислородных метаболитов (АКМ), к которым относятся активные формы кислорода, азота и хлора, дано представление об антиоксидантной системе и ее ферментативном звене. Показана важная роль полиморфизма генов АКМ-продуцирующих ферментов — *CYBA*, *CYBB*, *MT-ND1/2/4L*, *MT-CO1/3*, *XOR*, *CYP*, *NOS2/3*, *MPO* — в индукции окислительного стресса при ожирении. Подчеркивается дуализм АКМ при ожирении, с одной стороны, необходимых для нормального адипогенеза и сигналинга, а с другой — выполняющих триггерную роль в развитии окислительного стресса. Продемонстрировано, что дисбаланс в антиоксидантной системе при ожирении и метаболических расстройствах может быть связан с вариабельностью генов ключевых антиоксидантных ферментов и белков — *SOD1/2/3*, *CAT*, *GPX1-8*, *GSR*, *GSTP1*, *GSTM1*, *GSTT1*, *PRDX3*, *TXNIP*, *HMOX1*, *NQO1*, *NFE2L2*, *KEAP1*. Показана критическая роль полиморфизма гена фактора транскрипции Nrf2, главного регулятора редокс-гомеостаза в физиологических условиях и при ожирении. Продемонстрировано, что нарушение редокс-гомеостаза вследствие вариабельности генов системы оксиданты – антиоксиданты способствует развитию патологического фенотипа ожирения. Понимание генетических механизмов, лежащих в основе окислительного стресса при ожирении и метаболических заболеваниях, необходимо для расширения знаний о механизмах патогенеза данных заболеваний и разработки эффективных способов их коррекции.

Ключевые слова: ожирение; метаболические заболевания; окислительный стресс; полиморфизм генов.

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ЭКО•ВЕКТОР

BACKGROUND

Obesity is a multifactorial chronic disease characterized by excessive accumulation of fat mass in the body, which poses a health risk [1]. It is one of the most common diseases globally, which has recently reached pandemic levels. The prevalence of obesity has tripled over the past four decades [1, 2]. According to World Health Organization, almost 20% of the global population will be obese by 2025, if this trend continues.

The etiology of obesity includes many factors, with eating disorders (alimentary hedonism and changes in diet), genetic predisposition, physical inactivity, adverse environmental influences, and social factors being the most important [1]. The heritability of obesity ranges from 40% to70% [3]. The most common form of obesity is polygenic, caused by many gene variants that form the pathological phenotype of obesity. To date, due to large-scale genome-wide association searches, more than 1,100 loci associated with obesity have been identified, but research in this area continues [1].

Obesity usually results from energy imbalance, when the amount of energy obtained from the food consumed exceeds the energy expended in life processes. If case of excess energy, lipids accumulate in adipose tissue cells, thus leading to an increase in their mass [2]. Obesity is diagnosed by body mass index (BMI), which is calculated as the ratio of body weight in kilograms to the square of height in meters. Normal BMI ranges from 18.5–24.9 kg/m^2. BMI of 25 kg/m^2 and higher is classified as overweight, whereas BMI of 30 kg/m^2 and higher is classified as obesity.

Obesity is often accompanied by concomitant metabolic disorders, the most common of them being metabolic syndrome (MS), insulin resistance (IR), type 2 diabetes mellitus (T2DM), cardiovascular diseases, dyslipidemia, reproductive disorders, chronic liver and kidney diseases, arthrosis, and some types of cancer [4]. Chronic oxidative stress (OS) plays a critical role in the pathogenesis of obesity and associated metabolic disorders [5, 6].

OS is defined as an imbalance in the oxidants ↔ antioxidant system, accompanied by high free radical oxidation against the antioxidant system dysfunction, which leads to damage to biomolecules and cell structures [7, 8]. The most important inducers of OS are highly reactive intermediates that are formed during metabolism as a result of redox reactions or by electron excitation with the participation of molecular oxygen [8]. Depending on the nature of the reactive atom (oxygen, nitrogen, or halogens), reactive species are grouped into reactive oxygen species (ROS, $O_2^{-\cdot}$, H_2O_2, $OH^{\cdot}$, $^1O_2$), reactive nitrogen species (RNS, $NO^{\cdot}$, $NO_2^{\cdot}$, $ONOO^-$), and reactive halogen species (RHS, HOCl, HOBr, HOI) [8]. Generally, all these compounds are prooxidants and called activated oxygen metabolites (AOM), i.e., a class of highly reactive oxygen compounds of radical and nonradical nature [9]. The maintenance of redox homeostasis is ensured by the antioxidant system including enzymatic and nonenzymatic antioxidants [9, 10]. By definition [11], "an antioxidant is any substance that, when present in low concentrations compared to the oxidized substrate, delays significantly or prevents its oxidation."

The regulation of OS is under strict genetic and epigenetic control, which maintains redox homeostasis of the body as a necessary condition for normal functioning [12, 13]. Any uncompensated imbalance in the redox system contributes to the development of OS and various pathological conditions [7]. OS is classified into eustress and distress [8]. During oxidative eustress, the increase in AOM levels does not exceed physiological limits, which ensures signal transmission and protection against pathogens. In contrast, oxidative distress is accompanied by a significant increase in of AOM levels, which leads to irreversible oxidative modification of macromolecules, cell death, and the initiation of pathological processes.

The leading processes associated with obesity, along with OS, include inflammation and hypoxia [14, 15]. Additionally, obesity is accompanied by OS, and OS can initiate the development of obesity by stimulating the deposition of white adipose tissue, an increase in differentiation of preadipocytes, proliferation of adipocytes, and an increase in the size of mature fat cells [5].

The most important molecular mechanisms that induce the production of AOM and systemic OS in obesity include hyperglycemia and autoxidation of glucose, dyslipidemia, high activity of oxidants that leads to overproduction of AOM, antioxidant system deficiency, mitochondrial and endothelial dysfunction, chronic inflammation, and hyperleptinemia [16–18]. The severity of systemic OS positively correlates with BMI and obesity [6].

Among the various determinants of obesity associated with OS, the most important role is played by genetic factors, namely, polymorphism of genes that regulate OS and epigenetic regulation. Figure 1 presents the composition of redox-sensitive genes and their role in the development of OS in obesity and metabolic pathologies. Redox-sensitive genes that control the development of OS are represented by two groups with oppositely directed functions, namely, genes of AOM-producing enzymes that contribute to the development of OS (*CYBA*, *CYBB*, *MT-ND1/2/4L*, *MT-CO1/3*, *XOR*, *CYP*, *NOS1/2/3*, and *MPO*) and genes of antioxidant enzymes (*SOD1/2/3*, *CAT*, *GPX1–8, GSR*, *GSTP1*, *GSTM1*, *GSTT1*, *PRDX3*, *TRX*, *TXNIP*, *HMOX1*, and *NQO1*), as well as proteins of Nrf2-dependent signaling system (*NFE2L2* and *KEAP1*), which counteract oxidative distress, i.e., the state of acute OS.

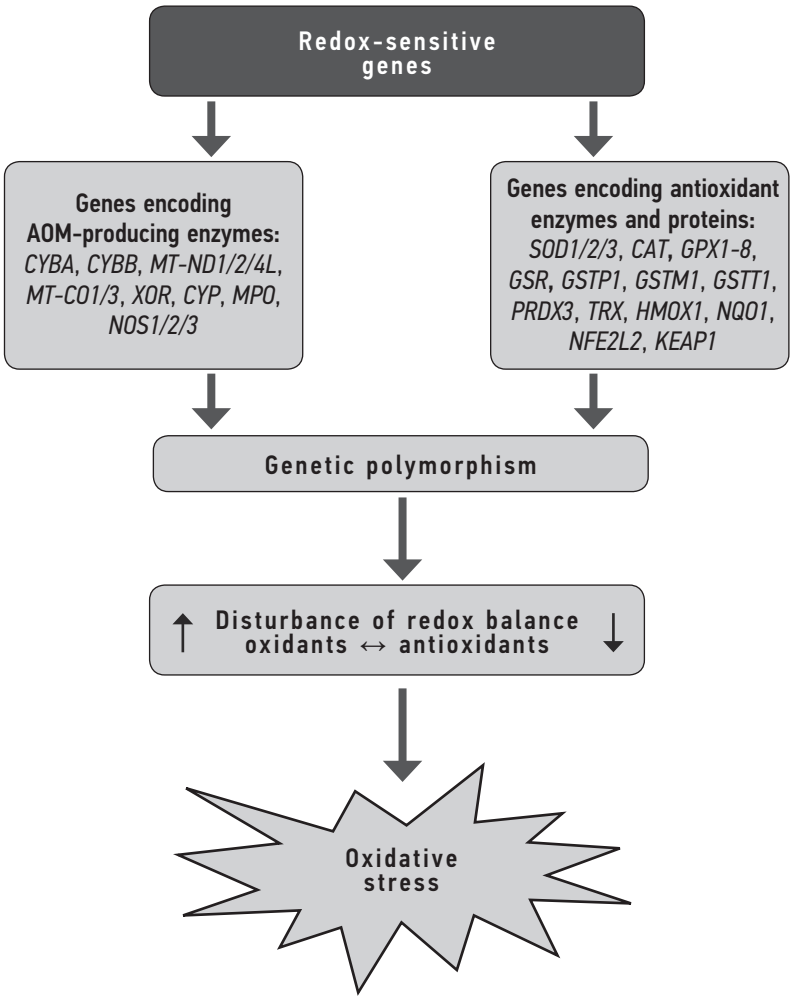

Fig. 1. Composition of redox-sensitive genes and their role in the development of oxidative stress in obesity and metabolic diseases
Рис. 1. Состав редокс-чувствительных генов и их роль в развитии окислительного стресса при ожирении и метаболических заболеваниях

Accordingly, this review aimed to examine the characteristics of the influence of polymorphism of genes of AOM-producing and antioxidant enzymes on changes in the redox balance leading to OS in obesity and concomitant metabolic diseases.

POLYMORPHISM OF GENES CODING AOM-PRODUCING ENZYMES IN OBESITY AND METABOLIC DISEASES

The most important sources of AOM in obesity are prooxidant enzymes that produce ROS, RNS, and RHS [14, 19, 20]. Additionally, dysfunction of prooxidant enzymes due to polymorphism of coding genes can modulate the formation of AOM, thereby increasing or decreasing the level of OS [12, 13]. AOMs are effectively generated by the family of NADPH oxidases, enzyme complexes of the electron transport chain (ETC) of mitochondria, xanthine oxidase (XO), the family of cytochrome P 450 isoforms (CYP), and NO synthases, myeloperoxidase. [9, 10].

NADPH oxidase and mitochondrial ETC play a leading role in generating ROS in obesity and associated metabolic disorders [21, 22]. NADPH oxidase (NOX) is a multisubunit protein complex that generates $O_2^{-\cdot}/H_2O_2$ by transferring electrons from cytosolic NADPH to molecular oxygen [23]. The structure of NOX consists of six heterogeneous subunits, two of which are membrane-bound (gp91phox and p22phox) and four are cytosolic (p47phox, p40phox, p67phox, and Racl/2). NADPH oxidases form a family that includes seven homologous isoforms (NOX1–NOX5, Duox1 and 2) [23, 24]. The membrane subunits of the enzyme complex, p22phox (α-subunit) and gp91phox (β-subunit), form a heterodimeric flavohemoprotein cytochrome b-245, which forms the catalytic electron transport oxidase system [23]. After cellular activation, cytosolic components are transferred to the membrane and associate with cytochrome b-245, resulting in the formation of a functionally active NADPH oxidase.

The expression of various NOX isoforms is characterized by tissue specificity, as Nox4 is predominantly

localized in adipocytes, whereas Nox2, Nox4, and Duox1,2 are predominantly localized in muscle tissue [25]. Additionally, depending on the stage of obesity, the mechanism of $O_2^{-\cdot}/H_2O_2$ generation has its own characteristics [25]. The main contribution to the generation of ROS in adipocytes is Nox4 at the early stage of obesity, and Nox2 at the intermediate stage, due to the infiltration of adipose tissue by macrophages and leukocytes. At the later stages of obesity, the mitochondrial ETC plays a key role in generating ROS, which, due to hyperglycemia and dyslipidemia, experiences an overload, leading to electron leakage from the ETC and the reduction of molecular oxygen with the formation of $O_2^{-\cdot}/H_2O_2$. ROS generated by NADPH oxidases can induce the formation of mito-ROS by mitochondria and vice versa, which forms a vicious circle and increases the development of OS in obesity [22].

In obesity, ROS play a dual role. They are necessary for adipogenesis and are the most important secondary messengers in adipocyte signaling cascades, but when overproduced, they contribute to hypertrophy and hyperplasia of adipose tissue, i.e., its dysfunction and various metabolic disorders [26].

Many allelic variants in the genes of NADPH oxidase subunits can affect enzymatic activity and ROS production [12]. Subunit p22phox functions as a scaffold that stabilizes cytochrome b-245, and promotes the initiation of superoxide production by NOX1–NOX4 isoforms [23]. It is encoded by the *CYBA* (cytochrome b-245 alpha chain) gene located on chromosome 16q24.2.

The *–930A>G* substitution (rs9932581) in *CYBA* occurs in a potential binding site for transcription factors C/EBP (CCAAT/enhancer-binding proteins). The *–930G* allele increases the affinity of C/EBP for the promoter [27] and increases gene expression by 30% [28]. Accordingly, the *GG CYBA* genotype promotes high enzyme levels and high ROS production, which is associated with the development of OS, higher BMI, HOMA-IR and insulin levels, the risk of insulin resistance, and hypertension [21, 27, 28].

A substitution in the *CYBA* gene (rs4673 His72Tyr) at the *242C>T* locus also affects NOX activity [29, 30]. The *242T* allele is associated with low stability and activity of the enzyme complex and low levels of ROS production [31]. However, the *CC* genotype provides protection against obesity and diabetes mellitus and is associated with lower plasma glucose levels and visceral fat in patients with hypertension [30].

Yu. Azarova et al. [32] reported that, in the Russian population, the *AA* genotype of the *CYBA* gene (rs4673, *G>A*) in the general group was associated with a high risk of developing T2DM and high BMI. The association of rs4673 a high risk of T2DM and high MBI occurred only in women. The *242C>T* substitution is associated with the development of metabolic syndrome in Iranian men, as the *T* allele was associated with a low risk of developing MS in men, but not in women [33]. Additionally, this substitution in the *CYBA* gene significantly affects endothelial function in T2DM patients, and the *T* allele has a protective effect [34]. Patients with T2DM and the *CT* or *TT* genotype have significantly lower BMI values and insulin concentrations than patients with the *CC* genotype [35].

In central Russia, rs1049255 *640A>G CYBA* is associated with the development of IHD only in men and is not associated with a predisposition to the disease in women [36]. This single-nucleotide substitution, localized in the 3'UTR region of the *CYBA* gene, does not lead to an amino acid substitution; however, the *AA* genotype is associated with a 30% higher ROS production than in *GG* homozygotes [37], suggesting that the *G* allele is protective. Analysis of mQTL (methylation quantitative trait locus) revealed that the risk allele *A* rs1049255 *CYBA* is associated with cis-mQTL associated with a decrease in DNA methylation in peripheral blood. Thus, carriage of the *A* allele may contribute to high *CYBA* expression through mQTL-associated decrease in methylation.

In Slavic population, single-nucleotide substitutions in *CYBB* introns (beta chain of cytochrome b-245, gp91phox), rs5963327 *G>T* and rs6610650 *G>A* are associated with a high risk of T2DM [38]. *CYBB* is located on the short arm of the X chromosome at position 21.1 and contains 13 exons. The mechanism of relationship between these allelic variants and the disease involves a more intense synthesis of CYBB in carriers of the minor alleles, which manifests as an increase in the concentration of ROS and a prooxidant shift in redox homeostasis in the blood plasma. Among all the subunits of NADPH oxidase (nicotinamide adenine dinucleotide phosphate, reduced form), only gp91phox contains binding sites for the cofactors NADPH, FAD (flavin adenine dinucleotide), and two heme molecules, crucial for the catalytic activity of the enzyme and electron transport that results in the formation of superoxide anion radical [23].

Increasing evidence suggests the role of mitochondrial dysfunction in the pathogenesis of obesity and associated metabolic disorders [14, 39]. Metabolic overload of mitochondria in obesity leads to lipo- and glucotoxicity, OS, and mitochondrial damage. Recent studies have shown a decrease in the number of mitochondria, suppression of the activity of mitochondrial enzymes, and dysregulation of mitophagy in patients with obesity, T2DM, or MS [16, 40].

Mitochondrial dysfunction in obesity can be caused by single-nucleotide substitutions in genes encoding proteins of the mitochondrial respiratory chain [41–43]. In an association search to identify genetic markers associated with high BMI and obesity, 984 mitochondrial single-nucleotide substitutions (mtSNPs) were tested in a sample

of 6528 adults aged from 24 to 85 years [42]. The authors identified three mtSNPs (*mt3336T>G, mt4851C>T,* and *mt10550A>G*) localized in the genes of subunits of ETC complex I, NADH dehydrogenase (MT-ND1, MT-ND2, and MT-ND4L) and two mtSNPs (*mt6663A>G* and *mt9698T>C*) located in genes encoding subunits of complex IV, cytochrome-c-oxidase (MT-CO1 and MT-CO3), as being associated with obesity. Disruption of the structure of ETC complexes is accompanied by inhibition of the electron transport function of the ETC, electron leakage, and one-electron reduction of O_2 with the formation of ROS, which initiates the development of mitochondrial OS [44].

The *3497C>T* (A64V) substitution in the NADH dehydrogenase subunit 1 gene (ND1) is associated with obesity and reduces the functional activity of complex I, increasing the production of ROS [41]. More than 11 ROS generation sites have been identified in mitochondria, which, under physiological conditions, can produce up to 2–3% of $O_2^{-\cdot}/H_2O_2$, whereas under pathological conditions, including obesity, the intensity of ROS formation can increase ten-fold, creating a conducive environment for the development of OS [44].

Prooxidant enzymes involved in the generation of ROS include XO, an isoform of xanthine oxidoreductase (XOR). XOR is encoded by the *XOR* gene (*XDH*, 2p23.1) and is involved in the catabolism of purines to uric acid; is represented by two isoforms, namely, dehydrogenase (XD) and oxidase (XO) [45]. Conversion of XD to XO post-translationally and can be reversed by oxidation of cysteine residues (Cys535 and Cys992), but can be rendered irreversible through limited proteolysis of a fragment of the XD polypeptide chain [45]. The transformation of XD to XO can also be a consequence of the *XOR* gene polymorphism [46]. Nonsynonymous single-nucleotide substitutions are decisive in the XD/XO ratio. With His1221Arg and Ile703Val substitutions, the oxidase isoform of the enzyme predominates over the dehydrogenase isoform, which makes a significant contribution to the development of OS in obesity.

In a study of 118 overweight/obese individuals, it was revealed that high XO activity is closely associated with obesity [47].

The polymorphism of the *XOR* gene determines the different role of the enzyme in obesity, as XOR has various types of activity [45]. Additionally, with all types of XOR activity, uric acid is formed, and, as a result of oxidase activity, $O_2^{-\cdot}/H_2O_2$ is also produced, and with nitrite/nitrate reductase activity, nitric oxide is produced.

An important ROS source in the body is the cytochrome P450 (CYP) superfamily, which is represented by 57 functionally active genes [48]. The CYP superfamily is a diverse group of heme-containing monooxygenases that are involved in the metabolism or biotransformation of xenobiotics and drugs and in the biosynthesis of endogenous molecules, such as sterols, fatty acids, eicosanoids, and vitamins. CYPs are expressed and localized on the cytoplasmic side of the endoplasmic reticulum (50 CYPs) and luminal side of the inner mitochondrial membrane (7 CYPs) of cells in most tissues [48]. However, during the functioning of CYP, ROS can be formed during the catalytic cycle and its uncoupling [49]. Particularly, the substitutions Ile269Phe (*CYP2C8*2*) and Arg139Lys with Lys399Arg (*CYP2C8*3*) of epoxygenase are localized not in the active site but in the apoenzyme, which affects the interaction with redox partners (cytochrome P450 reductase) in the catalytic cycle. This increases the rate of electron transfer and substrate turnover, which is accompanied by excess production of hydrogen peroxide and other ROS [50]. Modulation of CYP activity in obesity, associated with polymorphism of coding genes, is involved in disruption of the catalytic cycle and increasing generation of ROS [51].

A study of the Russian population examined the association of single-nucleotide substitutions in genes encoding the subfamily of cytochrome P450 CYP2C enzymes involved in the metabolism of arachidonic acid to form various vasoactive products with the risk of IHD development [52]. A protective effect of the *CYP2C19*2* allele (rs4244285) against the risk of IHD was revealed. This *681G>A* substitution in exon 5 creates an aberrant splice site that changes the reading frame of the mRNA and leads to the formation of a truncated, nonfunctional protein. The *CYP2C19*2* variant is associated with a partial loss of function, a decrease in enzyme activity, thereby leading to a decrease in ROS production by cytochrome P450, which, to a certain extent, protects against OS characteristic of IHD.

The source of RHS is the enzyme myeloperoxidase (MPO), a hemoprotein that is abundantly expressed in neutrophils and, to a lesser extent, in monocytes and macrophages. It is involved in inflammatory response initiation in adipose tissue [53]. The prooxidant enzyme MPO (*MPO*, 17q23.1) catalyzes the formation of RHS (HOCl, HOBr, etc.), which have a bactericidal effect and are early biomarkers of inflammation [54]. When produced excessively, RHS damages various macromolecules, causing halogenation stress [54]. The number of neutrophils and peripheral blood level of MPO are significantly increased in the plasma of obese patients, which indicates a positive correlation between MPO activation and metabolic disorders associated with obesity [55].

A functionally significant substitution, *463G>A* (rs2333227), was identified in the *MPO* gene promoter [56]. The presence of guanine at position *–463* creates a binding site for the SP1 transcription factor in the *MPO* gene promoter, which increases transcription of the gene 25-fold. However, MPO expression level depends on the cell type [57]. The *GA* genotype is characterized by 1.6–2.5 times higher MPO mRNA levels than the *GG* genotype in human peripheral blood mononuclear cells; however,

in macrophages, the *GG* genotype is associated with 4.6–7 times higher levels of MPO than the *GA* genotype.

A study [58] revealed that the *–463GA* and *AA MPO* genotypes are associated with an increased risk of arterial hypertension in patients with obesity and T2DM. In [59], in examination of 97 obese children with MS, it was established that the *GG* genotype at rs2333227 of the *MPO* gene contributed to the greatest risk of developing OS and IR.

In a population in central Russia, an association of rs2333227–*463G>A* MPO with the development of ischemic heart disease has been reported [36]. Allele *A* is protective, whereas the functionally more active allele *G* contributes to high risk of developing IHD and OS due to increased generation of RHS. Hypochlorite (HOCl), the most important product of the MPO reaction, in the presence of Fe^{2+} generates a highly toxic hydroxyl radical ($OH^{\cdot}$), which initiates lipid peroxidation (LPO) and causes oxidative damage to biomembranes and biomolecules [9, 10].

Another important source of AOM in obesity is the family of NO synthases (NOS), which, in a monooxygenase reaction, produce nitric oxide (NO), a precursor of RNS ($NO_2^{\cdot}$, $ONOO^{-}$, etc.) [60]. NO is formed by the oxidation of the guanidine group of L-arginine with oxygen involving NO synthases. Moreover, L-citrulline is formed in the reaction. NO synthase, which is a dimeric flavohemoprotein, is represented by three isoforms, namely, NOS1 (neuronal), NOS2 (inducible), and NOS3 (endothelial), each of which is encoded by a separate gene. These three NOS isoenzymes may influence the etiology of obesity through the production of NO, which plays an important role in regulating obesity, energy expenditure, and insulin sensitivity [60].

NO is one of the central factors that regulate obesity and systemic metabolism [60, 61]. The role of *NOS3* gene polymorphism (7q36.1) in obesity and associated metabolic disorders has been extensively studied [60, 62]. Clinical and experimental studies have reported a decrease in NO bioavailability in individuals with obesity owing to an imbalance between the synthesis and elimination of nitric oxide, post-translational modifications of the enzyme, and the presence of single-nucleotide substitutions in *NOS3* [62]. A genetic study of the African-American population showed that carriers of the *Asp* allele with the Glu298Asp *NOS3* substitution (rs1799983) had a higher BMI, waist circumference, and the amount of subcutaneous fat than those who did not, which may indicate a predisposition to obesity [63]. The *894G>T* substitution of *NOS3* leads to a change in the enzyme primary structure, which weakens the binding of NOS3 to caveolin-1 in caveolar rafts of endothelial cell membranes and reduces the availability of NOS3, thus leading to reduced enzyme activity and NO production [64].

A genetic analysis of apparently healthy Russian individuals in the Moscow region revealed a relationship between the *GG* genotype (*894G>T*) of the *NOS3* gene with endothelial dysfunction and metabolic status [65]. Presence of the *GG* genotype is associated with high levels of blood pressure, total cholesterol, and low-density lipoprotein cholesterol, high incidences of endothelial dysfunction, albuminuria, and IR.

As predisposition to obesity manifests itself at an early age, an analysis of *NOS3* gene markers in children and adolescents was performed [66, 67]. The study revealed that the 4a4a polymorphism genotype in *NOS3* intron 4 and the *C-T-G-C* haplotype (NOS3-tagSNPs rs3918226, rs3918188, rs743506, and rs7830) are associated with obesity in children and adolescents. VNTR sequences (27 bp long) in intron 4 of the *NOS3* gene regulate the gene post-transcriptionally, influencing the formation of microRNAs, which, when interacting with the mRNA of the target gene, lead to its degradation. The most common are alleles with five (4b) or four (4a) repeats [68].

The antiobesogenic role of *NOS3* has been confirmed in many experimental studies [62]. Mice with a triple knockout of the *eNOS, nNOS,* and *iNOS* genes exhibit high visceral obesity, hypertension, hypertriglyceridemia, and impaired glucose tolerance [69]. In contrast, mice overexpressing *eNOS* in the vascular endothelium have an antiobesogenic phenotype associated with a high metabolic rate on a high-fat diet, resistance to the accumulation of white adipose tissue, hyperinsulinemia, and low levels of free fatty acids and triglycerides in the blood plasma [70].

The *NOS3* gene genotype influences susceptibility to metabolic disorders associated with obesity [66, 67]. Indeed, the *CC –786T>C NOS3* genotype is associated with MS in children and adolescents [71]. Haplotype C-4b-Glu (*–786T>C*, 4b/4aVNTR, Glu298Asp) has been associated with hypertension in obese children and adolescents and with lower NO levels in adults with the obesity phenotype in various ethnic groups [60, 71].

In the Iranian population, a single-nucleotide substitution in the inducible NO synthase gene, *NOS2 1823C>T* (rs2297518), is associated with susceptibility to metabolic syndromes in the general group and in women [72]. The *T* allele and *CT+TT* genotypes demonstrated an association with obesity and the risk of MS. Substitution of an amino acid in the enzyme structure (Ser608Leu), localized in the catalytic domain, increases the activity of NOS2, leads to overproduction of nitric oxide, and creates the preconditions for the development of nitrosyl stress and the formation of cytotoxic RNS.

Table 1 presents the influence of single-nucleotide substitutions in the genes of AOM-producing enzymes on the development of OS in obesity and metabolic disorders.

Table 1. Single-nucleotide substitutions in the genes of AOM-producing enzymes regulating the development of oxidative stress in obesity and metabolic diseases

Таблица 1. Однонуклеотидные замены в генах АКМ-продуцирующих ферментов, регулирующих развитие окислительного стресса, при ожирении и метаболических заболеваниях

Single-nucleotide substitution	Gene, chromosome	Gene expression, enzyme activity, AOM production, OS level	Effects of single-nucleotide substitution	Population, gender, age (years)	References
–930A>G (rs9932581)	*CYBA* 16q.24.2	Allele *–930G*: *CYBA*↑, NOX↑, ROS↑, OS↑	Allele *–930G* and genotype *–930GG* are associated with high BMI, HOMA-IR, insulin resistance, and hypertension	Spaniards (m/f, 20–60). Caucasians (m/f, 48–56). Spaniards (m/f, 58–60)	[21] [27] [28]
242C>T (rs4673) *640A>G* (rs1049255)	*CYBA* 16q.24.2	*242C>T (72*His>Tyr in p22phox): NOX↓, ROS↓, OS↓ *640* AA (3'UTR *CYBA*): NOX↑, ROS↑, OS↑	The *T* allele reduces the risk of metabolic syndrome in Iranian men. Protective role of the *T* allele: *CT* or *TT* genotypes are associated with low BMI and low insulin levels in T2DM. The *AA* genotype is associated with a high risk of T2DM and high BMI in the general group and in women. The *AA* genotype is associated with the development of IHD in men. Allele *G* is protective.	Iranians (m, 48–60). Poles (m, 56–60). Japanese (m/f, 50–64) Russians (m/f, female, 54–68). Russians (m, 61)	[33] [34] [35] [32] [36]
G>T (rs5963327) *G>A* (rs6610650)	*CYBB* Xp21.1	rs5963327T, rs6610650A (introns *CYBB*): *CYBB*↑, ROS↑, OS↑	Minor alleles *T* and *A* are associated with a high risk of T2DM	Russians (m/f, 54–68)	[38]
mt3336T>G *mt4851C>T* *mt10550A>G*	*MT-ND1* *MT-ND2* *MT-ND4L*	NADH-dehydrogenase↓, ROS↑, OS↑	Associated with obesity	Japanese (m/f, 58 ± 5). Germans (m/f, 24–85). Spaniards (m/f, 51 ± 15)	[41] [42] [43]
mt6663A>G *mt9698T>C*	*MT-CO1* *MT-CO3*	Cytochrome-c-oxidase↓, ROS↑, OS↑	Associated with obesity	Japanese (m/f, 58 ± 5). Germans (m/f, 24–85). Spaniards (m/f, 51 ± 15)	[41] [42] [43]
Ile703Val (rs17011368) *3662A>G* His1221Arg	*XOR (XDH),* 2p23.1	Amino acid substitutions in XOR: XO↑ $O_2^{-\bullet}$↑, NO•↑, OS↑	Associated with obesity, cardiovascular diseases in different populations	Japanese (m/f, 50–60). Montenegrins (m/f, 55 ± 15)	[46] [47]
*CYP2C8*2* (Ile269Phe) *CYP2C8*3* (Arg139Lys)	*CYP2C8* 10q24	Amino acid substitutions increase turnover of substrates: ROS↑, OS↑	Associated with high prevalence of BMI and metabolic disorders	Norwegians (m/f, 20–62)	[51]
*CYP2C19*2* *681G>A* (rs4244285)	*CYP2C19* 10q23.33	Synonymous substitution in exon 5: occurrence of an aberrant splicing site, loss of function, *CYP2C19*2*↓, ROS↓, OS↓	Protective effect against the risk of IHD	Russians (m, 62 ± 9)	[52]

Table 1 (continued)
Окончание таблицы 1

Single-nucleotide substitution	Gene, chromosome	Gene expression, enzyme activity, AOM production, OS level	Effects of single-nucleotide substitution	Population, gender, age (years)	References
–463G>A (rs2333227)	*MPO*, 17q23.1	Allele *–463G*: activity of MPO↑, HOCl↑, OS↑ Allele *–463A*: activity of MPO↓, RHS↓, OS↓	The *–463GG MPO* genotype is associated with the risk of developing OS and insulin resistance in children with obesity and metabolic syndrome. The *–463GA* and *AA MPO* genotypes are associated with a high risk of hypertension in obese individuals with T2DM. The *–463G* allele is associated with a high risk of IHD and the development of OS, the *A* allele is protective	Turks (m/f, children, 12 ± 2) Chinese (m/f, 69 ± 0,7) Russians (m/f, 55–69)	[59] [58] [36]
1823C>T (rs2297518)	*NOS2* 17q11.2	Substitution of Ser608Leu in the catalytic domain of NOS2: NOS2↑, NO↑, nitrosyl stress ↑	Allele *1823T* is associated with T2DM and obesity	Iranians (m/f, 50–60)	[72]
894G>T (rs1799983)	*NOS3* 7q36.1	Substitution of Glu298Asp in NOS3 disrupts the binding of the enzyme to caveolae, the activity of NOS3↓, NO•↓	The *Asp298* allele is associated with a predisposition to obesity (high BMI, large waist circumference and amount of subcutaneous fat)	African Americans (b/g, 11–29)	[63]
–786T>C (rs2070744)		Allele *–786C* leads to a decrease in promoter activity and gene transcription: NOS3↓, NO•↓	The *–786CC* genotype is associated with metabolic syndrome in children and adolescents. Haplotype C-Glu (*–786T>C*, Glu298Asp) is associated with hypertension in children and adolescents, obesity and low NO levels	Brazilians (b/g, 12 ± 3)	[66, 67, 71]

Note. ↑ — increase in gene expression, enzyme activity, level of activated oxygen metabolites (AOM) and oxidative stress (OS) relative to normal; ↓ — decrease in the above-mentioned indicators relative to the control; m/f — males/females, b/g — boys/girls; BMI — body mass index; IHD — ischemic heart disease; T2DM — type 2 diabetes mellitus; XOR — xanthine oxidoreductase; MPO — myeloperoxidase; RHS — reactive halogen species

Thus, polymorphism in the genes for enzymes producing ROS, RNS, and RHS, makes a significant contribution to the development of OS associated with obesity and metabolic disorders. AOMs exhibit a dual role, at low concentrations they participate in regulatory signaling cascades in adipocytes and cells of other tissues, and at high concentrations, they cause cytotoxic effects and initiate the development of OS.

POLYMORPHISM OF ANTIOXIDANT SYSTEM GENES IN OBESITY AND METABOLIC DISEASES

The antioxidant system (AOS), providing a balance between the production and elimination of AOM, plays a critical role in maintaining redox homeostasis in obesity. There is an imbalance in functioning of AOS in obesity and associated metabolic disorders, related to variability in the genes of key antioxidant enzymes [5, 7, 73].

In the functioning of AOS, a major role is played by enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, glutathione disulfide reductase, heme oxygenase 1, NAD(P)H: quinone oxido-reductase 1, peroxiredoxins, paraoxonase 1), whose activities can be regulated at transcriptional, post-transcriptional, and post-translational levels. Impaired antioxidant mechanisms in obesity have been revealed both in humans and in animal models [74].

Superoxide dismutase (SOD), which neutralizes the superoxide anion radical ($O_2^{-\cdot}$) forming H_2O_2 and O_2, is represented in humans by three isoforms, namely, cytosolic SOD1 (*SOD1*, 21q22.11), mitochondrial SOD2 (*SOD2*, 6q25.3),

and extracellular SOD3 (*SOD3*, 4p15.2) [75]. The active centers of SOD1 and SOD3 contain Cu^{2+} and Zn^{2+} ions, whereas that of SOD2 contains Mn^{3+} ions.

The *–251A>G* (rs2070424) substitution of *SOD1*, occurring in intron 3, may be associated with obesity in Mexican women, as the prevalence of *GA+GG* genotypes was significantly higher in the obese group than in the healthy group and was accompanied by a decrease in the enzyme activity [76]. Additionally, individuals with single-nucleotide substitutions *–251A>G SOD1, 47A>G SOD2*, and *–262C>T CAT* were characterized by higher accumulation of visceral fat.

Several studies have investigated the association of the *Ala16Val* (*47C>T*) substitution in human SOD2 with obesity [77, 78]. This substitution modifies the sequence encoding the N-terminal MTS (Matrix Targeting Signal) peptide, which directs the enzyme into the mitochondrial matrix. The SOD2 precursor containing Ala in the signal peptide is transported into mitochondria 30%–40% more efficiently, which contributes to higher enzyme activity. The Val variant of SOD2 has less activity, which causes high production of superoxide and other ROS [79]. In patients with the *TT SOD2* genotype, the probability to develop obesity was two times higher than in individuals with the *CC* or *CT* genotypes [78]. The *CT* genotype occurs in 90% of obese individuals, and the *TT* genotype is associated with low overall SOD activity [77].

A single-nucleotide substitution in the *SOD3* gene *172A>G* (rs2536512) plays a role in obesity and related disorders in a Middle Eastern population [73]. Additionally, the protective effect was associated with allele *A*, whose carriers were less likely to develop obesity. This single-nucleotide substitution causes the Ala58Thr amino acid substitution, which increases the activity of the SOD3 extracellular isoform. Activation of SOD3 in the extracellular compartment of endothelial cells enhances superoxide neutralization and blocks the formation of peroxynitrite, which is implicated in impaired endothelium-dependent vasodilation and the development of obesity-induced hypertension [73].

Catalase (*CAT*, 11p13), a peroxisomal heme-containing enzyme, plays a key role in OS by cleaving hydroperoxide to H_2O and O_2, which prevents the formation of the highly toxic hydroxyl radical from H_2O_2 in the presence of Fe^{2+}/Cu^{+} ions. Catalase gene polymorphism is associated with obesity and metabolic disorders [80]. Particularly, in T2DM patients, there was a fourfold increase in the concentration of H_2O_2 relative to that of healthy people against a decrease in catalase activity in blood cells. *CAT* variants, namely, *–262C>T* (rs1001179) and *–844A>G* (rs769214), are closely associated with T2DM. These substitutions in the promoter region of the gene have considerable functional significance, influencing the expression of CAT and the concentration of catalase in blood cells [80]. The presence of rare CAT variants rs769214 *(–844A>G)*, rs7943316 (*–89T>A*), and rs1049982 (*–20C>T*) was associated with prepubertal obesity in children [12, 81, 82]. Additionally, rs769214 is associated with high weight, BMI, and adipocyte fatty acid-binding protein (A-FABP) levels, without a significant effect on erythrocyte catalase activity. However, some studies in the Swedish population, reported that catalase levels are significantly higher in carriers of the *T* allele of rs1001179 than in individuals homozygous for the *C* allele [82].

A different contribution of the *–262C>T* substitution of the *CAT* gene (rs1001179) to the formation of arterial hypertension was reported in populations of adolescents of two ethnic groups (Russians and Buryats) [83]. In Buryat adolescents, the C allele is associated with a predisposition to hypertension. However, such association was not revealed in Russian adolescents.

Thus, *CAT* gene expression and catalase activity are involved in the mechanisms of protection against OS induced by obesity and metabolic disorders, whereas *CAT* polymorphism may reduce the efficiency of antioxidant protection in obesity.

The glutathione peroxidases (GPx) family is an important component of AOS involved in protecting cells from hydrogen peroxide and various organic hydroperoxides through reduction mediated by glutathione. The family includes eight isoenzymes encoded by different genes and with different tissue localizations and substrate specificity; isoforms GPx1–4 and 6 are selenoproteins, i.e., they contain selenocysteine (Sec) in the active center [84, 85].

Data on the activity of GPx isoforms in blood and adipose tissue are very contradictory. Most studies report a decrease in enzyme activity in obesity and associated pathologies; however some studies report of GPx activation, which is considered an adaptive response [86]. *GPX* polymorphism makes a major contribution to changes in enzyme activity. The *GPX1* gene (3p21.31) is expressed in almost all tissues. The missense mutation *594C>T* (Pro198Leu; rs1050450) is known for it. The Leu (*T*) allele is associated with more severe OS, obesity, and IR, with some gender differences [12]. Screening of the *GPX1* gene in 184 Japanese patients with T2DM revealed four variants of changes (*–602A>G*, *+2C>T*, Ala(5)/Ala(6), and Pro198Leu) [12]. The *in vitro* analysis showed that the Ala6/198Leu combination led to a 40% decrease in enzyme activity, and the *602G/+2T* substitution combination led to a 25% decrease in transcriptional activity. Additionally, functionally significant variants of the *GPX1* gene are associated with an increased risk of atherosclerosis in T2DM patients.

An association of rs4902346 (*A>G*) of the *GPX2* gene with a high risk of developing T2DM in men was reported in a Russian population [87]. The minor allele *G* of rs4902346 is associated with a decrease in the expression of the *GPX2* gene in subcutaneous and visceral

adipose tissue, liver, and other tissues, which is accompanied by the accumulation of enzyme substrates (hydrogen peroxide, peroxynitrite, and lipid hydroperoxides) and, consequently, disruption of redox homeostasis [87]. In women, rs4902346 was associated with a low content of reduced glutathione, which is an important low-molecular-weight antioxidant, in the blood plasma and a disturbance in redox homeostasis. These associations indicate the presence of sexual dimorphism in the relationship of the *GPX2* gene with the studied phenotypes [87].

An analysis of single-nucleotide substitutions in the *GPX* genes in Mexican children and adolescents revealed two haplotypes associated with obesity based on BMI in *GPX3, GPX5,* and *GPX6*, and a haplotype based on the percentage of body fat mass (PBFM) in *GPX3* [88]. However, a protective effect of rs922429 *GPX3* and rs2074451 *GPX4* in Mexican children and adolescents was reported according to the criterion of PBFM.

A study [12] that examined 59 single-nucleotide substitutions in the *GPX* 1–7 genes established that rs757228 and rs8103188 (*GPX4*) correlated negatively, and rs445870 (*GPX5*) and rs406113 (*GPX6*) correlated positively with obesity in Spanish children.

In conjunction with glutathione peroxidase, glutathione-S-transferase (GST) plays a significant role in cellular redox-dependent processes. GST belongs to the superfamily of phase II detoxification enzymes. These are multifunctional proteins that use reduced glutathione for conjugation and elimination of hydrophobic xenobiotics and neutralization of free radical intermediates and lipid peroxidation products, such as 4-hydroxynonenal [9, 10]. GSTs are classified into three families, namely, cytosolic, mitochondrial, and microsomal. Cytosolic GSTs represent the largest family and are divided into seven classes, namely, alpha (A), mu (M), omega (O), pi (P), sigma (S), theta (T), and zeta (Z).

Genetic variability of *GST* (16 genes) plays a key role in disrupting cell protection from pollutants, carcinogens, OS products, and a wide range of xenobiotics, and is associated with a risk of predisposition to obesity and metabolic disorders [89].

Common variants of changes in the *GSTM1* and *GSTT1* genes include extended deletions *GSTM1 del/del* and *GSTT1 del/del*, which are associated with a lack of enzyme synthesis, which prevents conjugation of xenobiotic metabolites with glutathione (GSH).

When replacing 313*A*>*G* (rs1695, Ile105Val) of the *GSTP1* gene, the active site of the enzyme, which interacts with reactive electrophiles, partially loses its substrate-binding ability and thermostability, which decreases its activity.

In a Russian population of the Central Black Earth Region [90], the *GSTP1* 105Ile/Val and 105Val/Val genotypes are associated with T2DM and obesity in women, whereas in men the *GSTT 1 del/del* genotype is associated with the pathology.

In a Brazilian population, an association of *GSTP1* rs1695 with overweight and obesity in old age (⩾60 years) was reported [91]. Regardless of gender, elderly patients with at least one *G* allele were 2.4 times more likely to be obese than those with the *AA* genotype. However, in a Korean population, there was no significant association between *GSTM1* rs1056806 and rs3815029 and the development of obesity [92]. In a Polish population, the *GSTP1* Val/Val genotype, which leads to a decrease in the level of the active enzyme, was two times more common in T2DM patients under the age of 40 years than in healthy people [93]. There was a higher frequency of the *GSTP1* Val/Val genotype and homozygous deletion of *GSTT1 del/del* and *GSTM1 del/del* in patients diagnosed with T2DM before 40 years of age than in patients who became ill later as well as in healthy controls. A decrease or loss of the functional activity of glutathione-S-transferases, which is the most important family of antioxidant enzymes, due to genetic variability can make a significant contribution toward the development of OS in obesity and related pathologies.

The redox balance of the body largely depends on the ability of cells to maintain a pool of the universal water-soluble antioxidant, reduced glutathione (L-γ-glutamyl-L-cysteinylglycine, GSH), which are generated from the oxidized form (GSSG) by glutathione disulfide reductase (GSR). The GSH tripeptide is not only associated with the control and maintenance of cell redox homeostasis by reducing ROS and is a cosubstrate of glutathione-dependent enzymes, but is also involved in the processes of detoxification, signal transduction, proliferation, differentiation, and cell death [9, 10]. Changes in the GSH/GSSG ratio are noted in many pathological conditions associated with OS, including obesity and metabolic disorders.

A relationship between three single-nucleotide substitutions rs2551715 (*C*>*T*), rs2911678 (*T*>*A*), rs3757918 (*T*>*C*) in the introns of the glutathione disulfide reductase gene *GSR* with a reduced risk of developing T2DM was reported in a Russian population, indicating the involvement of the gene in pathogenesis of this disease [94]. The *CT-TT* genotypes of the rs2551715 variant were significantly associated with a reduced risk of T2DM. However, no statistically significant differences were recorded in the genotypes of the rs2911678 and rs3757918 loci.

Bioinformatics analysis showed that minor alleles of the three single-nucleotide substitutions increase the expression of *GSR* in the pancreas, nervous system, subcutaneous, and visceral adipose tissue [94]. Additionally, the protective effect of minor alleles was noted only in patients with normal body weight (BMI < 25 kg/m^2), whose diet included a sufficient amount of fresh vegetables and fruits.

The *T/T* rs2551715 genotype was 2.5 times less common in T2DM patients than in the controls; genotype *A/A* rs2911678 was six times less common; and genotype *C/C* rs3757918 was 2.7 times less common in T2DM patients than in the controls. The protective effect of *GSR* on T2DM risk was not observed in patients who did not consume a plant-based diet or in those with a BMI higher than 25. The authors believe that polyoxyphenols in plant foods activate the expression of the redox-sensitive transcription factor Nrf2, which activates the expression of key antioxidant enzymes in response to OS and suppresses the proinflammatory effects of the NF-κB factor [9].

A vital role in maintaining redox homeostasis in the cell is played by the family of redoxins, which contain highly reactive cysteines and are involved in the removal of hydrogen peroxide, organic peroxides, and in the thiol-disulfide exchange of target proteins [95]. Redoxins include peroxiredoxins (PRX), thioredoxins (TRX), and glutaredoxins (GRX).

PRX represent a family of multifunctional antioxidant thioredoxin-dependent peroxidases that regulate intracellular peroxide levels and play an important role in redox signaling, participating in cell proliferation and differentiation, immune response, and apoptosis [95]. A special role in protection against OS is played by PRX3, which is localized in mitochondria and reduces up to 90% of H_2O_2 formed during functioning of the ETC. The level of PRX3 decreases in the adipose tissue of experimental animals and humans with obesity [96]. Additionally, *PRX3* knockout mice had increased fat mass and developed an obesity phenotype, as well as an increase in OS markers and impaired mitochondrial biogenesis.

A nutrigenomic study revealed that four allelic variants of the *PRDX3* gene, namely, rs3740562 (*A/G*), rs2271362 (*C/T*), rs7768 (*G/C*), and rs3377 (*A/C*), are associated with high BMI and obesity in a Japanese population in combination with a high-fat diet [97]. Additionally, the *T-G-C-C-C* haplotype showed a significant association with an increase in BMI, whereas the *A-A-T-G-A* haplotype showed a significant association with a decrease in BMI. Overall, these results suggest a critical role of *PRDX3* genetic variants and fat intake in modulating BMI and obesity risk.

A major component of AOS is the thioredoxin (Trx) system, consisting of NADPH, thioredoxin reductase (TrxR) and thioredoxin 1/2 (Trx 1/2), which protects cells from OS due to its disulfide reductase activity [98]. A negative regulator of Trx 1/2 is thioredoxin-interacting protein (TXNIP), which inhibits Trx reductase activity through disulfide exchange. The Trx/Txnip redox complex, called the redoxisome, is a critical regulator of intra- and extracellular redox signaling involved in the pathogenesis of various diseases, including metabolic disorders [98].

Genetic mapping detected a nonsense mutation in the *TXNIP* gene as the cause of a familial combined hyperlipidemia-like phenotype in Hcb-19 mutant mice [99]. The mutation causes a truncation of Txnip in a critical region that mediates the binding of Txnip to Trx1, which impairs redox status and lipid metabolism.

In a Brazilian population, carriers of genetic variants of *TXNIP* exhibit high expression of Trx-interacting protein, early signs of impaired glucose homeostasis, and high susceptibility to chronic metabolic pathologies such as diabetes and hypertension [100]. The mutants rs7211 (*C/T*) and rs7212 (*C/G*) *TXNIP* were associated with phenotypes associated with hyperglycemia and elevated blood pressure. The *Trs*7211/*Grs*7212 *TXNIP* haplotype is associated with diabetes. Carriers of the *G* allele of rs7212 *TXNIP* exhibit higher levels of Txnip expression than individuals with the *CC* genotype of rs7212.

TXNIP variants rs7212 and rs7211 were associated with a high risk of ischemic heart disease in a Chinese population, and their cumulative effect correlated with the severity of coronary atherosclerosis [101].

In the Mexican population the rs7211 (*C>T*) marker of the *TXNIP* gene is associated with obesity [102]. Additionally, the presence of at least one *T* allele reduces the risk of obesity in women, i.e., this allele is considered protective, and the authors believe that changes in the expression or function of Txnip will ensure that thioredoxin exhibits an antioxidant effect [102]. S. Das et al. [103] came to a similar conclusion that in Euro-American and African-American subjects living in the USA, the *T* allele is also associated with low BMI and high density lipoprotein cholesterol concentrations in obese and non-diabetic subjects [103].

Enzymes that play a leading role in the modulation of metabolic disorders and redox state include heme oxygenase (HO), which occurs in the form of inducible (HO-1) and constitutive (HO-2) isoforms, which are encoded by the *HMOX1* and *HMOX2* genes [104]. HO degrades heme, a powerful prooxidant, to form carbon monoxide (CO), iron, and biliverdin, which is then converted into bilirubin. The induction of HO-1 reduces obesity, reduces elevated heme levels, suppresses OS, and participates in the local and systemic maintenance of homeostasis through the regulation of the functions of adipocytes and adipose tissue [104, 105]. HO-1 exhibits pleiotropic effects in obesity, reducing inflammation, vasoconstriction, and OS levels.

Two polymorphic sites have been detected in the 5'-flanking region of the *HMOX1* gene (22q12), namely, the polymorphism in the number of dinucleotide repeats $(GT)_n$ (rs3074372) and single-nucleotide substitution *–413T>A* (rs2071746). The number of repeats $(GT)_n$ ranges from 12 to 45 [106]. Alleles with less than 25 repeats are designated as short (S); those with more than 25 $(GT)_n$ are classified as long (L). Short alleles correspond to higher

transcriptional activity of the gene than L alleles. In an Asian population, T2DM patients with high BMI carrying longer (⩾32) repeats $(GT)_n$ had high OS and a high risk of ischemic heart disease and atherosclerosis [106]. Patients exposed to IHD risk factors associated with obesity (hyperlipidemia, diabetes), but with shorter (<27) repeats $(GT)_n$ had a reduced risk of the disease.

A functionally significant single-nucleotide substitution in the *HMOX1* promoter, *413T>A* (rs2071746), has been detected, which affects the gene activity [107]. *In vitro* experiments have shown that the activity of the *HMOX1* gene promoter increases in the presence of A at position –413. The *AA* genotype of rs2071746 can reduce the incidence of IHD, myocardial infarction, and angina pectoris, which is due to the high level of expression of HO-1 [106].

An important role in the development of obesity and associated metabolic complications is played by NAD(P)H, namely, quinone oxidoreductase (NQO1), a flavoprotein that catalyzes the two-electron reduction of highly reactive endogenous and exogenous quinones and their derivatives. NQO1 (*NQO1*, 16q22.16) performs various functions in the cell, such as detoxification of quinone compounds, maintaining the reduced form of endogenous antioxidants and superoxide reductase activity, protein stabilization, and protection against proteasomal degradation, NAD^+ generation, and control of mRNA translation [108]. Activation of NQO1 through NADH/NADPH oxidation protects against obesity, dyslipidemia, impaired glucose tolerance, hypertension, and MS.

NQO1 is widely expressed in various human tissues, such as adipocytes. Additionally, NQO1 expression in adipose tissue decreases during diet-induced weight loss, and expression levels are positively correlated with obesity, dyslipidemia, glucose tolerance, and markers of liver dysfunction. These findings indicate the role of NQO1 in obesity and associated metabolic disorders [109].

More than 20 single-nucleotide substitutions were detected in *NQO1*, including *609C>T NQO1* (rs1800566) as the most common, designated as the *NQO1*2* allele [109]. The primary structure of NQO1, proline is replaced by serine (P187S), which is accompanied by a decrease in enzyme activity due to instability and proteasomal degradation. Consequently, the enzyme activity in *NQO1*2/*2* homozygotes is almost undetectable, whereas in *NQO1*1/*2* heterozygotes the level of enzyme activity occupies an intermediate position between the homozygous substitution genotype and the wild type (*NQO1*1/*1*) [108]. Another common single-nucleotide substitution of *NQO1* is *465C>T* (rs4986998), *NQO1*3* (Arg139Trp), which can lead to deletion of exon 4 and the formation of a protein lacking quinone substrate-binding sites and low enzymatic activity [108]. All of these *NQO1* variants lead to disruption of redox homeostasis, the development of OS, and are detected in obesity and related metabolic disorders [110].

The key regulator of the cellular response to OS is the transcription factor Nrf2 (Nuclear factor erythroid 2-related factor 2), encoded by the *NFE2L2* gene (2q31.2), and the redox-sensitive signaling system Keap1/Nrf2/ARE [111]. Nrf2 belongs to the Cap'n'Collar (CNC) family, a subfamily of leucine zipper (bZIP) transcription factors that controls the expression of various genes encoding antioxidant enzymes and cytoprotective proteins [111].

Nrf2 is at the center of a complex regulatory network, including the expression of more than 1000 genes (1 to 10% of the genome) containing antioxidant response elements (ARE, antioxidant response element, 5'-A/GTGAC/TnnnGCA/G 3') in their promoters [111].

Under homeostatic conditions, Nrf2 is localized in the cytoplasm, where it is associated with the repressor protein Kelch-like ECH-associated protein 1 (*KEAP1*, 19p13.2), which ensures the ubiquitinylation of Nrf2 and its proteasomal degradation. In the presence of oxidative/electrophilic stress, the Keap1–Nrf2 complex dissociates, resulting in Nrf2 migrating into the nucleus, where it interacts with ARE sequences in the promoters of Nrf2-dependent genes, stimulating their transcription [102, 112–114]. Activation of Nrf2 increases the expression of genes for antioxidant and detoxifying enzymes containing ARE sequences in their promoters, including *SOD1, CAT, GPX1, GST, PRX, TRX, TRXR, HMOX1,* and *NQO1*.

Regulation of the Keap1/Nrf2/ARE signaling system includes the presence of ARE sequences in the promoter of the *NFE2L2* gene, which ensures its own transcription and autoregulation of the gene [115].

Nrf2 is a major target of obesity and associated metabolic disorders [105]. Controlled activation of Nrf2 alleviates obesity and associated metabolic disorders, decreases ROS production and OS levels, moderates lipid accumulation during adipogenesis, decreases synthesis of proinflammatory cytokines, and improved glucose homeostasis [116, 117]. In contrast, continuous and excessive activation of Nrf2 under obese conditions can dramatically increase lipid accumulation and initiate lipid peroxidation, which in turn causes tissue damage [117]. There is no doubt that the most important role in OS regulation in obesity and related pathologies belongs to the polymorphism of the *Nrf2* genes and other components of the Keap1/Nrf2/ARE signaling system. However, deficiency in Nrf2 activity in various organs, demonstrated in experimental models and clinical studies, leads to the development of pathological conditions associated with OS [112].

According to the NCBI SNP database, 2107 single-nucleotide substitutions were detected in the human *NFE2L2* gene; 85 of them are localized in the protein-coding region, and the rest are localized in the promoter region,

introns, and 5'- or 3'-noncoding regions. Suppression of the Nrf2-dependent signaling pathway has been reported under conditions with a high risk of cardiovascular diseases, diabetes, hypertension, chronic inflammation, aging, and other metabolic disorders, caused by genetic polymorphisms [116]. In various pathological conditions, including those associated with obesity, the substitution *–617C>A* (*rs6721961*) in the ARE sequence of the *NFE2L2* gene promoter has been most studied. It leads to poor binding of Nrf2 to the ARE and a decrease in the expression of the *NFE2L2* gene and Nrf2-controlled genes [117]. In various populations, *NRF2* rs6721961 was significantly associated with OS, antioxidant status, obesity, and the risk of associated metabolic pathologies [112, 113].

The *C>A* substitution (rs11085735) plays an important role in the *KEAP1* gene, encoding the Keap1 protein, which is a critical negative regulator of the Nrf2 transcription factor and a sensitive OS sensor [119, 120]. The location of this substitution in intron 2 may have functional consequences, affecting mRNA splicing, protein structure, and the interaction of Keap1 with Nrf2. In the Iraqi Kurdish population, a higher frequency of the minor allele *A* and the *AA* genotype was recorded in obese individuals, which correlated with higher BMI, waist and hip circumference, than in carriers of the *AC* and *CC* genotypes [119]. In the Iranian population, the *AA* genotype was more common in T2DM patients and in patients with T2DM complicated by neuropathy than in healthy individuals [120].

Table 2 presents the effect of single-nucleotide substitutions in the most important genes of the antioxidant system on the development of OS in obesity and metabolic disorders.

Thus, research conducted in recent decades has demonstrated the critical role of OS in the mechanisms of obesity and associated pathologies and the major contribution of polymorphism in the genes of enzymes producing AOM, antioxidant enzymes, and proteins of

Table 2. Single-nucleotide substitutions in the genes of antioxidant enzymes and proteins regulating the development of oxidative stress in obesity and metabolic diseases

Таблица 2. Однонуклеотидные замены в генах антиоксидантных ферментов и белков, регулирующих развитие окислительного стресса, при ожирении и метаболических заболеваниях

Single-nucleotide substitution	Gene, chromosome	Gene expression, enzyme activity, AOM production, OS level	Effects of single-nucleotide substitution	Population, gender, age (years)	References
–251A>G (rs2070424)	*SOD1* 21q22.11	Nucleotide substitution in intron 3 of *SOD1* modulates enzyme activity and OS level	SNP is associated with obesity in women: the frequency of *GA+GG* genotypes is higher in obese than in normal individuals; high levels of visceral fat	Mexicans (m/f, 56 ± 5)	[76]
47C>T (rs4880)	*SOD2* 6q25.3	Substitution of Ala16Val changes the structure of the MTS signal peptide: SOD2↓, ROS ↑, OS↑	The *TT SOD2* genotype doubled the probability of obesity, relative to *CC* or *CT* genotypes.	Mexicans (m/f, 56 ± 5).	[76]
			The *CT* genotype was detected in 90% of obese patients,	Mexicans (m/f, 66 ± 8).	[78]
			and the *TT* genotype was associated with low total SOD activity	Poles (m/f, 37–57)	[77]
172A>G (rs2536512)	*SOD3* 4p15.3	Substitution of Ala58Thr in the structure of the enzyme: SOD3↑, ROS↓, OS↓	Allele *G* is associated with the development of obesity, allele *A* exhibits protective effect	Saudi Arabia (m/f, 42 ± 16)	[73]
–262C>T (rs1001179)	*CAT* 11p13	Single-nucleotide substitutions in gene regulatory regions: *CAT*↓, Cat↓, H_2O_2↑, OS↑	Substitution is associated with obesity and T2DM; catalase levels were significantly higher in carriers of the *–269T* allele than in homozygotes for the *C* allele	Spaniards (m/f, 8.7 ± 0.1).	[80]
				Swedes (m/f, 50 ± 10)	[81]
–844A>G (rs769214)			Substitution is associated with prepubertal obesity in children, with high weight, BMI and adipocyte fatty acid-binding protein levels	Spaniards (b/g, 8.7 ± 0.1)	[12]
–89T>A (rs7943316)			Substitution is associated with prepubertal obesity in children	Spaniards (b/g, 8.7 ± 0.1)	[12]
594C>T (rs1050450)	*GPX1* 3p21.31	Substitution of Pro198Leu, allele Leu (*T*): *GPX1*↓, Gpx↓, H_2O_2↑, lipid hydroperoxides↑, OS↑	The *T* allele is associated with obesity and insulin resistance in children;	Spaniards (b/g, 8.7 ± 0.1).	[12]
			this allele is associated with a high risk of atherosclerosis in T2DM patients	Japanese (m/f, 40–60)	[12]

Table 2 (continued)
Окончание таблицы 2

Single-nucleotide substitution	Gene, chromosome	Gene expression, enzyme activity, AOM production, OS level	Effects of single-nucleotide substitution	Population, gender, age (years)	References
14362A>G (rs4902346)	*GPX2* 14q23.3	Minor allele *G*: *GPX2*↓, Gpx↓, H_2O_2↑, lipid hydroperoxides↑, peroxynitrite↑, OS↑	Allele *G* is associated with the risk of T2DM in men	Russians (m/f, 61 ± 10)	[87]
1578A>G (rs1695)	*GSTP1* 11q13.2	Substitution of Ile105Val: GSTP1↓, xenobiotics↑, LPO products ↑, OS↑	Genotypes *105Ile/Val* and *105Val/Val* are associated with T2DM and obesity in women; the SNP is associated with overweight and obesity in old age; genotype *105Val/Val* is associated with T2DM	Russians (m/f, 61 ± 10). Brazilians (m/f, 60–98). Poles (m/f, 54 ± 11)	[90] [91] [93]
C>T (rs2551715), *T>A* (rs2911678), *T>C* (rs3757918)	*GSR* 8p12	Substitutions in introns of the *GSR* gene. Minor alleles increase *GSR* expression in the pancreas, nervous system, subcutaneous and visceral adipose tissue. GSH↑, AOS↑, OS↓	Association with a low risk of T2DM in a group of patients with normal body weight, with sufficient daily consumption of vegetables and fruits. The T/T rs2551715 genotype was 2.5 times less common in T2DM patients than in controls; genotype *A/A* rs2911678 was 6 times less common; genotype *C/C* rs3757918 was 2.7 times less common. The protective effect of *GSR* on the risk of T2DM was not observed in patients who did not consume a plant-based diet or in those with a BMI >25.	Russians (m/f, 61 ± 11)	[94]
C>T (rs7211), *C>G* (rs7212)	*TXNIP* 1q21.1	Minor alleles in the *TXNIP* gene: *TXNIP*↑, TXNIP↑, redoxisome inhibition, OS↑	Association with hyperglycemia, predisposition to T2DM, hypertension; correlate with the risk of IHD and atherosclerosis; the *T* allele (rs7211) is associated with low BMI and risk of obesity	Brazilians (m/f, 25–64). Chinese (m, 63 ± 10). Mexicans (m, 53 ± 9). Americans (m/f, 19–60)	[100] [101] [102] [103]
$(GT)_n$ (rs3074372)	*HMOX1* 22q12	Alleles with $(GT)_n < 25$: *HMOX1*↑; OS↓. Alleles with $(GT)_n > 25$: *HMOX1*↓, OS↑	Low risk of IHD. T2DM patients had a high BMI, risk of IHD and atherosclerosis	Caucasians (m/f, 57–72)	[106]
–413T>A (rs2071746)		Allele *–413A* (protective): *HMOX1*↑, OS↓. Allele *–413T*: *HMOX1*↓, OS↑	Reduces the incidence of IHD, myocardial infarction, angina pectoris	Caucasians (m/f, 57–72). East Asia (m/f, 62 ± 6)	[106] [107]
–617C>A (rs6721961)	*NFE2L2* 2q31.2	The substitution is localized in the gene promoter, in the ARE sequence. Minor allele is *–617A*: *NFE2L2*↓, gene expression AOS↓, OS↑	Associated with obesity and the risk of associated metabolic pathologies	Chinese (m, 50 ± 11)	[118]
C>A (rs11085735)	*KEAP1* 19p13.2	The substitution is localized in intron 2, it influences the interaction of Keap1 with Nrf2. Minor allele *A*: disruption of the KEAP1 structure, interaction with the transcription factor	The frequency of the *AA* genotype is higher in obesity; *AA* carriers have high BMI, as well as high waist and hip circumference. A higher frequency of the *AA* genotype in T2DM patients and in those with T2DM complicated by neuropathy than in healthy individuals	Kurds (m/f, 41 ± 10). Iranians (m/f, 56 ± 6)	[119] [120]

Note. ↑ — higher gene expression, enzyme activity, level of activated oxygen metabolites (AOM) and oxidative stress (OS) than in the normal; ↓ — decrease in the above-mentioned indicators relative to the control; m/f — males/females, b/g — boys/girls; BMI — body mass index; IHD — ischemic heart disease; T2DM — type 2 diabetes mellitus; XOR — xanthine oxidoreductase; MPO — myeloperoxidase; RHS — reactive halogen species; SOD — superoxide dismutase; AOS — antioxidant system.

the redox-sensitive signaling pathway Keap1/Nrf2/ARE, which controls redox homeostasis. Disruption of redox homeostasis due to genetic variability of the prooxidant–antioxidant system contributes to the development of the obesity phenotype.

The impact of polymorphisms in redox-sensitive genes on redox homeostasis and the risk of obesity and associated metabolic pathologies can vary significantly among various populations, and these differences are associated with interpopulation differences in minor allele frequencies and linkage disequilibrium between polymorphic loci. Most of single-nucleotide substitutions considered in this review are characterized by variability in population frequencies (Table 3). The frequency of the minor

Table 3. Population features of the frequency of the minor allele according to the studied single-nucleotide substitutions (according to the "1000 Genomes" project)

Таблица 3. Популяционные особенности частоты минорной аллели по исследуемым однонуклеотидным заменам (по данным проекта «1000 Genomes»)

Ген	Single-nucleotide substitution (allele)	Population frequency of minor alleles (mean value and variation range)		
		Africans	East Asia	Caucasians
CYBA	rs9932581 (*T*)	0.24 (0.11–0.32)	0.6 (0.46–0.68)	0.4 (0.34–0.47)
	rs4673 (*A*)	0.51 (0.45–0.59)	0.08 (0.05–0.13)	0.34 (0.21–0.47)
XDH	rs17011368(*C*)	0.12 (0.08–0.17)	0 (0–0.02)	0.05 (0.01–0.07)
CYP2C8	rs11572103 (*A*)	0.19 (0.14–0.23)	0	0 (0–0.01)
	rs11572080 (*T*)	0.01 (0–0.03)	0	0.12 (0.08–0.15)
	rs10509681 (*C*)	0.01 (0–0.03)	0	0.12 (0.08–0.15)
MPO	rs2333227 (*T*)	0.37 (0.56–0.69)	0.14 (0.12–0.17)	0.24 (0.19–0.29)
NOS3	rs1799983 (*T*)	0.07 (0.035–0.11)	0.13 (0.082–0.16)	0.34 (0.23–0.39)
	rs3918226 (*T*)	0 (0.0–0.025)	0	0.1 (0.07–0.12)
	rs3918188 (*A*)	0.37 (0.29–0.41)	0.29 (0.24–0.34)	0.31 (0.28–0.33)
	rs743506 (*G*)	0.47 (0.39–0.545)	0.2 (0.15–0.24)	0.29 (0.17–0.39)
	rs7830 (*T*)	0.19 (0.13–0.26)	0.41 (0.33–0.48)	0.35 (0.24–0.44)
	rs2070744 (*C*)	0.14 (0.08–0.18)	0.12 (0.1–0.15)	0.44 (0.31–0.5)
SOD1	rs2070424 (*G*)	0.2 (0.16–0.24)	0.51 (0.47–0.56)	0.07 (0.04–0.12)
SOD2	rs4880 (*G*)	0.42 (0.36–0.46)	0.12 (0.1–0.15)	0.47 (0.43–0.52)
CAT	rs1001179 *(T)*	0.02 (0–0.06)	0.03 (0.02–0.04)	0.23 (0.21–0.26)
	rs769214 (*G*)	0.44 (0.37–0.52)	0.73 (0.63–0.79)	0.33 (0.28–0.4)
	rs7943316 (*T*)	0.42 (0.34–0.52)	0.26 (0.19–0.34)	0.67 (0.59–0.71)
	rs1049982 (*T*)	0.44 (0.37–0.52)	0.73 (0.63–0.79)	0.33 (0.285–0.4)
GPX1	rs1050450 (*A*)	0.27 (0.22–0.34)	0.07 (0.05–0.12)	0.34 (0.28–0.4)
GPX2	rs4902346 (*G*)	0.41 (0.34–0.47)	0.13 (0.1–0.15)	0.19 (0.15–0.24)
GPX5	rs445870 (*G*)	0.59 (0.5–0.7)	0.51 (0.42–0.57)	0.31 (0.27–0.35)
GPX6	rs406113 (*C*)	0.75 (0.64–0.88)	0.51 (0.43–0.57)	0.33 (0.3–0.37)
GSTP1	rs1695 (*G*)	0.48 (0.4–0.54)	0.18 (0.1–0.22)	0.33 (0.28–0.39)
GSTM1	rs1056806 (*T*)	0.24 (0.21–0.31)	0.2 (0.17–0.25)	0.16 (0.09–0.22)
GSTM2	rs3815029 (*G*)	0.09 (0.06–0.12)	0.65 (0.64–0.67)	0.37 (0.34–0.38)
PRDX3	rs3740562 (*A*)	0.52 (0.46–0.55)	0.55 (0.52–0.58)	0.3 (0.26–0.32)
	rs2271362 (*T*)	0.37 (0.34–0.42)	0.49 (0.45–0.53)	0.27 (0.23–0.28)
	rs7768 (*C*)	0.48 (0.44–0.52)	0.57 (0.53–0.61)	0.31 (0.25–0.34)
	rs3377 (*G*)	0.11 (0.08–0.16)	0.31 (0.25–0.38)	0.56 (0.48–0.61)
TXNIP	rs7211 (*G*)	0.41 (0.36–0.46)	0.81 (0.69–0.87)	0.95 (0.94–0.97)
	rs7212 (*C*)	0.42 (0.34–0.46)	0.18 (0.11–0.31)	0.04 (0.03–0.05)
HMOX1	rs2071746 (*A*)	0.31 (0.23–0.37)	0.48 (0.45–0.5)	0.56 (0.53–0.59)
NQO1	rs1800566 (*A*)	0.18 (0.12–0.21)	0.42 (0.35–0.5)	0.21 (0.18–0.25)
	rs1131341 (*A*)	0 (0–0.02)	0.02 (0.02–0.03)	0.02 (0.01–0.03)
NFE2L2	rs6721961 (*T*)	0.06 (0.02–0.11)	0.24 (0.19–0.3)	0.13 (0.11–0.14)

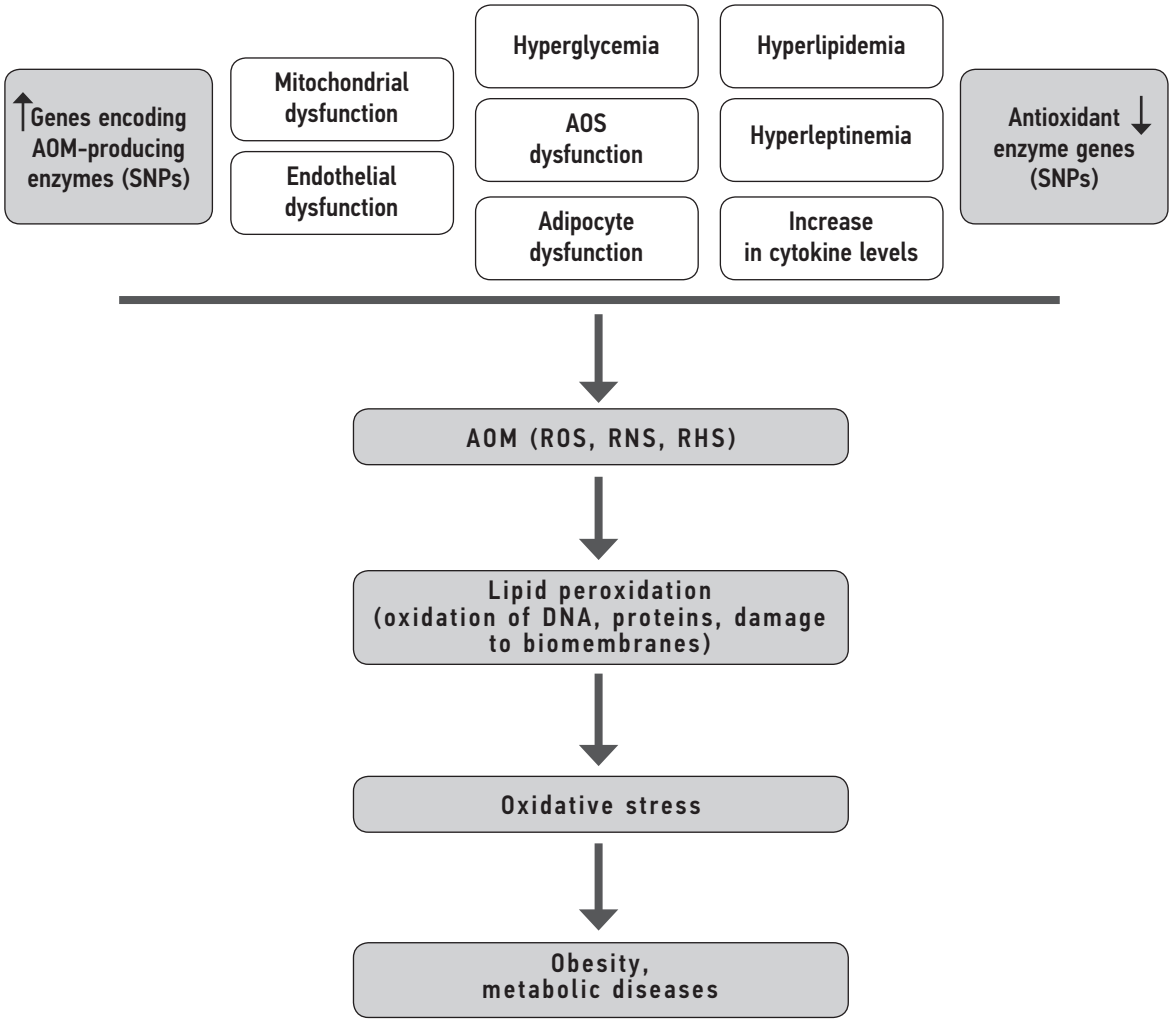

Fig. 2. Mechanisms of oxidative stress development in obesity and metabolic diseases
Рис. 2. Механизмы развития окислительного стресса при ожирении и метаболических заболеваниях

allele in different populations can differ by two orders of magnitude. For example, the frequency of the *T* allele at rs1001179 of the *CAT* gene is on average 11 times lower in Africans than in Caucasian populations. The frequency of allele *C* at rs7212 of the *TXNIP* gene among Africans is more than two times higher than that among residents of East Asian countries and 10 times higher than in populations in European countries (Table 3). In East Asian populations, the frequencies of alleles *G* (rs769214), *T* (rs1049982) of the *CAT* gene and allele *G* (rs3815029) of the *GSTM2* gene are predominant.

Thus, the intensity of various components of metabolism leading to the development of OS in obesity may have genetically determined ethnic and population characteristics.

CONCLUSIONS

An analysis of previous studies presented in this review shows that in obesity and concomitant metabolic diseases, disturbances in redox homeostasis and OS occur, which are caused by the insufficiency of the antioxidant system and excess production of ROS, RNS, and chlorine. The dependence of obesity on many exo- and endogenous factors emphasizes the critical role of imbalance in the prooxidant ↔ antioxidant system, associated with the variability of genes of AOM-producing enzymes that cause the development of OS, and the genes of AOS enzymes that prevent disruption of the redox balance. The reviewed studies show that polymorphism of genes associated with OS, leading to disruption of their functionality, is associated with the risk of obesity and metabolic disorders. Consequently, allelic variants of these genes may be of interest for testing genetic susceptibility to obesity. It has been demonstrated that disruption of redox homeostasis due to polymorphism of genes in the prooxidants ↔ antioxidant system contributes to the development of the pathological phenotype of obesity (Figure 2).

An in-depth understanding of the subtle mechanisms of genetic regulation of obesity-associated OS will contribute to the development of effective methods for treating obesity and associated metabolic diseases.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication. Personal contribution of the authors: N.P. Milyutina, T.P. Shkurat — conception and study design, critical revision for important intellectual content, editing, and supervision; M.A. Shkurat, E.V. Mashkina, N.P. Milyutina — search and analysis of literature, original draft preparation.

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